

From Alpha to Omega

n-6 & n-3 Fatty Acids and the Ratio Debate

The purpose of this learning module is to provide background knowledge in fatty acids and to present the n-6:n-3 fatty acid ratio debate.



Healthy Snacking Research Center (HSRC) Mission:

To develop and disseminate scientific information to support the development of Frito-Lay products in health and wellness.

The Healthy Snacking Research Center (HSRC) at Frito-Lay was formed as part of Frito-Lay's long-standing commitment to health and wellness. The HSRC was developed in order to educate and communicate with consumers and health professionals about Frito-Lay products and how they can fit into a healthier lifestyle, as well as to address myths and misconceptions about snack chips.

The HSRC seeks to educate health professionals and consumers about the company's use of healthier oils and healthier snacking options, as well as address some common misconceptions regarding snacking options.

The HSRC team launched www.snacksense.com, a website dedicated to health professionals. The website features current science on a variety of topics like fat, sodium, vitamins and minerals, and includes information to help health professionals communicate with their patients about healthier lifestyles.

American Dietetic Association Continuing Professional Education Certification

This activity has been approved by the Commission on Dietetic Registration.

Please visit www.snacksense.com for the online quiz.

Contributors

Elizabeth Dempsey MS, RD
Nutrition Scientist

Kari Hecker Ryan PhD, RD
Manager, Nutrition, Food Safety and Regulatory

Technical Review Panel

The following content experts have received an honorarium for reviewing this self-study learning module:

Dr. William Harris, PhD

Senior Scientist, Director – Nutrition and Metabolic Disease Research Institute, Sanford Research / USD
Professor, Basic Biomedical Sciences
University of South Dakota

Dr. Michael Lefevre, PhD

Professor, Center for Advanced Nutrition, USTAR
Utah State University

Dr. K.C. Hayes, DVM, PhD

Professor Biology (Nutr) and Director
Brandeis University

Writer

Katarina Yackley, BS
Nutrition Intern

Item Writer

Dr. Deborah D. Canter, PhD, RD, LD
Kansas State University

© 2008 Frito-Lay North America, Inc.

Learning Objectives

1. Identify the basic structure of fatty acids and differentiate between the different types.
2. Describe current recommendations for dietary fat intakes.
3. List benefits, sources, and health effects of n-6 and n-3 fatty acids.
4. Communicate and form an opinion on the ongoing n6:n3 fatty acid ratio vs. absolute intake debate.

Table of Contents

• Introduction to Fats	6
• “Bad Fats”	16
• “Beneficial Fats”	22
• Essential Fatty Acids	25
– Omega-6	26
– Omega-3	32
• The Ratio Debate	38
– Pro-Ratio	40
– Con-Ratio	46
• Conclusions	55
• Glossary*	56
• References	57

*The glossary contains a list of terms which are bolded throughout the learning module.

Introduction to Fats

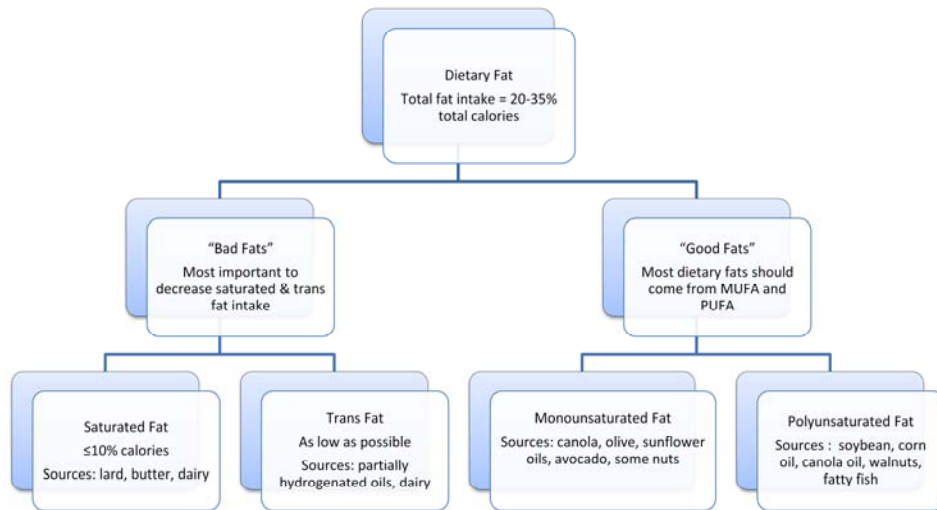
Introduction to Fats

- Fats Function in the Body
 - Provide energy
 - Normal growth and function
 - Absorption of fat soluble vitamins

Fats Function in the Body

Fat plays a vital role in the body and must be incorporated into the diet. Fats are a good source of energy, providing 9 kcals/g. Structurally, fat holds organs in place and cushions to protect against injury, is a component of cell membranes, as well as helps to maintain body temperature. Fat is necessary for normal growth and function of the brain, central nervous system and cell membranes. It also plays a vital role in the absorption and metabolism of fat-soluble vitamins, such as vitamins A, D, E, and K.

Introduction to Fats



Fats in the Diet

Contrary to popular consumer belief, all fats are not the same, all fats are not bad, and all fats should not be avoided. Most dietary lipid intake (>95%) is in the form of **triglycerides** (TG). A TG is made up of 3 **fatty acids** attached to a glycerol backbone.

Both saturated and trans fatty acids are not essential in the diet, and they do not confer health benefits. In fact, saturated and trans fats are of primary health concern because they often promote high levels of triglycerides and LDL cholesterol as well as cardiovascular disease. Therefore they should be minimized in the diet.

Monounsaturated fats (MUFA) and **polyunsaturated fats** (PUFA) have been found to confer cardiovascular benefits, and are recommended to replace as much **saturated fat** (SFA) and trans fat as possible in the diet.

Essential fatty acids include linoleic acid (LA) and alpha-linolenic acid (ALA), which are both polyunsaturated fatty acids. These are essential because they cannot be synthesized by the body and must be obtained in the diet.

Evolving Recommendations for Dietary Fat Intake

- 2005 Dietary Guidelines for Dietary Fat Intake
 - 20-35% of calories

Fat Dietary Guidelines for Americans 1980-2005

1980	1985	1990	1995	2000	2005*
Avoid too much fat, saturated fat and cholesterol	Avoid too much fat, saturated fat and cholesterol	Choose a diet <i>low in fat</i> , saturated fat and cholesterol	Choose a diet <i>low in fat</i> , saturated fat and cholesterol	Choose a diet low in saturated fat and cholesterol and <i>moderate in total fat</i>	Choose fats wisely for health (20-35% total fat)

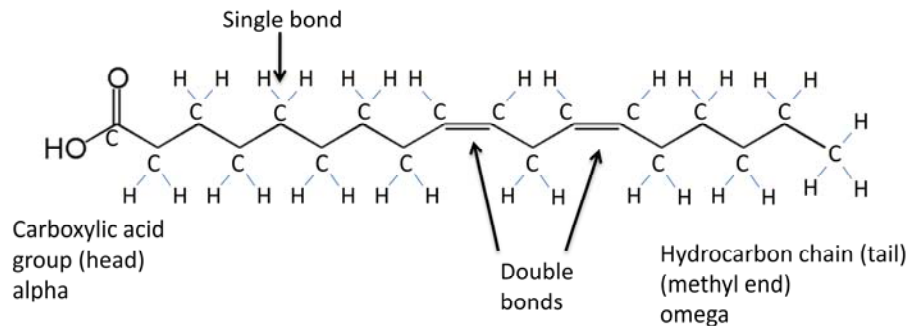
2005 Dietary Guidelines for Dietary Fat Intake

Recommendations for fatty acid intakes have changed as more scientific research on the effects and functions of fats in the body has become available. The 2005 US Dietary Guidelines for Americans recommends a diet of 20-35% of calories from fat, and most dietary fat should come from polyunsaturated and monounsaturated fatty acid sources (1). It is recommended to minimize saturated and trans fatty acid and cholesterol consumption while consuming a nutritionally adequate diet. Specifically, the recommendation for saturated fat is < 10% of calories, while intakes of trans fat should be as low as possible.

The range of 20-35% calories from fat is recommended because as fat intake decreases (especially below 20% of calories), carbohydrate intake increases in the diet. Higher levels of dietary carbohydrate can lead to higher triglyceride levels and lower HDL “good” cholesterol levels. Additionally, some fat-soluble vitamins may not be absorbed with a diet low in fat. On the other hand, saturated fat intake typically becomes too high when a diet is above 35% calories from fat.

Fatty Acid Structure

Linoleic Acid



Chemical nomenclature: "delta" counts from the COOH group

Nutritional nomenclature: "omega (or n)" counts from the methyl group

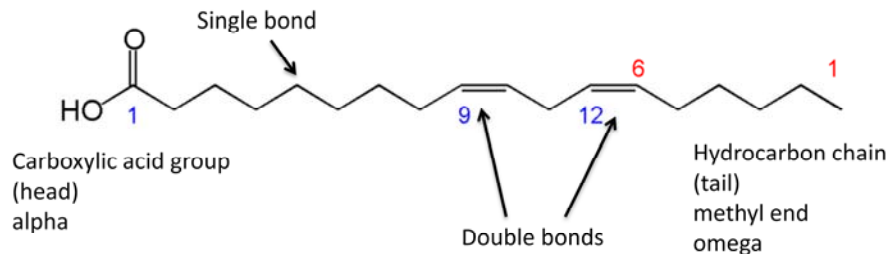
A **fatty acid** (FA) is comprised of:

- a carboxylic acid group (COOH)
 - the "head"
 - alpha
- hydrocarbon chain
 - the "tail"
 - omega
 - methyl end
- bonds
 - single
 - double

The carbon chain is the backbone of the fatty acid. In the carbon chain in the figure above, each line represents a bond between two carbon atoms (unless otherwise shown), and a double line represents a double bond. At the end of each bond (or line) there is a carbon atom, unless it is otherwise noted, such as the -OH (hydroxyl group) and =O (oxygen). Each carbon atom has four available bonds to link to adjacent molecules, many of which are hydrogen (depicted above).

Fatty Acid Classification

Linoleic Acid



Fatty acids are classified by:

- Chain length = 18 carbons
- Number of double bonds = 2
- Position of first double bond from methyl end = 6

Fatty acids are classified by:

1. Chain Length

- The length is determined by the number of carbon atoms present in the chain.
 - Short Chain Fatty Acids (SCFA) are < 6 carbons long.
 - Medium Chain Fatty Acids (MCFA) are 6 -10 carbons.
 - Long Chain Fatty Acids (LCFA) are ≥ 12 carbons.
 - Example: the figure above is a long chain fatty acid because it has 18 carbons

2. Number of double bonds

- The double lines (labeled in the figure above in blue at 9 & 12) represent double bonds.
- No double bonds = saturated fat (ie. Bonds are 'fully saturated' with hydrogen molecules)
- 1 double bond = monounsaturated fat (ie. One of the C-C links is missing two hydrogen molecules)
- 2 or more double bonds = polyunsaturated fat

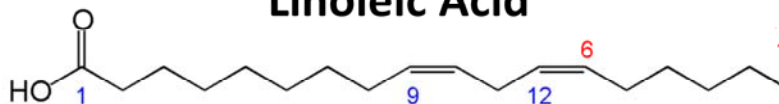
3. Position of the first double bond

- The double bond is counted from the tail or "omega" end of the fatty acid chain.
- The fatty acid is classified by the location of the first double bond, denoted by n-x.
 - Example from figure above: n-6

These properties give the fatty acid its particular characteristics for membrane structure and function as well as determine its melting point.

Nomenclature

Linoleic Acid



Five ways to name a fatty acid:

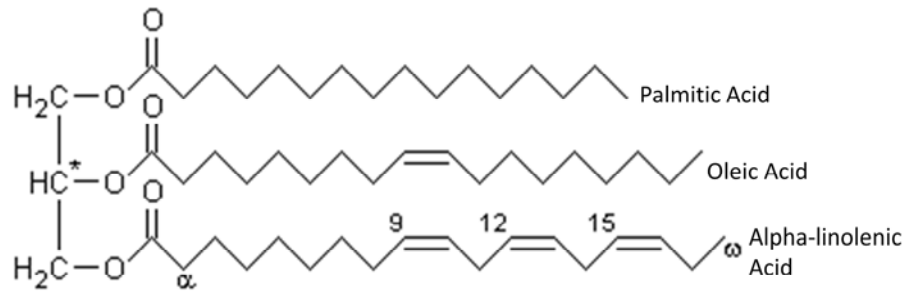
1. Trivial = linoleic acid
2. Systematic (IUPAC) = *cis, cis-9,12-octadecadienoic acid*
3. n-x (omega-x) = C18:2 n-6 (or ω -6)
4. Δ^x (delta-x) = C18:2 *cis* Δ^9 , *cis* Δ^{12}
5. Lipid numbers = C 18:2

Nomenclature

There are several different ways to name a fatty acid. The examples given for each type of name are for the structure above, commonly referred to as linoleic acid.

1. Trivial names are non-systematic historical names that are used most frequently in the literature.
Example: Linoleic Acid (See figure above)
2. Systematic (IUPAC) names come from standard IUPAC Rules for the Nomenclature of Organic Chemistry, published in 1979. They are very technically clear, but sometimes become long. Counting begins at the alpha end, and double bonds are labeled *cis/trans*.
Example: *cis, cis-9,12-octadecadienoic acid* (See figure above)
3. Another type of nomenclature classifies fatty acids by the notation n-x or omega-x. It does not provide names for specific fatty acids, but is a quick method by which to group fats according to their physiological properties. Double bonds are counted from the omega end and denoted as n-x, and shares properties with other similar fatty acids.
Example: n-6, omega-6 (See figure above)
4. Δ^x (delta-x) nomenclature denotes each double bond by a Δ^x , where the double bond is located on the xth carbon, counting from the alpha end, labeling *cis/trans*.
Example: C18:2 *cis* Δ^9 , *cis* Δ^{12} (See figure above)
5. Fatty acids are also classified by lipid numbers. The designation A:B is used, where A is the number of carbon atoms in the fatty acid and B is the number of double bonds present. Like the n-x nomenclature, multiple fatty acids could have the same formula, so it is sometimes paired with the n-x or Δ^x system.
Example: C 18:2 and C 18:2-n-6, n-9 (See figure above)

Triglyceride



More than 95% of dietary lipid intake is in the form of triglycerides (TG). A triglyceride is made up of three fatty acids attached to a glycerol backbone, and typically contains a mixture of fatty acids.

Fats present in food are mainly presented as triglycerides, therefore foods contain a variety of fatty acids. Foods known to be a source of a particular fatty acid also contain the other two fatty acids (ie. either saturated, monounsaturated, or polyunsaturated fatty acids in lesser amounts).

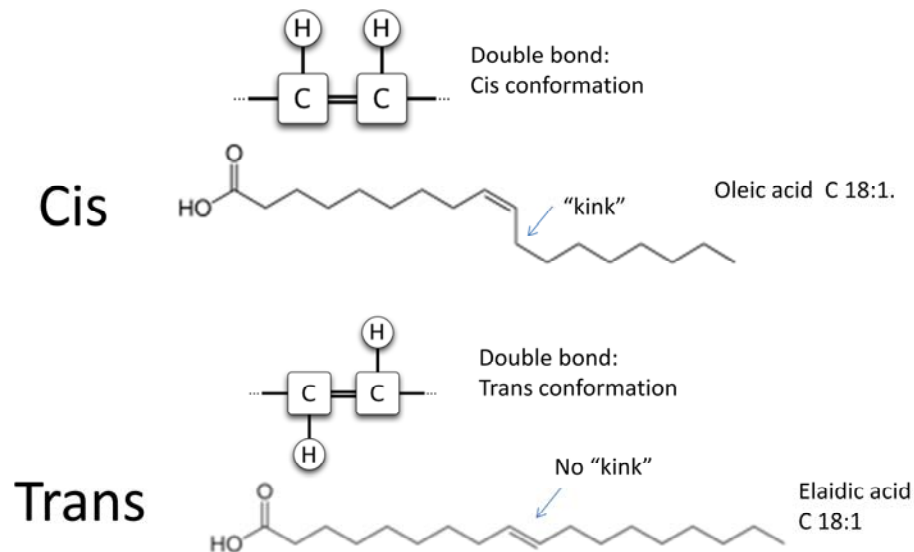
All three types of fatty acids (SFA, MUFA, and PUFA) behave differently in the body and are necessary for normal biological function. Since the body can make both SFA and MUFA, but not PUFA, only the latter has a dietary requirement. Too much dietary saturated fat, or even monounsaturated fat, in the relative absence in polyunsaturated fat can disturb lipid metabolism. Thus, recommended intakes have been suggested for each of these fat classes. High levels of triglycerides in the blood stream are related to atherosclerosis and CVD. The combination of increased TG, low HDL, and elevated numbers of small dense LDL is known as the 'atherogenic lipoprotein phenotype' and is associated with a higher risk for CVD (2).

Common Fatty Acids

Common Name	Lipid Number	Source
Lauric Acid	12:0	Coconut oil, Palm kernel oil
Myristic Acid	14:0	Butterfat, coconut oil
Palmitic Acid	16:0	Palm oil, animal fat
Stearic Acid	18:0	Cocoa butter, animal fat
Oleic Acid	18:1	Olive oil, canola oil
Linoleic Acid	18:2 n-6	Corn oil, soybean oil
Alpha-Linolenic Acid	18:3 n-3	Flax, canola, soybean oil
Arachidonic Acid	20:4 n-6	Animal fat
Eicosapentaenoic Acid	20:5 n-3	Fish oil
Docosahexaenoic Acid	22:6 n-3	Fish oil & algal oils

The table above shows a list of common fatty acids and some of their common sources.

Cis vs. Trans Conformation of Fatty Acids



Attached to the carbon molecules are hydrogen atoms, as seen above. In double bonds, the hydrogen bonds may vary in 2 different conformations, or the way in which the bonds are attached.

1. Cis

-In a **cis** bond (see the figure above) the hydrogens are on the same side of the carbon chain and do form a kink in the chain.

-Cis bonds naturally occur most often.

-Cis fats have a "kink" that do not allow them to pack tightly, and as a result they are liquid at room temperature, and have a lower melting point.

2. Trans

-In a **trans** bond (see the figure above) the hydrogen atoms are attached on opposite sides of the carbon chain, and the double bond does not form a kink in the fatty acid chain.

-Some trans bonds are found naturally in foods from ruminant animals (such as cattle).

-The majority of trans bonds are created by partial hydrogenation of polyunsaturated oils.

-Trans fatty acids have a straight chain like a saturated fatty acid, allowing them to pack tightly, so that fats that contain them behave more like a saturated fat, which is solid at room temperature. Trans fats have a higher melting temperature than their cis counterparts.

“Bad Fats”

- Types
 - Saturated fat
 - Esp. myristic and palmitic acids
 - Trans fat

Saturated fats, and especially trans fats, are known for being unhealthy or “bad” fats because they can promote **cardiovascular disease** (CVD) when consumed in excess.

Saturated fat

Saturated fat raises total cholesterol, including both low density lipoprotein (LDL) “bad” and high density lipoprotein (HDL) “good” cholesterol levels, with LDL being raised relatively more than HDL. Saturated fat raises serum LDL and total cholesterol levels by decreasing LDL receptor activity (3).

Trans fat

Trans fat, like saturated fat, raises LDL and total cholesterol levels, in addition to decreasing HDL “good” cholesterol levels. This combination further increases the risk for cardiovascular disease.

“Bad Fats”

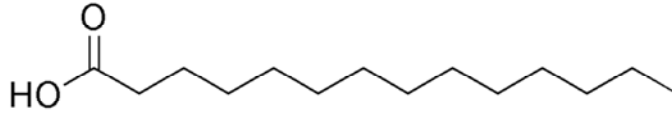
- Health Effects
 - ↑ risk for CVD
 - ↑ total cholesterol
 - ↑ LDL
 - ↓ HDL (trans only)

Health Effects

Cholesterol levels are an important factor in cardiovascular health. Very low density lipoprotein (VLDL) cholesterol transports triglycerides and some cholesterol from the liver to peripheral tissues, before ultimately being converted to LDL. The quantity and size of LDL particles is important in cardiovascular disease risk. A low-fat, high-carbohydrate diet that generates much VLDL can induce small dense LDL particle size in genetically predisposed individuals (2). Smaller, denser LDL particles enter arterial tissue more easily than larger, more buoyant LDL particles (2). Once in the arterial wall, LDL particles accumulate and may undergo a variety of modifications, particularly oxidation. Oxidized LDL particles are pro-inflammatory accelerating atherogenesis (4).

High density lipoprotein (HDL) is known as “good” cholesterol, in part because it can reduce the amount of oxidized cholesterol in LDL as well as transport cholesterol from tissues back to the liver. HDL cholesterol functions to remove excess cholesterol from cells (not just oxidized cholesterol) for delivery to the liver, which is known as reverse cholesterol transport. The liver can more readily receive cholesterol from HDL than LDL (5). In the liver, cholesterol may then be recycled or excreted.

Saturated Fat



Myristic acid. C 14:0.

- Role & structure
 - No double bonds
 - Solid at room temperature
 - Higher melting point

Role & Structure

A **saturated fatty acid** has no double bonds in its chain and it is fully hydrogenated. The carbon atom has four possible binding sites, two for carbons and two for hydrogen, and both hydrogen sites are fully “saturated” with hydrogens in this type of fatty acid. When approximately 30% or more of the fatty acids in a fat are saturated, it is solid at room temperature, and is labeled a saturated fat. Saturated fats also have a higher melting point than unsaturated fats.

Saturated Fat

- Health effects
 - Saturated fats typically increase both LDL and total cholesterol
- Sources
 - Animal fats
 - Dairy
 - Tropical oils
- Recommendations
 - < 10% energy

Health Effects

Saturated fats typically increase both LDL and total cholesterol, while PUFAs lower LDL and total cholesterol (6).

Sources

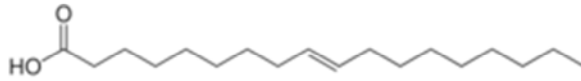
Saturated fats are found in:

- Animal fats
 - Meat
 - Lard
 - Eggs
- Dairy products
 - Whole fat milk
 - Ice cream
 - Yogurt
- Tropical oils
 - Coconut oil (12:0 + 14:0)
 - Palm oil (16:0 + 18:0)
 - Cocoa butter (chocolate) (18:0 + 16:0)

Recommendations

The 2005 Dietary Guidelines recommend that saturated fat should be < 10% of total energy (1). The current average American intake is 11-12% energy (7).

Trans Fat



- Role & structure
 - Hydrogenation
 - Double bond arrangement

A **trans bond** conformation is formed by partial hydrogenation of a liquid unsaturated oil. Hydrogen is added to an oil which is liquid at room temperature to create a more solid fat. When an oil is fully hydrogenated, it becomes a saturated fat that is relatively solid. Partially hydrogenated oils contain trans bonds, and are used to maintain texture, flavor, and shelf stability; but they have negative health effects.

Trans fats have a different arrangement around the double bond. The hydrogen atoms are on opposite sides (trans) of the double bond, rather than the same side (cis). This arrangement, or conformation, of having the hydrogens on opposite sides of the double bond causes the kink to disappear so that a straight hydrocarbon chain results. This is somewhat similar in conformation and function to a saturated fatty acid.

Trans Fat

- Health effects
 - Trans fats raise LDL, total cholesterol; lower HDL
- Sources
 - Partially hydrogenated vegetable oils (some baked & fried foods)
 - Dairy fats (minor amounts)
- Recommendations
 - <1% energy; as low as possible

Health effects

Trans fats behave physiologically like a saturated fat in that they raise LDL cholesterol and total cholesterol levels, but additionally, HDL cholesterol levels are decreased. These effects on cholesterol are thought to increase the risk for CHD above that of saturated fats.

Sources

Trans bonds do occur naturally at very low quantities in the milk and body fat of cattle and sheep, however they are mainly formed by hydrogenating (adding hydrogen to) an unsaturated fat, especially during commercial hydrogenation of polyunsaturated fats and their fatty acids.

Recommendations

The 2005 Dietary Guidelines recommend minimizing trans fat in the diet (1).

“Beneficial Fats”

- Unsaturated Fatty Acid
 - Polyunsaturated Fatty Acid
 - Omega – 3
 - Omega – 6
 - Monounsaturated Fatty Acid
 - Omega – 9

Unsaturated Fatty Acids

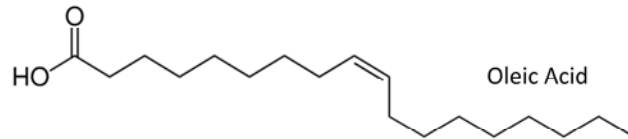
Fats can be beneficial? You bet. All fats are not equal, and all fats are not bad. Natural **unsaturated fats**, which contain one or more double bonds in the carbon chain, have been found to be beneficial in the diet and may decrease CVD risk. When unsaturated fats replace saturated fats in the diet, LDL and total cholesterol levels both decrease. There are two types of unsaturated fats.

Unsaturated fatty acids contain one or more double bonds. In this case, two of the four carbon atom's binding sites are unfilled by hydrogen and a double bond occurs between the adjacent carbons. If the fatty acid contains only one double bond, it is a monounsaturated fatty acid (MUFA). If it contains two or more double bonds, it is a polyunsaturated fatty acid (PUFA).

MUFAs, but especially PUFAs, when substituted for saturated and trans fatty acids or carbohydrates, have health benefits including reduced risk of CVD (8). Research shows that it is beneficial to substitute MUFAs and PUFAs for saturated and trans fat. Also, substituting PUFAs for carbohydrates leads to larger, more buoyant LDL particles, which is associated with a decreased risk of CVD (9). Unsaturated fatty acids have a major effect on the ratio of total:HDL cholesterol (a CVD risk factor); and the most effective method of improving blood lipid profiles is the replacement of trans fatty acids with unsaturated fatty acids (8).

Effective diet strategies for preventing coronary heart disease include: substituting “good” unsaturated fats for saturated and trans fats, consuming whole grains as the main source of carbohydrates, consuming ample fruits and vegetables, and eating an adequate amount of n-3 fatty acids (10).

Monounsaturated Fatty Acids



- **Role & Structure**
 - 1 Double Bond
 - Higher Melting Point than SFA
 - Liquid at room temperature
- **Health Effects**
 - Good effects on LDL and HDL
 - Effects on CHD risk unclear
- **Recommendations**
 - Up to 20% kcals
- **Sources**
 - Vegetable oils
 - Nuts
 - Avocados
 - All vegetable oils contain some oleic acid
 - Can be synthesized from carbohydrates *in vivo*

Role & Structure

Monounsaturated Fatty Acids (MUFAs) contain one double bond. The fluidity of the fatty acid increases with more double bonds. Monounsaturated fatty acids have a lower melting point than saturated fats, but higher than polyunsaturated fats.

Health Effects

MUFAs are called a “good” fat because they lower total and LDL cholesterol when replacing saturated fat. In addition, MUFAs also maintain HDL levels compared to carbohydrate, which is also beneficial for heart health.

Recommendations

The Dietary Advisory Committee Report recommends that up to 20% of energy comes from MUFAs.

Sources

MUFA rich oils and foods include:

- vegetable oils (olive, canola, peanut, palm)
- nuts
- avocados

All vegetable oils contain some oleic acid. Some MUFA can be synthesized from carbohydrates *in vivo*.

Polyunsaturated Fatty Acids

- Role & Structure
 - 2 or more Double Bonds
 - Melting Temperature
- Types
 - Omega-6
 - Linoleic Acid (LA)
 - Arachidonic Acid (AA)
 - Omega-3
 - Alpha- Linolenic Acid (ALA)
 - Eicosapentaenoic Acid (EPA)
 - Docosahexaenoic Acid (DHA)
- Essential vs. Non-essential Fatty Acids

Role & Structure

Polyunsaturated Fatty Acids (PUFAs) contain two or more double bonds. They are more fluid than saturated or monounsaturated fatty acids, and therefore, they have the lowest melting temperature of the three.

Two types of PUFAs are widely discussed:

1. Omega-6 fatty acids
 - 1st double bond is the 6th carbon from the omega end
 - Most common: LA (linoleic acid)
 - N-6 fatty acids are involved in the synthesis of **eicosanoids**, signaling molecules involved in many biological functions. Linoleic acid is the main fatty acid controlling the decrease in plasma cholesterol.
2. Omega-3 fatty acids
 - 1st double bond is at the 3rd carbon from the omega end
 - Involved in eicosanoid pathway (to prostaglandins and leukotrienes)
 - Two types:
 - Plant based – ALA (alpha-linolenic acid)
 - ALA is a precursor for EPA (eicosapentaenoic acid) & DHA (docosahexaenoic acid).
 - Fish / marine based – EPA & DHA
 - Omega-3's are known for their heart healthy properties provided by EPA and DHA.

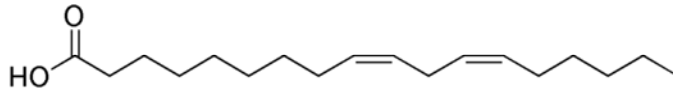
Essential Fatty Acids

- Alpha-linolenic acid, 18:3n3
- Linoleic acid, 18:2n6

Only polyunsaturated fatty acids are essential, meaning that they cannot be synthesized by the human body and must be obtained through the diet. Omega-3 (ALA) and omega-6 fats are the two essential fatty acids, with other polyunsaturated fatty acids in these classes being derived from them. Both omega-3 and omega-6 fatty acids are utilized in biological processes, such as eicosanoid synthesis. Both saturated fatty acids and monounsaturated fatty acids are non-essential and are primarily used by the body as an energy source.

Omega-6 Fatty Acids

Linoleic Acid (LA)



Linoleic acid

- Classification
 - Polyunsaturated Fatty Acid, n-6 family
 - Most commonly consumed PUFA in the diet
- Sources
 - Vegetable oils
 - Nuts
 - Grains (minor)

Classification

Linoleic acid (LA) is the most common n-6 fatty acid in the diet. Omega-6 fatty acids are classified by their structure. Linoleic acid's first double bond is located on the 6th carbon from the omega (tail) end. Linoleic acid is 18 carbons long, and is designated by the lipid number 18:2.

Sources

N-6 or omega-6 fatty acids in the diet are mainly consumed through linoleic acid in the form of:

- Sunflower oil
- Corn oil
- Soybean oil
- Safflower oil
- Other vegetable oils
- Grains
- Nuts

LA can be converted to arachidonic acid (AA) in the body. AA is the second most common n6 fatty acid and is mainly found in meat, poultry, and eggs; but most of body membranes 20:4n6 is derived by conversion from 18:2n6.

Omega-6 Fatty Acids

Linoleic Acid (LA)

- Recommendations

Organization	Recommendation (% energy)
Institute of Medicine and 2005 Dietary Guidelines Advisory Committee Report for Americans*	5-10%
European Commission	4-8%
Food and Agriculture Organization of the United Nations	5-8%
World Health Organization	5-8%
Japan Society for the Study of Fatty Acids and Lipids	3-4%

Source: ADA Position Paper on Fatty Acids, 2007.

*Adequate intake = 5-6% kcal; 12-17 g/d, women and men, respectively

Though a Recommended Dietary Allowance (RDA) has not been set for n-6 PUFA, several scientific bodies have made recommendations for n-6 fatty acid intake.

The Institute of Medicine's Dietary Reference Intakes (DRI) Report and the 2005 Dietary Guidelines Advisory Committee Report for Americans propose that n-6 PUFA should make up 5-10% of energy in the diet (1). The DRI Report established Adequate Intakes (AI) for LA for men (17 grams/day) and women (12 grams/day) which equals roughly 5-6% of calories in the diet. This recommendation is based on median intakes of n-6 FA in the United States, in addition to the beneficial effects seen from n-6 FA on heart disease and diabetes (11).

Global n-6 fatty acid intake recommendations differ by country and organization. Table 1 (above) from the American Dietetic Association (2007) summarizes some of the different recommendations for n-6 intake. Global organizations have lowered the recommendation for n-6 FA due to a concern that n-6 fats may increase oxidative stress and inflammation. This possible concern will be addressed in more detail to follow.

Omega-6 Fatty Acids

Linoleic Acid (LA)

- Health Effects
 - Clinical trials high in PUFA demonstrated a reduction in CVD events
 - Cholesterol
 - ↓LDL “bad” cholesterol
 - ↓ total cholesterol
 - Maintain HDL “good” cholesterol
 - ↓ CVD events

Health Effects

One of the chief health benefits associated with n-6 fatty acid consumption, is that it has been shown to lower coronary heart disease morbidity and mortality. In clinical trials, polyunsaturated fat significantly reduces total and LDL cholesterol to an even greater extent than low-fat diets, and polyunsaturated fat also significantly reduces triglycerides and they do not negatively impact HDL as do low-fat diets (12). Total cholesterol can be reduced by increasing LA in the diet (13). In fact, studies have shown that LA is the most potent fatty acid for lowering LDL and total cholesterol (14). Since LA reduces total and LDL cholesterol and may slightly raise or have no negative effect on HDL, unless consumed in excess of 12% energy, it typically has a positive effect in lowering the total-to-HDL and LDL-to-HDL ratios (14).

Omega-6 Fatty Acids

Linoleic Acid (LA)

- Possible mechanisms:
 - Upregulate hepatic LDL receptors
 - Most effective when substituted for saturated, trans, and/or carbohydrates in the diet

Mechanism

The mechanisms of action by which LA reduces total and LDL cholesterol are still uncertain. Most evidence suggests that LA upregulates hepatic LDL receptors, which results in reduced LDL cholesterol. In addition, PUFA (especially omega-3 PUFA) reduce VLDL output by the liver, leading to less LDL formation. In many situations, simply replacing saturated fat, trans fat, and/or carbohydrate in the diet with PUFAs reduces LDL cholesterol (14). One study on oil substitution altered the dietary fatty acid profile and showed that replacing saturated fats with polyunsaturated and monounsaturated fatty acids can significantly reduce total and LDL cholesterol (15). Another study by St-Onge, et al., 2007 showed that substitution of saturated, trans fat, or carbohydrate with polyunsaturated fats leads to the best overall cardiovascular disease risk profile (9). The substitution of 25g or 10% of calories from saturated fat with unsaturated fats resulted in a reduction of coronary heart disease risk by 19% in men and 16% in women (16).

Omega-6 Fatty Acids

Linoleic Acid (LA)

- Health Effects
 - Lower non-fasting triglycerides
 - May be more indicative of CVD than fasting levels

Postprandial triglyceridemia

Another benefit of dietary intake of omega-6 fatty acids includes their positive effects on postprandial triglyceridemia. Postprandial refers to the 4 to 8 hours after consumption of food where blood TG can rise. There is some evidence to suggest that postprandial triglyceride levels may be more indicative of cardiovascular disease than fasting triglyceride levels (14).

Omega-6 Fatty Acids

Linoleic Acid (LA)

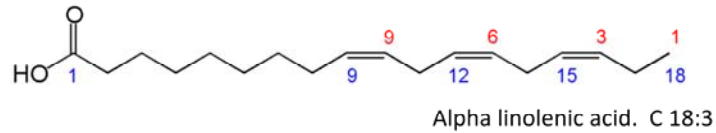
- Possible Mechanism
 - High % energy from n-6 reduces triglyceride levels

High % energy from n-6 reduces triglyceride levels

There are limited studies in this area, however, Bergeron et al. (17) showed that a diet high in percent calories from n-6 PUFA reduces the fasting plasma triglycerides of hepatic origin, when compared to a diet with percent calories high in saturated fat. One possible mechanism behind this reduction involves chylomicrons. A chylomicron is a large lipoprotein particle that transports dietary lipids from the intestines to the liver, adipose tissue, cardiac and skeletal muscle. One possible mechanism involved in reducing triglyceride levels may deal with diets higher in polyunsaturated fat resulting in greater chylomicron and chylomicron remnant removal rates from circulation than diets higher in saturated fat (18).

Plant Omega-3 Fatty Acids

Alpha Linolenic Acid (ALA)



- Structure
- Sources
 - Plant Based
 - Soybean oil
 - Flaxseed
 - Walnuts
 - Canola oil

Structure

In the figure above, the structure of alpha linolenic acid, the plant based omega-3 fatty acid, is depicted. The first double bond is on the third carbon from the omega end (tail) of the fatty acid. Alpha-linolenic acid is 18 carbons long, with three double bonds. Its lipid number is 18:3 n3.

Sources

Omega-3 fatty acids are often recommended for their health benefits.

Some sources rich in alpha linolenic acid include:

- Soybean oil
- Flaxseed
- Walnuts
- Canola oil

Plant Omega-3 Fatty Acids

Alpha Linolenic Acid (ALA)

Organization	Recommendation for ALA
Accepted Macronutrient Distribution Range (AMDR)	0.6-1.2% energy
Institute of Medicine Adequate Intake (AI) 2002	
Men (19-50 years)	1.6 g/d
Women (19-50 years)	1.1 g/d

- Health Effects (non-conclusive)
 - Precursor to long chain n-3 (EPA and DHA)
 - Minimal conversion
 - May ↓ cardiovascular disease risk
 - May ↓ risk of colon cancer

Recommendations

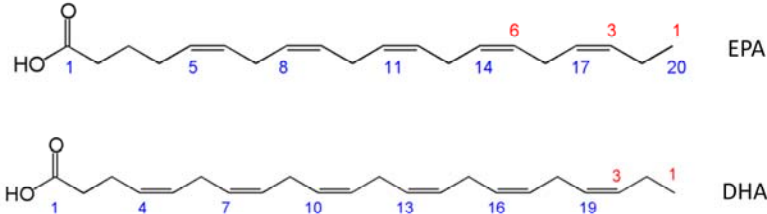
Omega-3 fatty acid recommendations to achieve nutritional adequacy are defined as the amount necessary to prevent deficiency symptoms. The Accepted Macronutrient Distribution Range (AMDR) for ALA is 0.6-1.2% of energy. The Adequate Intake for ALA is 1.6 g/d for men, 1.1 g/d for women age 19-50 years (19).

Health Effects (non-conclusive)

Omega-3 fatty acids' health benefits are mostly discussed with regard to EPA and DHA intake. ALA may be involved in cardiovascular health and reducing the risk of colorectal cancer and various intestinal inflammatory disorders (20). Studies specifically conducted with ALA are not as conclusive as those with EPA and DHA. Because ALA is a precursor of EPA and DHA, it is thought to play a role in vascular tone, heart rate, serum lipid levels, platelet function, inflammatory responses, growth rates of atherosclerotic plaques, and blood pressure (21). When ALA intake is increased, plasma and cell lipid concentrations of ALA and EPA are increased (21). The mechanism behind the reduction of risk for CVD by ALA is unclear, but is likely due to cardiac function rather than blood lipids (22).

Marine Omega-3 Fatty Acids

EPA & DHA



- Classification
- Sources
 - Marine Based
 - Fatty fish
 - Tuna (esp. albacore)
 - Salmon
 - Mackerel
 - Herring
 - Sardines
 - Trout

Sources

EPA and DHA are mainly found in fatty fish, also known as coldwater fish. They aren't considered essential because they may be synthesized from ALA. However, the conversion to EPA and DHA is not efficient, especially the formation of DHA (23). Research shows that n-3 and n-6 dietary intakes affect the conversion mechanism, with high n-6 fatty acids depressing the elongation of ALA (23). One possible conversion mechanism states that sex hormones (particularly estrogen) regulate the conversion rate in humans. This mechanism may explain why women have a higher conversion than men of ALA to EPA and DHA (24). Diets supplemented with 6.5 g/day DHA showed a 76% reduction in EPA synthesis and 88% reduction in DHA synthesis (24). Conversion rates vary depending on gender and dietary intake.

Some examples of fish rich in these fatty acids include:

- Salmon
- Tuna
- Herring
- Sardines
- Mackerel
- Trout
- Flounder

Fish oils are often talked about as having “heart healthy” effects. The main n-3 fatty acids found in fish oils are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Marine Omega-3 Fatty Acids

EPA & DHA

American Heart Association Recommendations

Purpose	Recommendation for EPA & DHA
CVD Risk Reduction (Primary Prevention)	2 preferably oily, fish meals per week (about 400-500 mg/d)
Secondary Prevention of CVD	About 1 g/d

Recommendations

Evidence supports dietary recommendations of ~500 mg/d of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for primary prevention of cardiovascular disease. Therapeutic levels would include 1 g/d for treatment of existing cardiovascular disease (25).

The American Heart Association (AHA) recommends consuming 2 servings of fatty fish per week for primary prevention of coronary heart disease.

Up to 10% of the n-3 fatty acid requirement may be consumed as EPA + DHA. The Accepted Macronutrient Distribution Range for n-3 fatty acids is 0.6-1.2% of energy (25). EPA and DHA are not essential in the diet because it can be obtained through the conversion of ALA. ALA is essential because can only be obtained in the diet.

Marine Omega-3 Fatty Acids

EPA & DHA

- Health Effects
 - ↓ mortality risk from cardiovascular disease
 - Sudden death
 - ↓ triglyceride levels (fasting and non-fasting)
 - ↑ visual and brain development, especially in premature infants
 - N-3 fatty acids may reduce postprandial levels more than n-6

Health Effects

Research suggests that omega-3 fatty acids may help in reducing the risk of sudden death from cardiac arrhythmias, specific cancers, depression, and other neurological disorders. EPA and DHA may reduce overall mortality risk for individuals with risk factors for CVD. The cardiovascular benefits from omega-3 fatty acids are proposed to be through their anti-arrhythmic and inflammatory properties (21). In cross-sectional and prospective studies, EPA and DHA supplementation was associated with slower rates of cognitive decline and development of dementia (26). EPA and DHA may be helpful in slowing the progression of Alzheimer's and dementia. EPA and DHA may reduce overall mortality risk for individuals with risk factors for CVD.

Therapeutic doses (~3g/d) of EPA+DHA may help lower triglyceride levels in individuals who have hypertriglyceridemia. While decreasing triglycerides, EPA and DHA supplementation may slightly increase LDL cholesterol by reducing liver uptake of LDL, but the increase is not clinically significant (27). In general, omega-3 fats and fatty acids do not seem to significantly impact cholesterol levels.

Studies have also shown that EPA + DHA supplementation (up to 4g/d) may reduce postprandial triglyceridemia (28). Postprandial (4-8 hrs after last meal eaten) triglyceride levels are an independent risk factor for CVD. Omega-3 fatty acids reduce postprandial TG levels more than omega-6 PUFA.

Some studies also indicate that consumption of DHA by pregnant and lactating women may enhance the infant's visual and brain development.

Additionally, both n-3 and n-6 appear to be better at reducing postprandial triglyceride levels than monounsaturated and saturated fatty acids, however, n-3 appear to be more potent (14). More conclusive research is needed in PUFAs and postprandial triglyceridemia to confirm postprandial effects of fatty acids.

Marine Omega-3 Fatty Acids

EPA & DHA

- Possible Mechanism
 - Anti-inflammatory properties
 - Decrease in platelet aggregation
 - Improved vascular activity
 - Anti-arrhythmic function
 - Inhibition of triglyceride synthesis
 - Enhanced triglyceride clearance from blood

EPA and DHA in the diet help reduce the risk for CVD and sudden death (28). EPA and DHA (doses >3g) function to decrease platelet aggregation, improve vascular reactivity, as well as decrease **inflammation** (28). The mechanism behind the reduction is unclear, however, it may be attributed to the anti-inflammatory properties of n-3 fatty acids. The anti-inflammatory mechanism may decrease oxidative modification of LDL cholesterol and resulting arterial wall damage that causes plaque formation.

Another possible mechanism is omega-3 fatty acid's anti-arrhythmic functions in which they may decrease atrial fibrillation and heart rate. This mechanism may work to inhibit the fast, voltage dependent sodium current (28).

Another suggested mechanism is involved in the hemostatic process. A blood clot that stops the flow of blood in a coronary artery (occlusive thrombosis) is the immediate cause of many myocardial infarctions. Thrombosis risk via platelet aggregation is decreased with n-3 supplementation (30).

Although the main effect of n-6 PUFA is to lower plasma cholesterol, all effects of dietary PUFA on CHD risk are not through traditional lipoprotein risk factors. Thus, as mentioned, DHA can inhibit platelet aggregation and stabilize the heart against arrhythmias (29).

The Ratio Debate

Everything in moderation**RATIO**n

The n6:n3 Ratio Debate

- What is moderation here?
 - Is risk for disease reduced more effectively by achieving a specific dietary n-6:n-3 Ratio or specific n-6 and n-3 intakes
- Ratio vs. Absolute Intake
 - No nutrient recommendation is currently expressed as a ratio of nutrients
 - All nutrient recommendations are currently expressed as absolute amounts per day

What is moderation here?

Both n-3 and n-6 FA are essential fatty acids and are required in the diet for normal growth and biological function. There has been much controversy over whether or not the risk for CVD can be better targeted and reduced more effectively by considering the n-6:n-3 ratio or absolute dietary intakes for the specified fatty acids. Unfortunately, this is a complex issue. There are many factors implicated in the debate, like the synthesis pathway of eicosanoids, as well as the experimental variables present in research such as epidemiology, genetics, environment, and the overall health effects and benefits of both fatty acids. All of these work together to confound the possible significance of the ratio.

Ratio vs. Absolute Intake

Ratio– the ratio debate is based on the total intakes of n-6 to n-3.

Absolute Intake – evaluates the actual intake, in mg or g, of n-3 and n-6 fatty acids independent of one another.

Dietary requirements have always been based on absolute amounts, not ratios. The possible recommendation of a ratio rather than a specific amount is a novel concept whose possible benefits and limitations need to be assessed.

Pro-Ratio

- Supporters believe:
 - Current diet differs from our ancestry
 - ↑ energy intake
 - ↑ saturated, trans and omega-6 fat intake
 - ↓ omega-3 fat intake
 - ↓ fruits & vegetable & fiber intake

Diet differs from our ancestry

The human diet during evolution was very different than today's average diet. Evidence comes from studies that focus on the evolutionary aspect of the diet (31). Energy intake and energy expenditure has changed throughout the past 10,000 years. The biggest change has occurred in the past 150 years in the type and amount of fat as well as vitamin C and E intake (31).

The diet of industrialized civilizations has seen an:

1. Increase in energy intake and decrease in energy expenditure
2. Increase in saturated fat, trans fat, omega-6 fat and decrease in omega-3 fat
3. Decrease in complex carbohydrates and fiber
4. Increase in cereal grains and decrease in fruits and vegetables
5. Decrease in protein, antioxidants and calcium intake (31).

Pro-Ratio

- Supporters believe:
 - The Mediterranean Crete diet is more similar to the ancestral diet
 - Current omega-6 intake is excessive

The Mediterranean Crete diet is more similar to the ancestral diet

In clinical interventions, the Mediterranean Crete diet (Seven Countries Study) showed a number of protective substances as compared with the Northern European & US diets (31). These protective substances include: selenium, glutathione, a balanced ratio of n-6:n-3, high fiber, high antioxidants including vitamin C and vitamin E. All of these are shown to be beneficial in reducing the risk of cardiovascular disease. The Crete diet more closely resembles the historical human diet in that it has a lower ratio of n-6:n-3. This epidemiological data provides a comparison between a historical human diet and current dietary intakes. Many lifestyle factors have changed besides diet, which limits the evidence which may be compared. For instance, the many protective substances in the traditional Crete diet may have different health effects than the components of the historical Paleolithic human diet.

Current omega-6 intake is excessive

The human diet during our evolution had a ratio of n-6:n-3 of $\sim 1:1$, while today's diet has a ratio of $>10:1$. Since the current dietary intake of fatty acids differs from the Paleolithic period, the excessive omega-6 intake may be problematic (31).

Pro-Ratio

- Supporters believe:
 - Omega-6 causes inflammation
 - ↑ risk for disease
 - Optimal n-6:n-3 ratio is lower than current intake

Omega-6 causes inflammation

As stated earlier, n-6 fatty acids are pro-inflammatory; and high amounts of n-6 in the diet could increase the number of inflammatory mediators. While inflammation has some beneficial effects and is necessary, in excess it has also been associated with some chronic diseases such as cardiovascular disease, diabetes, asthma, and Alzheimer's.

Optimal ratio

Supporters advocate a lower n-6:n-3 ratio, however, a specific ratio has not been determined because the optimal dose varies depending on the disease considered. Chronic diseases are multigenetic and multifactorial, so a therapeutic dose may vary depending on the severity of the disease and the individual. Examples of some recommended ratios are: 4:1 for cardiovascular disease, 2.5:1 is recommended for patients with colorectal cancer, and other recommendations exist for rheumatoid arthritis, asthma, and other diseases (31).

Inflammation

- Necessary to protect the body
- Chronic inflammation
 - Central to some diseases (e.g. rheumatoid arthritis, Chron’s disease, asthma, etc.)
 - Contributes to some diseases (e.g. atherosclerosis, diabetes, Alzheimer’s disease, etc.)
- Inflammation and n-6 fatty acids
 - The major PUFA in most tissues is AA
 - Some AA eicosanoids are pro-inflammatory while others provoke a lesser inflammatory response

Necessary to protect the body

Inflammation is a process the body uses to defend itself from pathogens, harmful debris, and dead cells. It is necessary to isolate and prevent the spread of inflammation and maintain homeostasis in the body. While inflammation has a somewhat negative connotation, it is a vital part of physiology and allows the body to make repairs and expel harmful material. The complete mechanism behind inflammation is not fully understood, as there are numerous inflammatory mediators that perform various functions to protect the body from pathogens, but eicosanoids generated from PUFA are key factors.

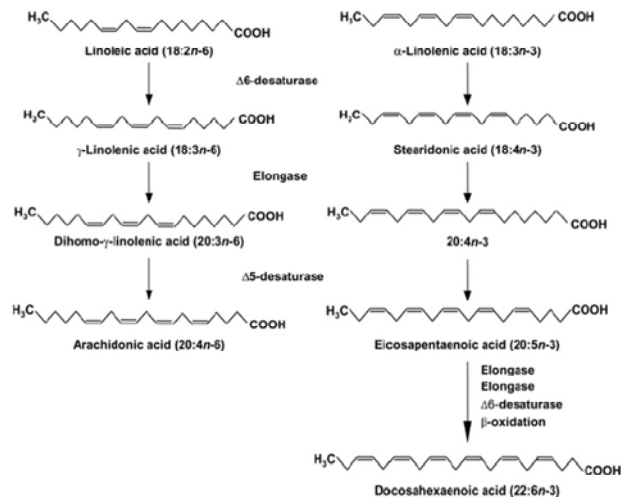
Chronic inflammation

Sustained and chronic inflammation occurs when the body is fighting a continuous problem or disease. Chronic inflammation may begin to damage healthy tissue when inflammatory mediators are elevated and consequently pose a health risk. Chronic inflammation may also promote incorrect cellular division, causing a secondary problem in the body, such as cancer. Many diseases, such as Alzheimer’s, type 2 diabetes, asthma, Crohn’s disease, cardiovascular and others have been associated with chronic inflammation.

Inflammation and n-6 Fatty Acids

One reason the recommendation for n-6 FA has been lowered by some scientific organizations is because there is a concern that n-6 FA may increase or promote oxidative stress and inflammation which are associated with CVD. Both n-3 and n-6 polyunsaturated fats lead to inflammatory mediators, however, n-6 fatty acids, particularly arachidonic acid, have been shown to generate eicosanoids that are pro-inflammatory while n-3 fatty acids act as a counter balance to the inflammation response (32). Inflammatory cells, like all body cells, contain a higher proportion of n-6 fatty acids than n-3 fatty acids (32).

Metabolic Pathway



Structure and Metabolism of n-6 and n-3 PUFAs

Reproduced with permission from: Calder, P.C. "Polyunsaturated Fatty Acids and Inflammation." *Biochemical Society Transactions*. 33(2): 423-7, 2005.

Formation of arachidonic acid

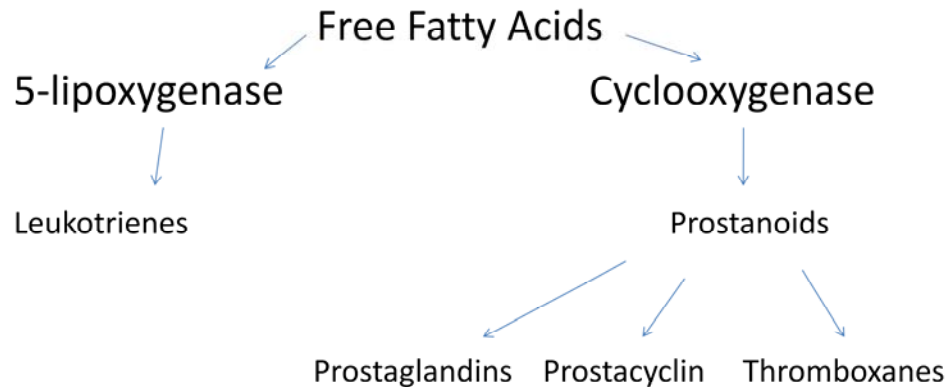
Linoleic acid (n-6) is converted by the $\Delta 6$ desaturase enzyme and goes through a few intermediate steps to form arachidonic acid. Arachidonic acid is a precursor for the formation of **prostaglandins**, leukotrienes and other inflammation regulators (33). The formation of these important biological mediators requires arachidonic acid; and therefore arachidonic acid, as its LA precursor, is a necessary part of the diet.

n-6/n-3 Competition

Linoleic (n-6) and linolenic (n-3) fatty acids compete for the $\Delta 6$ desaturase enzyme. N-3 fatty acids (such as ALA) generate EPA and DHA via $\Delta 6$ desaturase. N-6 fatty acids (such as LA) go through a few intermediate steps to synthesize arachidonic acid. One might think that by decreasing LA intake would decrease tissue content of AA, but the conversion enzymes actually become increased so that AA increases (11). One way to reduce AA tissue content is by increasing intake of EPA and DHA, as the n-3 and n-6 pathways are depressed by the opposite PUFA substrate fatty acids (11).

Additionally, an increase in n-3 fatty acids has been shown to reduce CVD incidents. On the other hand, decreasing n-6 fatty acids in the diet has not been shown to reduce risk of heart disease (11). Increasing n-3 fatty acids in the diet, regardless of n-6 fatty acid intake, will result in a lower CVD risk because they work in different ways, as indicated earlier (11).

Eicosanoid Synthesis Pathway



Eicosanoid Pathway

Both n-3 and n-6 fatty acids are a part of the eicosanoid pathway, which modulates inflammatory mediators of varying degrees. Omega-3 and omega-6 fatty acids compete as substrates in the eicosanoid pathway. While polyunsaturated fats are generally accepted as heart healthy when substituted for saturated and trans fatty acids in the diet, the n-6 pathway leads to more pro-inflammatory compounds than does the n-3 pathway, which is anti-inflammatory.

Since polyunsaturated fatty acids can be **elongated and desaturated**, they are the source of many biological functions, and the eicosanoid pathways are critical to human physiology (34). It is essential to consider the role of n-3 and n-6 fatty acids in overall physiology in addition to their function in the inflammation cascade and possible CHD risk.

All mediators of the pathway produce inflammation. It is simply that they vary in their potency and direction of inflammatory effects.

Con-Ratio

- Opponents believe:
 - Omega-6 does not “cause” inflammation
 - N-6 fatty acids produce pro- and anti-inflammatory factors under complex control systems
 - Omega-6 = inflammation is far too simplistic
 - Optimal n-6:n-3 ratio is lowered by increasing n-3
 - N-3 levels too low; need to be raised
 - Natural consequence of raising EPA/DHA intake is reduction of n-6 tissue levels
 - “Ratio” is best changed by raising EPA/DHA intake, not lowering n-6 intake

Omega-6 fatty acids do not cause inflammation in the body, but contain precursors that are used in the inflammatory response. Omega-6's have a complex set of control systems that serve as checks and balances in the inflammation cascade; both pro- and anti-inflammatory compounds are produced. Because omega-6's have various biological roles (11), the idea that omega-6 causes inflammation is far too simplistic.

Current levels of omega-3 in the diet are too low and should be raised. This is one way to achieve a more desired “ratio”. By increasing EPA/DHA levels, a reduction in omega-6 tissue levels will be seen. Increasing dietary omega-3 fatty acids has been seen to reduce CHD incidents, while reducing dietary omega-6 has not (11).

Con-Ratio

- Opponents believe:
 - Omega-6 are healthy
 - Linoleic acid lowers LDL cholesterol and improves the total: HDL ratio
 - Higher n-6 PUFA diets lower risk for CHD events in randomized trials
 - Higher blood levels of omega-6 fatty acids are associated with reduced, not increased, risk for CHD events

Lowers cholesterol and the ratio

Increasing omega-6 fatty acids in the diet lowers total cholesterol (13). In fact, studies have shown that LA is the most potent fatty acid for lowering LDL and total cholesterol (14). The total:HDL ratio is also improved with increasing omega-6 dietary intake.

Increased n-6 intakes lower risk for CHD in randomized trials

Five randomized trials have evaluated effects of replacing saturated fatty acids with polyunsaturated fatty acids on CHD events (35-40). A meta-analysis of these trials indicated that replacing saturated fatty acids with polyunsaturated fatty acids lowered CHD risk by 17% with polyunsaturated fatty acid intakes between 11% and 12% of calories.

Higher n-6 levels associated with lower risk for CHD events

In a meta-analysis of 25 case-control studies (including 1,998 cases and 6,913 controls) evaluating blood/tissue omega-6 PUFA content and CHD events, LA content was inversely associated with CHD risk, while AA was related to CHD risk (41). Even very high LA intakes have been associated with lower risk; in one study in Israel (42), where 25% of the population consumes >12% of energy as omega-6 PUFA, there was an inverse association between adipose LA and acute myocardial infarction after controlling for other omega-6 PUFA.

Con-Ratio

- Opponents believe:
 - Ancestral diets may not be informative for understanding what causes chronic diseases of aging
 - The ancient humans (even until the end of the 18th century) rarely lived past 40
 - Current life spans are the longest in recorded history
 - Excess calories / deficient exercise contribute to chronic disease today

Opponents believe that the ancestral diets may not be informative for understanding what causes chronic diseases of aging today. Historically, humans rarely lived past age 40, even until the end of the 18th century.

Current life spans are the longest in recorded history.

Excess calories in combination with a deficiency in exercise contribute to chronic disease today. Current nutritional behavior leads to excess caloric and fat intake, which requires more n-6 to help regulate higher cholesterol levels, which n-3 fatty acids do not do effectively.

Con-Ratio

- Opponents believe:
 - Ratio does not account for absolute intake
 - Total fat recommendations
 - Omega-6 recommendations
 - Omega-3 recommendations

Ratio does not account for absolute intake

Opponents of the ratio theory argue that all other dietary requirements are based on absolute requirements, not ratios. Dr. William Harris at North Dakota State University, a leading researcher in n-3 fatty acids, points out that the ratio theory does not take into account the absolute dietary requirement for both n-6 and n-3 fatty acids (11). If the absolute intake of PUFA is not at an acceptable level, the ratio concept is futile. Also, research shows that the conversion of ALA to longer fatty acid derivatives is not determined by the n-6:n-3 ratio, but by amounts of LA and ALA in the diet (23).

Fats are needed in the diet in certain amounts for proper biological functions, and these functions vary somewhat based on populations and individuals. The 2005 Dietary Guidelines for Americans has recommended that total fat intake consist of 20-35% of energy. According to 2005 Dietary Guideline recommendations, 5-10% of energy should come from n-6 fatty acids and 0.6-1.2% energy from n-3 fatty acids (1). Research recommends increasing n-3 in the diet as EPA and DHA while limiting saturated fatty acids and maintaining n-6 fat intake (22).

Opponents argue that outside of these recommended intakes, the total amount of fatty acid may be harmful to health and affect CVD risk. When the amount of fat in the diet is less than the recommendation (20% calories), high carbohydrates may increase TG, and when fat intake exceeds recommendations (35% calories), saturated fat intake will likely raise LDL and total cholesterol levels. And when plasma cholesterol becomes elevated, lower saturated fat and increased n-6 PUFA intakes are the preferred initial approach, so the mass of n-6 PUFA is often dictated by circumstances. Under such conditions, advising consumers on consuming a healthy ratio rather than a healthy amount would prove challenging.

Methods of Changing a Ratio

n-6	n-3
↓	↑
↑	↑↑
No change	↑
↓↓	↓
↓	No change

*Adapted from Harris, W. The omega-6/omega-3 ratio and cardiovascular disease risk: uses and abuses. *Current Atherosclerosis Reports* 2006; 8:453-459.

There are many approaches to achieve a specified ratio by altering variables as seen in the table above (11).

Some ways to change the ratio are:

1. Decrease n-6 and increase n-3.
2. Slightly increase n-6 and greatly increase n-3.
3. Do not change n-6 and increase n-3.
4. Greatly decrease n-6 and slightly decrease n-3 .
5. Decrease n-6 and leave n-3 unchanged.

With each of these methods of changing the ratio, a different total value may be achieved, which could have a different effect on overall health. This is not taken into account with a simple ratio recommendation.

It is known and accepted that n-6 and n-3 are required in certain amounts in the diet for important biological functions. It may be argued that greatly increasing or decreasing one or both to achieve an “optimal” ratio may have adverse health effects when consumed without regard to recommended fat intake.

Con-Ratio

- Opponents believe the ratio:
 - Fails to distinguish between longer and shorter chain fatty acids
 - “high” n-6 levels in tissues = “low” n-3 levels
 - The latter is the problem, not the former

Fails to distinguish between LCFA & SCFA

The ratio fails to distinguish between long & short chain fatty acids within each class. Within omega-3's, there is alpha linolenic acid which is an 18 carbon chain (18:3) & eicosapentaenoic acid with a 20 carbon chain (20:3) and docosahexaenoic acid that also has a 20 carbon chain (20:3). N-6's include linoleic acid which is 18 carbons long (18:2), and arachidonic acid (20:2). The 18 carbon species have clearly different physiologic properties than 20 carbon species on TG lowering effects.

Conditions necessary for a ratio

A ratio consists of a higher level of one factor and an independently lower level of another (an inverse relationship) which has a greater magnitude when variable values are further apart. A good example of a ratio used in health is the LDL:HDL ratio. High LDL levels alone are predictive of CVD risk. Independently, low HDL levels are also predictive of increased CVD risk. Together in a ratio, a higher ratio of LDL:HDL can determine a higher risk of CVD.

In the n-6:n-3 ratio, low n-6 is associated with an increased risk of CVD and similarly a low n-3 intake is also associated with a higher CVD risk. Based on our “low-low” relationship between n-6 and n-3, a higher ratio would not predict a higher incidence of CVD risk. Opponents argue that the relationship between variables in the ratio has its limitations.

Lowering the N-6:N-3 Ratio to the Same Value with Different Strategies Results in Different Risk
(Baseline diet has typical US intakes)

	LA n-6	AA n-6	ALA n-3	EPA+DHA n-3	n-6:n-3
Baseline Diet	17.8 g	0.1 8g	1.7 g	0.15 g	9.7
Lower LA	13.8 g	0.1 8g	1.7 g	0.15 g	7.6
Raise ALA	17.8 g	0.1 8g	2.2 g	0.15 g	7.7
Raise EPA+DHA	17 .8g	0.1 8g	1.7 g	0.65 g	7.7

*Table adapted from Gehbauer et al. AJCN 2006; 83 (suppl):1526S-35S. Values are taken from men, 40-59 years old.

Although all three changes achieve the same ratio, only raising EPA+DHA has been shown or would be expected to reduce CHD risk.

Con-Ratio

- Opponents believe:
 - Omega-6 are healthy
 - Higher serum n-6 and n-3 fatty acid levels = lower levels of inflammatory biomarkers
 - Lowering linoleic acid intakes does not lower arachidonic levels in tissues (above EFA deficiency levels)

Serum FA is not related to inflammatory biomarkers

If a higher ratio is, in fact, detrimental to health, it should be expected that high serum levels would be associated with a high level of inflammatory markers. Raatz et al. found that when feeding LA at 6% or 12% of energy for 4 weeks there was no significant difference in plasma phospholipid n-6 levels. AA proportions were actually higher on the lower LA diet (11). This suggests that n-6 tissue levels are not altered over a wide range of LA intakes. The AHA and 2005 US dietary guidelines are still based on the reduction in risk for heart disease with higher LA intakes. With the assumption that lowering AA in tissues will be beneficial to health, lower AA levels cannot be realized through reduction of LA. An increase in EPA and DHA, regardless of LA intake, is successful in reducing AA levels.

Furthermore, reducing n-6 FA intakes is not associated with a decreased risk of CVD, but increasing n-3 does reduce risk of CVD. Perhaps increasing n-3 in the diet is of greater importance than a specified ratio. While n-6 is related to inflammatory response and inflammation is linked to increased risk of CVD, clinical and epidemiological data have conclusively shown that n-6 intake is related to a decreased risk of CVD (9). The current research does not show that omega-6 fatty acids promote cardiovascular disease risk. In fact, the opposite is true.

Health effects of diets in different populations are not comparable

One consideration in some epidemiological data is that the comparison of unrelated populations such as Eskimos vs. Americans differs in many aspects besides simply diet.

The Greenland Eskimo studies in the 1970s (Dyerberg and Jorgenson) found that the intake of n-3 FA was roughly 7g/day while an average western diet included < 0.6 g/day (31). The difference between the Eskimo diet and western diet in amount of n-3 fatty acids has generated much scientific interest in n-3s ability to reduce CVD risk (43). One limitation is that the diets are very different, so it is difficult to make a comparison.

While dietary intake of n-3 is now accepted as a major factor in heart health, epidemiological differences such as genetics, environmental factors, and lifestyle, all play a fundamental role in the health status of an individual as well as population trends. Epidemiology studies cannot conclude that dietary differences, such as n-3 intake, are a lone factor in cardiovascular disease risk.

Highlights of n-6 and n-3 Biology:

- Current dietary intakes are different from the Paleolithic time. One component that has changed drastically is the increase of n-6 and the decrease of n-3.
- EPA and DHA have more potent biological activity than ALA.
- LA and ALA compete for $\Delta 6$ desaturase needed to synthesize various eicosanoids.
- Chronic diseases are associated with an increase in some eicosanoids.
- An increase in n-3 intake is associated with lower incidence of CVD. Lower n-6 intake has not been shown to decrease CVD, while higher intakes have.

Conclusions

- Focusing on the n-6:n-3 ratio distracts from the real issue of raising the intake (tissue levels) of EPA and DHA
- Increase the intake of long-chain n-3 fatty acids
- There is no compelling need to supplement with ALA, particularly if EPA and DHA can be eaten
- A ratio recommendation would be difficult to put into practice

The question of the n-6:n-3 ratio has been under debate for many years and a clear consensus has yet to be reached. Ultimately, the issue is whether or not the ratio is valid and scientifically useful for providing guidelines to influence the health of the general population or those of a specific disease state (e.g. cardiovascular disease). Focusing on the ratio distracts from the issue of raising EPA and DHA intake.

In discussing one aspect of the ratio, there is evidence to conclude that increasing n-3 intake will decrease CVD risk (21). However, evidence is very weak for supporting the notion that decreasing n-6 intake will decrease CVD risk. Current research links diets higher in n-6 with decreased CVD risk (7). Perhaps it is only necessary to increase n-3 in the diet, while remaining within recommended intake totals. When EPA and DHA are consumed in adequate amounts, there is less need to convert ALA to EPA and DHA (24).

In application to dietetics, there are a few limitations in the use of the ratio. For instance, it may be more difficult to counsel patients in achieving a desired ratio of n-6:n-3 fatty acid intake rather than an absolute amount (44). Additionally, one need consider how and in what time frame to measure individual ratios? Would they simply be measured as dietary intake, or as serum lipid levels?

There is a plethora of scientific evidence available to develop public policy regarding dietary recommendations for n-6 and n-3 fatty acids. A consensus among scientists is needed, as well as the willingness of public officials to establish guidelines and make changes. The education of professionals and the public is also vital to enact changes in consumer habits and health.

This self-study program was intended to provide an objective view of the n-6:n-3 ratio debate. Further health professional education and formation of opinions are of great importance in affecting the health and well-being of the public.

Glossary

- Cis Conformation (Cis Fat) – in a double bond, the hydrogens are on the same side of the carbon chain and form a kink in the chain

- Cardiovascular Disease – a cluster of diseases related to the heart and blood vessels, often refers to atherosclerosis development

- Eicosanoids – prostaglandin and leukotriene-related signaling molecules built from n-6 and n-3 fatty acids that play a role in inflammation and many other biological functions

- Fatty Acid (FA) – is comprised a carboxylic acid group which is known as the “head” with a long unbranched hydrocarbon chain as the “tail”.

- Inflammation – the complex biological response that functions as the body’s defense mechanism to harmful stimuli, such as pathogens or damaged cells

- Monounsaturated Fat – an oil containing primarily fatty acids with one cis-double bond in natural oils

- Prostaglandin – any member of n-6 or n-3 fatty acid-derived compounds that have important biological effects; they have 20 carbon atoms

- Polyunsaturated Fat – an oil containing mostly fatty acids with 2 or more double bonds in an n-6 or n-3 configuration

- Saturated Fat – a fat that contains most fatty acids with no double bonds, ie. bonds are fully saturated with hydrogens

- Trans conformation (Trans Fat) – in a double bond in a fatty acid where the hydrogen atoms are attached on opposite sides of the carbon chain and do not form a bend in the hydrocarbon chain

- Triglyceride – a glycerol backbone with three fatty acids attached. This is the form in which we consume, transport, and store fat in the body

- Unsaturated Fat – contain one or more double bonds in most of the fatty acid chains in its triglyceride molecules

References

1. US Department of Health and Human Services and US Department of Agriculture. Dietary Guidelines for Americans 2005. Washington, DC: US Government Printing Office, 2005.
2. Rizzo M., Berneis K. Low-density lipoprotein size and cardiovascular risk assessment. *Q J Med* 2006; 99:1-14.
3. Shils M., Shike M., et al. Modern Nutrition in Health and Disease. 10th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2006.
4. Steinberg D., Parthasarathy S., Carew T., Khoo J., Witztum J. Beyond Cholesterol: Modifications of Low-Density Lipoprotein that Increase Its Atherogenicity. *N Engl J Med* 1989; 320:915-924.
5. Garner B, Waldeck A., Witting P., Rye K., Stocker. Oxidation of High Density Lipoproteins. II. Evidence for Direct Reduction of Lipid Hydroperoxides by Methionine Residues of Apolipoproteins AI and AII. *J Biol Chem* 1998; 273: 6088-6095.
6. Yu-Poth S., et al. Effects of the National Cholesterol Education Program's Step I and Step II Dietary Intervention Programs on Cardiovascular Disease Risk Factors: A Meta Analysis. *Am J Clin Nutr.* 1999; 69:632-46.
7. Lichtenstein A., et al. Diet and Lifestyle Recommendations Revision 2006: A Scientific Statement From the American Heart Association Nutrition Committee. *Circulation.* 2006; 114:82-96.
8. Mensink R., Zock P., Kester A., Katan M. Effects of Dietary Fatty Acids and Carbohydrates on the Ratio of Serum Total to HDL Cholesterol and on Serum Lipids and Apolipoproteins: a Meta-Analysis of 60 Controlled Trials. *Am J Clin Nutr.* 2003; 77:1146-55.
9. St-Onge M. Snack Chips Fried in Corn Oil Alleviate Cardiovascular Disease Risk Factors When Substituted for Low-Fat or High-Fat Snacks. *Am J Clin Nutr* 2007; 85:1503-10.
10. Hu F., Willett W. Optimal Diets for Prevention of Coronary Heart Disease. *JAMA* 2002; 288 (20) 2569-78.
11. Harris W. The Omega-6/Omega-3 Ratio and Cardiovascular Disease Risk: Uses and Abuses. *Curr Atheroscler Rep.* 2006 Nov;8(6):453-9.
12. Gardner, et al.: Monounsaturated versus polyunsaturated dietary fat and serum lipids: a meta-analysis. *Arterioscler Thromb Vasc Biol.* 1995;15(11):1917-27.
13. Kris-Etherton et al. American Dietetic Association. Position of the American Dietetic Association and Dietitians of Canada: Dietary Fatty Acids. *JADA* 2007, 107:1599-1611.
14. Kris-Etherton P., Hecker K., Binkoski A. Polyunsaturated Fatty Acids and Cardiovascular Health. *Nutr Rev.* 2004 Nov;62(11):414-26.
15. Binkoski, AE. et al.: Balance of unsaturated fatty acids is important to a cholesterol-lowering diet: comparison of mid-oleic sunflower oil and olive oil on CVD risk factors. *J Am Diet Assoc* 2005, 105:1080-6.
16. Sacks et al. Randomized clinical trials on the effects of dietary fat and carbohydrates on plasma lipoproteins and cardiovascular disease. *Am J Med* 2002, 113:13-24.
17. Bergeron N., Havel R. Influence of Diets Rich in Saturated and Omega-6 Polyunsaturated Fatty Acids on the Postprandial Responses of Apolipoproteins B-48, B-100, E, and Lipids in Triglyceride-Rich Lipoproteins. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 1995; 15:2111-2121.
18. Demacker, PN, et al.: Increased removal remnants of triglyceride-rich lipoproteins on a diet rich in polyunsaturated fatty acids. *Eur J Clin Invest.* 1991, 21:197-203.
19. IOM (Institute of Medicine). Dietary Reference Intakes: Energy, Carbohydrates, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. National Academy Press, Washington, DC, 2002.
20. Chapkin R., Seo J., McMurray D., Lupton J. Mechanisms by which docosahexaenoic acid and related fatty acids reduce colon cancer risk and inflammatory disorders of the intestine. *Chemistry and Physics of Lipids* 2008; 153:14-23.
21. Stark A., Crawford M., Reifen R. Update on alpha – linolenic acid. *Nutr Rev* 2008; 66(6):326-332.
22. Wijendran V., Hayes K.C., Dietary n-6 and n-3 fatty acid balance and cardiovascular disease. *Annu Rev Nutr* 2004; 24:597-615.

References (con't)

23. Goyers P., Spilker M., Zock P., Katan M., Mensink R. Conversion of alpha-linolenic acid in humans is influenced by the absolute amounts of alpha linolenic acid and linoleic acid in the diet and not by the ratio. *Am J Clin Nutr* 2006; 84:44-53.
24. Burdge G., Calder P. Conversion of alpha-linolenic acid to longer-chain polyunsaturated fatty acids in human adults. *Reprod. Nutr. Dev.* 2005; 45:581-97.
25. Gehbauer S., Pstoa T., Harris W., Kris-Etherton P. n-3 Fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. *Am J Clin Nutr* 2006; 83(suppl): 1526S-35S.
26. Freund-Levi Y. et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate alzheimers disease: OmegAD study. *Arch Neurol.* 2006; 63: 1402-1408.
27. Akabas S., Deckelbaum R. Summary of a workshop on n-3 fatty acids: current status of recommendations and future directions. *Am J Clin Nutr* 2006; 83(suppl): 1536S-8S.
28. Breslow J. N-3 fatty acids and cardiovascular disease. *Am J Clin Nutr* 2006; 83(suppl): 1477S-1482S.
29. Kris-Etherton P., Harris W., Appel L. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation.* 2002; 106:2747-2757.
30. Lefevre M., Kris-Etherton P., Xhao G., Tracy R. Dietary fatty acids, hemostasis, and cardiovascular disease risk. *Journal of the American Dietetic Association* 2004; 104: 410-419.
31. Simopoulos, A. Omega-6/Omega-3 Essential Fatty Acid Ratio and Chronic Diseases. *Food Reviews International.* 2004; 20:77-90.
32. Calder P. n-3 Polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr.* 2006; 83(suppl): 1505S-19S.
33. Calder P. Polyunsaturated fatty acids and inflammation. *Biochemical Society Transactions.* 2005; 33(2):423-427.
34. Harris, W. Fish Oils and Plasma Lipid and Lipoprotein Metabolism in Humans: A Critical Review. *Journal of Lipid Research.* 1989; 30:785-807.
35. Dayton S., Pearce M., Goldman H. et al. Controlled trial of a diet high in unsaturated fat for prevention of atherosclerotic complications. *Lancet* 1968;2:1060-1062.
36. Medical Research Council. Controlled trial of soya-bean oil in myocardial infarction. *Lancet.* 1968;2:693-699.
37. Leren P. The Oslo diet-heart study. Eleven-year report. *Circulation.* 1970; 42:935-942.
38. Turpeinen O., Karvonen M., Pekkarinen M., et al. Dietary prevention of coronary heart disease in women: the Finnish mental hospital study. *Int J Epidemiol.* 1983;12:17-25.
39. Frantz I. Jr., Dawson E., Ashman P., et al. Test of effect of lippid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey. *Arteriosclerosis.* 1989; 9: 129-135.
40. Woodhill J., Palmer A., Leelarthaein B., et al. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. *Adv Exp Med Biol.* 1978; 109:317-330.
41. Harris W., Poston W., Haddock C. Tissue n-3 and n-6 fatty acids and risk for cornoary heart disease events. *Atherosclerosis.* 2007; 193:1-10.
42. Karak J., Kaufmann N., Binka F., et al. Adipose tissue n-6 fatty acids and acute myocardial infarction in a population consuming a diet high in polyunsaturated fatty acids. *Am J Clin Nutr.* 2003; 77: 796-802.
43. Dyerberg J., Jorgensen K. Marine Oils and Thrombogenesis. *Prog. Lipid Res.* 1982; 21: 255-69.
44. Sanderson, P. Et al. UK Food Standards Agency Alpha-linolenic Acid Workshop Report. *British Journal of Nutrition.* 2002; 88: 573-579.