Working Material

Tharos Ltd

Omega-3 fatty acid

Types of fats in food

- Unsaturated fat
  - Monounsaturated fat
  - Polyunsaturated fat
  - Trans fat
  - Omega fatty acids:
    - **ω−3**
    - ω−6
    - ω−9
- Saturated fat
  - Interesterified fat

***n*−3 fatty acids** (popularly referred to as **ω−3 fatty acids** or **omega-3 fatty acids**) are a family of unsaturated fatty acids that have in common a carbon–carbon double bond in the *n*−3 position; that is, the third bond from the methyl end of the fatty acid.

Important nutritionally essential *n*−3 fatty acids are: α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). The human body cannot synthesize *n*−3 fatty acids *de novo*, but it can form 20- and 22-carbon unsaturated *n*−3 fatty acids from the eighteen-carbon *n*−3 fatty acid, α-linolenic acid. These conversions occur competitively with *n*−6 fatty acids, which are essential closely related chemical analogues that are derived from linoleic acid. Both the *n*−3 α-linolenic acid and *n*−6 linoleic acid are essential nutrients which must be obtained from food. Synthesis of the longer *n*−3 fatty acids from linolenic acid within the body is competitively slowed by the *n*−6 analogues. Thus accumulation of long-chain *n*−3 fatty acids in tissues is more effective when they are obtained directly from food or when competing amounts of *n*−6 analogs do not greatly exceed the amounts of *n*−3.

Chemistry

Chemical structure of alpha-linolenic acid (ALA), an essential *n*−3 fatty acid, (18:3Δ9c,12c,15c, which means a chain of 18 carbons with 3 double bonds on carbons numbered 9, 12 and 15). Although chemists count from the carbonyl carbon (blue numbering), physiologists count from the *n* (ω) carbon (red numbering). Note that from the *n* end (diagram right), the first double bond appears as the third carbon-carbon bond (line segment), hence the name "*n*−3". This is explained by the fact that the *n* end is almost never changed during physiologic transformations in the human body, as it is more stable energetically, and other carbohydrates compounds can be synthetized from the other carbonyl end, for example in glycrids, or from double bonds in the middle of the chain.

The term ***n*−3** (also called **ω−3** or **omega-3**) signifies that the first double bond exists as the **third** carbon-carbon bond from the terminal methyl end (*n*) of the carbon chain.

n−3 fatty acids which are important in human nutrition are: α-linolenic acid (18:3, *n*−3; ALA), eicosapentaenoic acid (20:5, *n*−3; EPA), and docosahexaenoic acid (22:6, *n*−3; DHA). These three polyunsaturates have either 3, 5 or 6 double bonds in a carbon chain of 18, 20 or 22 carbon atoms, respectively. All double bonds are in the *cis*-configuration, i.e. the two hydrogen atoms are on the same side of the double bond.

Most naturally-produced fatty acids (created or transformed in animalia or plant cells with an even number of carbon in chains) are in *cis*-configuration where they are more easily transformable. The *trans*-configuration results in much more stable chains that are very difficult to further break or transform, forming longer chains that aggregate in tissues and lacking the necessary hydrophilic properties. This *trans*-configuration can be the result of the transformation in alkaline solutions, or of the action of some bacterias that are shortening the carbonic chains. Natural transforms in vegetal or animal cells more rarely affect the last *n*−3 group itself. However, *n*−3 compounds are still more fragile than *n*−6 because the last double bond is geometrically and electrically more exposed, notably in the natural *cis* configuration.

List of *n*−3 fatty acids

This table lists several different names for the most common *n*−3 fatty acids found in nature.

Common name	**Lipid name**	**Chemical name**
	16:3 (*n*−3)	*all-cis*-7,10,13-hexadecatrienoic acid
α-Linolenic acid (ALA)	18:3 (*n*−3)	*all-cis*-9,12,15-octadecatrienoic acid
Stearidonic acid (STD)	18:4 (*n*−3)	*all-cis*-6,9,12,15-octadecatetraenoic acid
Eicosatrienoic acid (ETE)	20:3 (*n*−3)	*all-cis*-11,14,17-eicosatrienoic acid
Eicosatetraenoic acid (ETA)	20:4 (*n*−3)	*all-cis*-8,11,14,17-eicosatetraenoic acid
Eicosapentaenoic acid (EPA)	20:5 (*n*−3)	*all-cis*-5,8,11,14,17-eicosapentaenoic acid
Docosapentaenoic acid (DPA), Clupanodonic acid	22:5 (*n*−3)	*all-cis*-7,10,13,16,19-docosapentaenoic acid
Docosahexaenoic acid (DHA)	22:6 (*n*−3)	*all-cis*-4,7,10,13,16,19-docosahexaenoic acid
Tetracosapentaenoic acid	24:5 (*n*−3)	*all-cis*-9,12,15,18,21-docosahexaenoic acid
Tetracosahexaenoic acid (Nisinic acid)	24:6 (*n*−3)	*all-cis*-6,9,12,15,18,21-tetracosenoic acid

Biological significances

The biological effects of the n−3 *are largely mediated by their interactions with the* n−6 *fatty acids; see Essential fatty acid interactions for detail.*

A 1992 article by biochemist William E.M. Lands provides an overview of the research into *n*−3 fatty acids, and is the basis of this section.

The 'essential' fatty acids were given their name when researchers found that they were essential to normal growth in young children and animals. (Note that the modern definition of 'essential' is more strict.) A small amount of *n*−3 in the diet (~1% of total calories) enabled normal growth, and increasing the amount had little to no additional benefit.

Likewise, researchers found that *n*−6 fatty acids (such as γ-linolenic acid and arachidonic acid) play a similar role in normal growth. However, they also found that *n*−6 was "better" at supporting dermal integrity, renal function, and parturition. These preliminary findings led researchers to concentrate their studies on *n*−6, and it was only in recent decades that *n*−3 has become of interest.

In 1963 it was discovered that the *n*−6 arachidonic acid was converted by the body into pro-inflammatory agents called prostaglandins. By 1979 more of what are now known as eicosanoids were discovered: thromboxanes, prostacyclins and the leukotrienes. The eicosanoids, which have important biological functions, typically have a short active lifetime in the body, starting with synthesis from fatty acids and ending with metabolism by enzymes. However, if the rate of synthesis exceeds the rate of metabolism, the excess eicosanoids may have deleterious effects. Researchers found that *n*−3 is also converted into eicosanoids, but at a much slower rate. Eicosanoids made from *n*−3 fats often have opposing functions to those made from *n*−6 fats (ie, anti-inflammatory rather than inflammatory). If both *n*−3 and *n*−6 are present, they will "compete" to be transformed, so the ratio of *n*−3:*n*−6 directly affects the type of eicosanoids that are produced.

This competition was recognized as important when it was found that thromboxane is a factor in the clumping of platelets, which leads to thrombosis. The leukotrienes were similarly found to be important in immune/inflammatory-system response, and therefore relevant to arthritis, lupus, and asthma. These discoveries led to greater interest in finding ways to control the synthesis of *n*−6 eicosanoids. The simplest way would be by consuming more *n*−3 and fewer *n*−6 fatty acids.

Health benefits

On September 8, 2004, the U.S. Food and Drug Administration gave "qualified health claim" status to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) *n*−3 fatty acids, stating that "supportive but not conclusive research shows that consumption of EPA and DHA [*n*−3] fatty acids may reduce the risk of coronary heart disease." This updated and modified their health risk advice letter of 2001 (see below).

People with certain circulatory problems, such as varicose veins, benefit from fish oil. Fish oil stimulates blood circulation, increases the breakdown of fibrin, a compound involved in clot and scar formation, and additionally has been shown to reduce blood pressure. There is strong scientific evidence that *n*−3 fatty acids significantly reduce blood triglyceride levels and regular intake reduces the risk of secondary and primary heart attack.

Some benefits have been reported in conditions such as rheumatoid arthritis and cardiac arrhythmias.

There is a promising preliminary evidence that *n*-3 fatty acids supplementation might be helpful in cases of depression and anxiety. Studies report highly significant improvement from *n*-3 fatty acids supplementation alone and in conjunction with medication.

Some research suggests that fish oil intake may reduce the risk of ischemic and thrombotic stroke. However, very large amounts may actually increase the risk of hemorrhagic stroke (see below). Lower amounts are not related to this risk, and many studies used substantially higher doses without major side effects (for example: 4.4 grams EPA/2.2 grams DHA in 2003 study). No clear conclusion can be drawn at this time, however.

A 2006 report in the Journal of the American Medical Association concluded that their review of literature covering cohorts from many countries with a wide variety of demographic characteristics demonstrating a link between *n*−3 fatty acids and cancer prevention gave mixed results. This is similar to the findings of a review by the British Medical Journal of studies up to February 2002 that failed to find clear effects of long and shorter chain *n*−3 fats on total mortality, combined cardiovascular events and cancer.

In 1999, the GISSI-Prevenzione Investigators reported in the Lancet, the results of major clinical study in 11,324 patients with a recent myocardial infarction. Treatment 1 gram per day of $n-3$ fatty acids reduced the occurrence of death, cardiovascular death and sudden cardiac death by 20%, 30% and 45% respectively. These beneficial effects were seen already from three months onwards.

In April 2006, a team led by Lee Hooper at the University of East Anglia in Norwich, UK, published a review of almost 100 separate studies into $n-3$ fatty acids, found in abundance in oily fish. It concluded that they do not have a significant protective effect against cardiovascular disease. This meta-analysis was controversial and stands in stark contrast with two different reviews also performed in 2006 by the American Journal of Clinical Nutrition and a second JAMA review that both indicated decreases in total mortality and cardiovascular incidents (i.e. myocardial infarctions) associated with the regular consumption of fish and fish oil supplements. In addition $n-3$ has shown to aid in other mental disorders such as aggression and ADHD (Attention-deficit hyperactivity disorder).

Several studies published in 2007 have been more positive. In the March 2007 edition of the journal *Atherosclerosis*, 81 Japanese men with unhealthy blood sugar levels were randomly assigned to receive 1800 mg daily of eicosapentaenoic acid (EPA - an *n*−3 essential fatty acid from fish oil) with the other half being a control group. The thickness of the carotid arteries and certain measures of blood flow were measured before and after supplementation. This went on for approximately two years. A total of 60 patients (30 in the EPA group and 30 in the control group) completed the study. Those given the EPA had a statistically significant decrease in the thickness of the carotid arteries along with improvement in blood flow. The authors indicated that this was the first demonstration that administration of purified EPA improves the thickness of carotid arteries along with improving blood flow in patients with unhealthy blood sugar levels.

In another study published in the American Journal of Health System Pharmacy March 2007, patients with high triglycerides and poor coronary artery health were given 4 grams a day of a combination of EPA and DHA along with some monounsaturated fatty acids. Those patients with very unhealthy triglyceride levels (above 500 mg/dl) reduced their triglycerides on average 45% and their VLDL cholesterol by more than 50%. VLDL is a bad type of cholesterol and elevated triglycerides can also be deleterious for cardiovascular health.

There was another study published on the benefits of EPA in *The Lancet* in March 2007. This study involved over 18,000 patients with unhealthy cholesterol levels. The patients were randomly assigned to receive either 1,800 mg a day of EPA with a statin drug or a statin drug alone. The trial went on for a total of five years. It was found at the end of the study those patients in the EPA group had superior cardiovascular function. Non-fatal coronary events were also significantly reduced in the EPA group. The authors concluded that EPA is a promising treatment for prevention of major coronary events, especially non-fatal coronary events.

Another study regarding fish oil was published in the *Journal of Nutrition* in April 2007. Sixty four healthy Danish infants from nine to twelve months of age received either cow's milk or infant formula alone or with fish oil. It was found that those infants supplemented with fish oil had improvement in immune function maturation with no apparent reduction in immune activation.

There was yet another study on $n-3$ fatty acids published in the April 2007 *Journal of Neuroscience*. A group of mice were genetically modified to develop accumulation of amyloid and tau proteins in the brain similar to that seen in people with poor memory. The mice were divided into four groups with one group receiving a typical American diet (with high ratio of $n-6$ to $n-3$ fatty acids being 10 to 1).

The other three groups were given food with a balanced 1 to 1 *n*−6 to *n*−3 ratio and two additional groups supplemented with DHA plus long chain *n*−6 fatty acids. After three months of feeding, all the DHA supplemented groups were noted to have a lower accumulation of beta amyloid and tau protein. Some research suggests that these abnormal proteins may contribute to the development of memory loss in later years.

There is also a study published regarding *n*−3 supplementation in children with learning and behavioral problems. This study was published in the April 2007 edition of the *Journal of the Developmental and Behavioral Pediatrics* (5), where 132 children, between the ages of seven to twelve years old, with poor learning, participated in a randomized, placebo-controlled, double-blinded interventional trial. A total of 104 children completed the trial. For the first fifteen weeks of this study, the children were given polyunsaturated fatty acids (*n*−3 and *n*−6, 3000 mg a day), polyunsaturated fatty acids plus multi-vitamins and minerals or placebo. After fifteen weeks, all groups crossed over to the polyunsaturated fatty acids (PUFA) plus vitamins and mineral supplement.

Parents were asked to rate their children's condition after fifteen and thirty weeks. After thirty weeks, parental ratings of behavior improved significantly in nine out of fourteen scales. The lead author of the study, Dr. Sinn, indicated the present study is the largest PUFA trial to date with children falling in the poor learning and focus range. The results support those of other studies that have found improvement in poor developmental health with essential fatty acid supplementation.

Research in 2005 and 2006 has suggested that the in-vitro anti-inflammatory activity of *n*−3 acids translates into clinical benefits. Cohorts of neck pain patients and of rheumatoid arthritis sufferers have demonstrated benefits comparable to those receiving standard NSAIDs. Those who follow a Mediterranean-style diet tend to have less heart disease, higher HDL ("good") cholesterol levels and higher proportions of *n*−3 in tissue highly unsaturated fatty acids. Similar to those who follow a Mediterranean diet, Arctic-dwelling Inuit - who consume high amounts of *n*−3 fatty acids from fatty fish - also tend to have higher proportions of *n*−3, increased HDL cholesterol and decreased triglycerides (fatty material that circulates in the blood) and less heart disease. Eating walnuts (the ratio of *n*−3 to *n*−6 is circa 1:4 respectively) was reported to lower total cholesterol by 4% relative to controls when people also ate 27% less cholesterol.

A study examining whether omega-3 exerts neuroprotective action in Parkinson's disease found that it did, using an experimental model, exhibit a protective effect (much like it did for Alzheimer's disease as well). The scientists exposed mice to either a control or a high omega-3 diet from two to twelve months of age and then treated them with a neurotoxin commonly used as an experimental model for Parkinson's. The scientists found that high doses of omega-3 given to the experimental group completely prevented the neurotoxin-induced decrease of dopamine that ordinarily occurs. Since Parkinson's is a disease caused by disruption of the dopamine system, this protective effect exhibited could show promise for future research in the prevention of Parkinson's disease.

A study carried out involving 465 women showed serum levels of eicosapentaenoic acid is inversely related to the levels of anti-oxidized-LDL antibodies. Oxidative modification of LDL is thought to play an important role in the development of atherosclerosis.

In 2008 a German study suggested that Omega-3 fatty acids have a positive effect on atopic dermatitis

Health risks

In a letter published October 31, 2000, the United States Food and Drug Administration Center for Food Safety and Applied Nutrition, Office of Nutritional Products, Labeling, and Dietary Supplements noted that known or suspected risks of EPA and DHA *n*−3 fatty acids may include the possibility of:

- Increased bleeding if overused (normally over 3 grams per day) by a patient who is also taking aspirin or warfarin. However, this is disputed.
- Hemorrhagic stroke (only in case of very large doses)
- Oxidation of *n*−3 fatty acids forming biologically active oxidation products.
- Reduced glycemic control among diabetics.
- Suppression of immune and inflammation responses, and consequently, decreased resistance to infections and increased susceptibility to opportunistic bacteria.
- An increase in concentration of LDL cholesterol in some individuals.

Subsequent advices from the FDA and national counterparts have permitted health claims associated with heart health.

Cardiac risk

Persons with congestive heart failure, chronic recurrent angina or evidence that their heart is receiving insufficient blood flow are advised to talk to their doctor before taking $n-3$ fatty acids. It may be prudent for such persons to avoid taking $n-3$ fatty acids or eating foods that contain them in substantial amounts.

In congestive heart failure, cells that are only barely receiving enough blood flow become electrically hyperexcitable. This, in turn, can lead to increased risk of irregular heartbeats, which, in turn, can cause sudden cardiac death. $n-3$ fatty acids seem to stabilize the rhythm of the heart by effectively preventing these hyperexcitable cells from functioning, thereby reducing the likelihood of irregular heartbeats and sudden cardiac death. For most people, this is obviously beneficial and would account for most of the large reduction in the likelihood of sudden cardiac death. Nevertheless, for people with congestive heart failure, the heart is barely pumping blood well enough to keep them alive. In these patients, $n-3$ fatty acids may eliminate enough of these few pumping cells that the heart would no longer be able to pump sufficient blood to live, causing an increased risk of cardiac death.

Research frontiers

Developmental differences

Essential fatty acid supplements have gained popularity for children with ADHD, autism, and other developmental differences. A 2004 Internet survey found that 29% of surveyed parents used essential fatty acid supplements to treat children with autism spectrum disorders.

Fish oils appear to reduce ADHD-related symptoms in some children. A 2007 double-blind, placebo-controlled trial of small groups of children found that omega-3 fatty acids reduced hyperactivity in children with autism spectrum disorders, Additional double blind studies have showed "medium to strong treatment effects of omega 3 fatty acids on symptoms of adhd.

Low birth weight

In a study of nearly 9,000 pregnant women, researchers found women who ate fish once a week during their first trimester had 3.6 times less risk of low birth weight and premature birth than those who ate no fish. Low consumption of fish was a strong risk factor for preterm delivery and low birth weight. However, attempts by other groups to reverse this increased risk by encouraging increased pre-natal consumption of fish were unsuccessful. This lead some researchers to consider that maybe women who ate fish in their first trimester were more likely to be able to afford better overall nutrition throughout pregnancy, and less likely to do drugs.

Psychiatric disorders

n−3 fatty acids are known to have membrane-enhancing capabilities in brain cells. One medical explanation is that *n*−3 fatty acids play a role in the fortification of the myelin sheaths. Not coincidentally, *n*−3 fatty acids comprise approximately eight percent of the average human brain according to Dr. David Horrobin, a pioneer in fatty acid research. Ralph Holman of the University of Minnesota, another major researcher in studying essential fatty acids, who gave Omega-3 its name, surmised how *n*−3 components are analogous to the human brain by stating that "DHA is structure, EPA is function."

A benefit of *n*−3 fatty acids is helping the brain to repair damage by promoting neuronal growth. In a six-month study involving people with schizophrenia and Huntington's disease who were treated with EPA or a placebo, the placebo group had clearly lost cerebral tissue, while the patients given the supplements had a significant increase of grey and white matter.

In the prefrontal cortex (PFC) of the brain, low brain *n*−3 fatty acids are thought to lower the dopaminergic neurotransmission in this brain area, possibly contributing to the negative and neurocognitive symptoms in schizophrenia. This reduction in dopamine system function in the PFC may lead to an overactivity in dopaminergic function in the limbic system of the brain which is suppressively controlled by the PFC dopamine system, causing the positive symptoms of schizophrenia. This is called the *n*−3 polyunsaturated fatty acid/dopamine hypothesis of schizophrenia (Ohara, 2007).

This mechanism may explain why *n*−3 supplementation shows effects against both positive, negative and neurocognitive symptoms in schizophrenia.

Consequently, the past decade of *n*−3 fatty acid research has procured *some* Western interest in *n*−3 fatty acids as being a legitimate 'brain food.' Still, recent claims that one's intelligence quotient, psychological tests measuring certain cognitive skills, including numerical and verbal reasoning skills, are increased on account of *n*−3 fatty acids consumed by pregnant mothers remain unreliable and controversial. An even more significant focus of research, however, lies in the role of *n*−3 fatty acids as a non-prescription treatment for certain psychiatric and mental diagnoses and has become a topic of much research and speculation.

In 1998, Andrew L. Stoll, MD and his colleagues at Harvard University conducted a small double-blind placebo-controlled study in thirty patients diagnosed with bipolar disorder. Most subjects in this study were already undergoing psychopharmacological treatment (e.g. 12 out of the 30 were taking lithium). Over the course of four months, he gave 15 subjects capsules containing olive oil, and another 15 subjects capsules containing nine grams of pharmaceutical-quality EPA and DHA. The study showed that subjects in the *n*−3 group were less likely to experience a relapse of symptoms in the four months of the study. Moreover, the *n*−3 group experienced significantly more recovery than the placebo group.

However, a commentary on the Stoll study notes that the improvement in the *n*−3 group was too small to be clinically significant. Though Stoll believes that the 1999 experiment was not as optimal as it could have been and has accordingly pursued further research, the foundation has been laid for more researchers to explore the theoretical association between absorbed *n*−3 fatty acids and signal transduction inhibition in the brain.

"Several epidemiological studies suggest covariation between seafood consumption and rates of mood disorders. Biological marker studies indicate deficits in omega−3 fatty acids in people with depressive disorders, while several treatment studies indicate therapeutic benefits from omega-3 supplementation. A similar contribution of omega-3 fatty acids to coronary artery disease may explain the well-described links between coronary artery disease and depression. Deficits in omega-3 fatty acids have been identified as a contributing factor to mood disorders and offer a potential rational treatment approach." In 2004, a study found that 100 suicide attempt patients on average had significantly lower levels of EPA in their blood as compared to controls.

In 2006, a review of published trials in the American Journal of Clinical Nutrition found that "the evidence available provides little support" for the use of fish or the n–3 long-chain polyunsaturated fatty acids contained in them to improve depressed mood. The study used results of twelve randomized controlled trials in its meta-analysis. The review recommended that "larger trials with adequate power to detect clinically important benefits" be performed.

Dietary sources

Daily values

As macronutrients, fats are not assigned recommended daily allowances. Macronutrients have AI (Acceptable Intake) and AMDR (Acceptable Macronutrient Distribution Range) instead of RDAs. The AI for *n*−3 is 1.6 grams/day for men and 1.1 grams/day for women while the AMDR is 0.6% to 1.2% of total energy.

"A growing body of literature suggests that higher intakes of α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) may afford some degree of protection against coronary heart disease. Because the physiological potency of EPA and DHA is much greater than that for α-linolenic acid, it is not possible to estimate one AMDR for all *n*−3 fatty acids.

Approximately 10 percent of the AMDR can be consumed as EPA and/or DHA." There was insufficient evidence as of 2005 to set a UL (upper tolerable limit) for *n*−3 fatty acids.

Researchers believe the ideal *n*−6 intake should be no more than 4 to 5 times that of our *n*−3 intake. The National Institutes of Health recently published recommended daily intakes of fatty acids, specific recommendations include 650 mg of EPA and DHA, 2.22 g/day of alpha-linolenic acid and 4.44 g/day of linoleic acid.

A perceived risk of fish oil *n*−3 supplementation has been heavy metal poisoning by the body's accumulation of traces of heavy metals, in particular mercury, lead, nickel, arsenic and cadmium as well as other contaminants (PCBs, furans, dioxins), which potentially might be found especially in less-refined fish oil supplements. An independent test in 2006 of 44 fish oils on the US market found that all of the products passed safety standards for potential contaminants. The FDA recommends that total dietary intake of *n*−3 fatty acids from fish not exceed 3 grams per day, of which no more than 2 grams per day are from nutritional supplements.

Historically, the Council for Responsible Nutrition (CRN) and the World Health Organization (WHO) have published acceptable standards regarding contaminants in fish oil. The most stringent current standard is the International Fish Oils Standard (IFOS). Fish oils that typically make this highest grade are those that are molecularly distilled under vacuum, and have virtually no measurable level of contaminants (measured parts per billion and parts per trillion).

n−3 supplementation in food has been a significant recent trend in food fortification, with global food companies launching *n*−3 fortified bread, mayonnaise, pizza, yogurt, orange juice, children's pasta, milk, eggs, confections and infant formula.

Fish

The most widely available source of EPA and DHA is cold water oily fish such as salmon, herring, mackerel, anchovies and sardines. Oils from these fish have a profile of around seven times as much n−3 as n−6. Other oily fish such as tuna also contain n−3 in somewhat lesser amounts. Consumers of oily fish should be aware of the potential presence of heavy metals and fat-soluble pollutants like PCBs and dioxins which may accumulate up the food chain. Some supplement manufacturers remove heavy metals and other contaminants from the oil through various means, such as molecular distillation (see above), which increases purity, potency and safety.

Even some forms of fish oil may not be optimally digestible. Of four studies that compare bioavailability of the triglyceride form of fish oil vs. the ester form, two have concluded that the natural triglyceride form is better, and the other two studies did not find a significant difference. No studies have shown the ester form to be superior although it is cheaper to manufacture.

Although fish is a dietary source of n−3 fatty acids, fish do not synthesize them; they obtain them from the algae in their diet.[citation needed]

Eggs

Eggs produced by chickens fed a diet of greens and insects produce higher levels of *n*−3 fatty acids (mostly ALA) than chickens fed corn or soybeans. In addition to feeding chickens insects and greens, fish oils may be added to their diet to increase the amount of fatty acid concentrations in eggs.

Other sources

Krill, which are small, shrimp-like zooplankton, also contain the n−3 fatty acids EPA and DHA. One advantage of extracting n−3 fatty acids from krill, as opposed to sources higher in the food chain, is that krill contain fewer heavy metals and PCBs harmful to humans. However, in comparison to higher animals, they also contain fewer n−3 fatty acids per gram.

The n−6 to n−3 ratio of grass-fed beef is about 2:1, making it a more useful source of n−3 than grain-fed beef, which usually has a ratio of 4:1. Commercially available lamb is almost always grass-fed, and subsequently higher in n−3 than other common meat sources.[citation needed] Milk and cheese from grass-fed cows may also be good sources of n−3. One UK study showed that half a pint of milk provides 10% of the recommended daily intake (RDI) of ALA, while a piece of organic cheese the size of a matchbox may provide up to 88%".

The microalgae Crypthecodinium cohnii and Schizochytrium are rich sources of DHA (22:6 n−3) and can be produced commercially in bioreactors. Oil from brown algae (kelp) is a source of EPA. Walnuts are one of few nuts that contain appreciable n−3 fat, with approximately a 1:4 ratio of n−3 to n−6. Acai palm fruit also contains n−3 fatty acids.

Omega 3 is also found in softgels in pharmacies and nowadays it is also found in combination with omega 6, omega 9 and shark liver oil

The *n*−6 to *n*−3 ratio

Clinical studies indicate that the ingested ratio of *n*−6 to *n*−3 (especially Linoleic vs Alpha Linolenic) fatty acids is important to maintaining cardiovascular health.

Both n−3 and n−6 fatty acids are essential, i.e. humans must consume them in the diet. n−3 and n−6 compete for the same metabolic enzymes, thus the n−6:n−3 ratio will significantly influence the ratio of the ensuing eicosanoids (hormones), (e.g. prostaglandins, leukotrienes, thromboxanes etc.), and will alter the body's metabolic function. Generally, grass-fed animals accumulate more n−3 than do grain-fed animals which accumulate relatively more n−6. Metabolites of n−6 are significantly more inflammatory (esp. arachidonic acid) than those of n−3. This necessitates that n−3 and n−6 be consumed in a balanced proportion; healthy ratios of n−6:n−3 range from 1:1 to 4:1. Studies suggest that the evolutionary human diet, rich in game animals, seafood and other sources of n−3, may have provided such a ratio.

Typical Western diets provide ratios of between 10:1 and 30:1 - i.e., dramatically skewed toward n−6. Here are the ratios of n−6 to n−3 fatty acids in some common oils: canola 2:1, soybean 7:1, olive 3–13:1, sunflower (no n−3), flax 1:3, cottonseed (almost no n−3), peanut (no n−3), grapeseed oil (almost no n−3) and corn oil 46 to 1 ratio of n−6 to n−3. It should be noted that olive, peanut and canola oils consist of approximately 80% monounsaturated fatty acids, (i.e. neither n−6 nor n−3) meaning that they contain relatively small amounts of n−3 and n−6 fatty acids. Consequently, the n−6 to n−3 ratios for these oils (i.e. olive, canola and peanut oils) are not as significant as they are for corn, soybean and sunflower oils.

Conversion efficiency of ALA to EPA and DHA

It has been reported that conversion of ALA to EPA and further to DHA in humans is limited, but varies with individuals. Women have higher ALA conversion efficiency than men, probably due to the lower rate of utilization of dietary ALA for beta-oxidation. This suggests that biological engineering of ALA conversion efficiency is possible. In the online book of *The Benefits of Omega 3 Fatty Acids found in Seal Oil, as Opposed to Fish and Flaxseed Oils*, Dr. Ho listed the several factors that inhibit the ALA conversion, which again indicate that the efficiency of ALA conversion could be adjusted by altering one's dietary habits, such as rebalancing the ratio of *n*−3 and *n*−6 fatty acid intake, restraining direct alcohol consumptions, and supplementing vitamins and minerals. However, Goyens *et al.* argues that it is the absolute amount of ALA, rather than the ratio of *n*−3 and *n*−6 fatty acids, which affects the conversion.

Nomenclature

In chemistry, especially biochemistry, a fatty acid is a carboxylic acid often with a long unbranched aliphatic tail (chain), which is either saturated or unsaturated. Carboxylic acids as short as butyric acid (4 carbon atoms) are considered to be fatty acids, whereas fatty acids derived from natural fats and oils may be assumed to have at least 8 carbon atoms, e.g., caprylic acid (octanoic acid). Most of the natural fatty acids have an even number of carbon atoms, because their biosynthesis involves acetyl-CoA, a coenzyme carrying a two-carbon-atom group (see fatty acid synthesis).

Fatty acids are produced by the hydrolysis of the ester linkages in a fat or biological oil (both of which are triglycerides), with the removal of glycerol. See oleochemicals.

Definition

Fatty acids are aliphatic monocarboxylic acids, derived from, or contained in esterified form in an animal or vegetable fat, oil or wax. Natural fatty acids commonly have a chain of 4 to 28 carbons (usually unbranched and even numbered), which may be saturated or unsaturated. By extension, the term is sometimes used to embrace all acyclic aliphatic carboxylic acids. This would include acetic acid, which is not usually considered a fatty acid because it is so short that the triglyceride triacetin made from it is substantially miscible with water and is thus not a lipid.

Fatty acids can be saturated and unsaturated, depending on double bonds. In addition, they also differ in length.

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Saturated fatty acids

Saturated fatty acids do not contain any double bonds or other functional groups along the chain. The term "saturated" refers to hydrogen, in that all carbons (apart from the carboxylic acid [-COOH] group) contain as many hydrogens as possible. In other words, the omega (ω) end contains 3 hydrogens (CH3-), and each carbon within the chain contains 2 hydrogen atoms.

Saturated fatty acids form straight chains and, as a result, can be packed together very tightly, allowing living organisms to store chemical energy very densely. The fatty tissues of animals contain large amounts of long-chain saturated fatty acids. In IUPAC nomenclature, fatty acids have an [-oic acid] suffix. In common nomenclature, the suffix is usually -ic.

The shortest descriptions of fatty acids include only the number of carbon atoms and double bonds in them (e.g., C18:0 or 18:0). C18:0 means that the carbon chain of the fatty acid consists of 18 carbon atoms, and there are no (zero) double bonds in it, whereas C18:1 describes an 18-carbon chain with one double bond in it. Each double bond can be in either a cis- or trans- conformation, and stands in a different position with respect to the ends of the fatty acid; therefore, not all C18:1s (for example) are identical. If there is one or more double bonds in the fatty acid, it is no longer considered saturated, but rather, mono- or polyunsaturated.

Most commonly-occurring saturated fatty acids are of the following varieties:

Common name	**IUPAC name**	**Chemical structure**	**Abbr.**	**Melting point** (°C)
Butyric	Butanoic acid	$CH_3(CH_2)_2COOH$	C4:0	-8
Caproic	Hexanoic acid	$CH_3(CH_2)_4COOH$	C6:0	-3
Caprylic	Octanoic acid	$CH_3(CH_2)_6COOH$	C8:0	16-17
Capric	Decanoic acid	$CH_3(CH_2)_8COOH$	C10:0	31
Lauric	Dodecanoic acid	$CH_3(CH_2)_{10}COOH$	C12:0	44-46
Myristic	Tetradecanoic acid	$CH_3(CH_2)_{12}COOH$	C14:0	58.8
Palmitic	Hexadecanoic acid	$CH_3(CH_2)_{14}COOH$	C16:0	63-64
Stearic	Octadecanoic acid	$CH_3(CH_2)_{16}COOH$	C18:0	69.9
Arachidic	Eicosanoic acid	$CH_3(CH_2)_{18}COOH$	C20:0	75.5
Behenic	Docosanoic acid	$CH_3(CH_2)_{20}COOH$	C22:0	74-78
Lignoceric	Tetracosanoic acid	$CH_3(CH_2)_{22}COOH$	C24:0	

Unsaturated fatty acids

Unsaturated fatty acids are of similar form, except that one or more alkenyl functional groups exist along the chain, with each alkene substituting a single-bonded " -CH2-CH2-" part of the chain with a double-bonded "-CH=CH-" portion (that is, a carbon double-bonded to another carbon).

The two next carbon atoms in the chain that are bound to either side of the double bond can occur in a cis or trans configuration.

cis

A cis configuration means that adjacent hydrogen atoms are on the same side of the double bond. The rigidity of the double bond freezes its conformation and, in the case of the cis isomer, causes the chain to bend and restricts the conformational freedom of the fatty acid. The more double bonds the chain has in the cis configuration, the less flexibility it has. When a chain has many cis bonds, it becomes quite curved in its most accessible conformations. For example, oleic acid, with one double bond, has a "kink" in it, whereas linoleic acid, with two double bonds, has a more pronounced bend. Alpha-linolenic acid, with three double bonds, favors a hooked shape. The effect of this is that, in restricted environments, such as when fatty acids are part of a phospholipid in a lipid bilayer, or triglycerides in lipid droplets, cis bonds limit the ability of fatty acids to be closely packed, and therefore could affect the melting temperature of the membrane or of the fat.

trans

A *trans* configuration, by contrast, means that the next two hydrogen atoms are bound to *opposite* sides of the double bond. As a result, they do not cause the chain to bend much, and their shape is similar to straight saturated fatty acids.

In most naturally-occurring unsaturated fatty acids, each double bond has 3*n* carbon atoms after it, for some n, and all are cis bonds. Most fatty acids in the *trans* configuration (trans fats) are not found in nature and are the result of human processing (e.g., hydrogenation).

The differences in geometry between the various types of unsaturated fatty acids, as well as between saturated and unsaturated fatty acids, play an important role in biological processes, and in the construction of biological structures (such as cell membranes).

Essential fatty acids

The human body can produce all but two of the fatty acids it needs. These two, linoleic acid (LA acid) and alpha-linolenic acid (ALA), are widely distributed in plant oils. In addition, fish oils contain the longer-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Other marine oils, such as from seal, also contain significant amounts of docosapentaenoic acid (DPA), which is also an omega-3 fatty acid. Although the body to some extent can convert LA and LNA into these longer-chain omega-3 fatty acids, the omega-3 fatty acids found in marine oils help fulfill the requirement of essential fatty acids (and have been shown to have wholesome properties of their own).

Since they cannot be made in the body from other substrates and must be supplied in food, they are called essential fatty acids. Mammals lack the ability to introduce double bonds in fatty acids beyond carbons 9 and 10. Hence linoleic acid and alpha-linolenic acid are essential fatty acids for humans.

In the body, essential fatty acids are primarily used to produce hormone-like substances that regulate a wide range of functions, including blood pressure, blood clotting, blood lipid levels, the immune response, and the inflammation response to injury infection.

Essential fatty acids are polyunsaturated fatty acids and are the parent compounds of the omega-6 and omega-3 fatty acid series, respectively. They are essential in the human diet because there is no synthetic mechanism for them. Humans can easily make saturated fatty acids or monounsaturated fatty acids with a double bond at the omega-9 position, but do not have the enzymes necessary to introduce a double bond at the omega-3 position or omega-6 position.

The essential fatty acids are important in several human body systems, including the immune system and in blood pressure regulation, since they are used to make compounds such as prostaglandins. The brain has increased amounts of linolenic and alpha-linoleic acid derivatives. Changes in the levels and balance of these fatty acids due to a typical Western diet rich in omega-6 and poor in omega-3 fatty acids is alleged"Study Links Brain Fatty Acid Levels To Depression", ScienceDaily, Bethesda, MD: American Society For Biochemistry And Molecular Biology (2005-05-25). Retrieved on 2008-01-18. to be associated with depression and behavioral change, including violence. The actual connection, if any, is still under investigation. Further, changing to a diet richer in omega-3 fatty acids, or consumption of supplements to compensate for a dietary imbalance, has been associated with reduced violent behavior and increased attention span, but the mechanisms for the effect are still unclear. So far, at least three human studies have shown results that support this: two school studies as well as a double blind study in a prison.

Fatty acids play an important role in the life and death of cardiac cells because they are essential fuels for mechanical and electrical activities of the heart.

Trans fatty acids

A trans fatty acid (commonly shortened to trans fat) is an unsaturated fatty acid molecule that contains a trans double bond between carbon atoms, which makes the molecule less 'kinked' in comparison to fatty acids with cis double bonds. These bonds are characteristically produced during industrial hydrogenation of plant oils. Research suggests that amounts of trans fats correlate with circulatory diseases such as atherosclerosis and coronary heart disease more than the same amount of non-trans fats, for reasons that are not fully understood. It is known, however, that trans fats raise the LDL (bad) cholesteral and lowers the HDL (good) cholestrol. They have also been shown to have other harmful effects such as increasing triglycerides and Lp(a) lipoproteins. It is also thought to cause more inflammation, which is thought to occur through damage to the cells lining of blood vessels.

Long and short

In addition to saturation, fatty acids are short, medium or long.

- Short chain fatty acids (SCFA) are fatty acids with aliphatic tails of less than eight carbons.
- Medium chain fatty acids (MCFA) are fatty acids with aliphatic tails of 8–14 carbons, which can form medium chain triglycerides.
- Long chain fatty acids (LCFA) are fatty acids with aliphatic tails of 16 carbons or moreLong chain fatty acids (LCFA) are fatty acids with aliphatic tails of 16 carbons or more.

When discussing essential fatty acids, (EFA) a slightly different terminology applies. Short-chain EFA are 18 carbons long; long-chain EFA have 20 or more carbons.[

Free fatty acids

Fatty acids can be bound or attached to other molecules, such as in triglycerides or phospholipids. When they are not attached to other molecules, they are known as "free" fatty acids.

The **uncombined fatty acids** or **free fatty acids** may come from the breakdown of a triglyceride into its components (fatty acids and glycerol). However as fats are insoluble in water they must be bound to appropriate regions in the plasma protein albumin for transport around the body. The levels of "free fatty acid" in the blood are limited by the number of albumin binding sites available.

Free fatty acids are an important source of fuel for many tissues since they can yield relatively large quantities of ATP. Many cell types can use either glucose or fatty acids for this purpose. In particular, heart and skeletal muscle prefer fatty acids. The brain cannot use fatty acids as a source of fuel; it relies on glucose, or on ketone bodies. Ketone bodies are produced in the liver by fatty acid metabolism during starvation, or during periods of low carbohydrate intake.

Fatty acids in dietary fats

The following table gives the fatty acid, vitamin E and cholesterol composition of some common dietary fats.

	Saturated	Monounsaturated	Polyunsaturated	Cholesterol	Vitamin E
	g/100g	g/100g	g/100g	mg/100g	mg/100g
Animal fats					
Lard	40.8	43.8	9.6	93	0.00
Butter	54.0	19.8	2.6	230	2.00
Vegetable fats					
Coconut oil	85.2	6.6	1.7	0	.66
Palm oil	45.3	41.6	8.3	0	33.12
Cottonseed oil	25.5	21.3	48.1	0	42.77
Wheat germ oil	18.8	15.9	60.7	0	136.65
Soya oil	14.5	23.2	56.5	0	16.29
Olive oil	14.0	69.7	11.2	0	5.10
Corn oil	12.7	24.7	57.8	0	17.24
Sunflower oil	11.9	20.2	63.0	0	49.0
Safflower oil	10.2	12.6	72.1	0	40.68
Rapeseed/Canola oil	5.3	64.3	24.8	0	22.21

Acidity

Short chain carboxylic acids such as formic acid and acetic acid are miscible with water and dissociate to form reasonably strong acids (pKa 3.77 and 4.76, respectively). Longer-chain fatty acids do not show a great change in pKa. Nonanoic acid, for example, has a pKa of 4.96. However, as the chain length increases the solubility of the fatty acids in water decreases very rapidly, so that the longer-chain fatty acids have very little effect on the pH of a solution. The significance of their pKa values therefore has relevance only to the types of reactions in which they can take part.

Even those fatty acids that are insoluble in water will dissolve in warm ethanol, and can be titrated with sodium hydroxide solution using phenolphthalein as an indicator to a pale-pink endpoint. This analysis is used to determine the free fatty acid content of fats, i.e., the proportion of the triglycerides that have been hydrolyzed.

Reaction of fatty acids

Fatty acids react just like any other carboxylic acid, which means they can undergo esterification and acid-base reactions. Reduction of fatty acids yields fatty alcohols. Unsaturated fatty acids can also undergo addition reactions, most commonly hydrogenation, which is used to convert vegetable oils into margarine. With partial hydrogenation, unsaturated fatty acids can be isomerized from cis to trans configuration. In the Varrentrapp reaction certain unsaturated fatty acids are cleaved in molten alkali, a reaction at one time of relevance to structure elucidation.

Auto-oxidation and rancidity

Fatty acids at room temperature undergo a chemical change known as auto-oxidation. The fatty acid breaks down into hydrocarbons, ketones, aldehydes, and smaller amounts of epoxides and alcohols. Heavy metals present at low levels in fats and oils promote auto-oxidation. Fats and oils often are treated with chelating agents such as citric acid.

Digestion and intake

Short- and medium chain fatty acids are absorbed directly into the blood via intestine capillaries and travel through the portal vein just as other absorbed nutrients do. However, long chain fatty acids are too large to be directly released into the tiny intestine capillaries.

Instead they are absorbed into the fatty walls of the intestine villi and reassembled again into triglycerides. The triglycerides are coated with cholesterol and protein (protein coat) into a compound called a chylomicron.

Within the villi, the chylomicron enters a lymphatic capillary called a lacteal, which merges into larger lymphatic vessels. It is transported via the lymphatic system and the thoracic duct up to a location near the heart (where the arteries and veins are larger). The thoracic duct empties the chylomicrons into the bloodstream via the left subclavian vein. At this point the chylomicrons can transport the triglycerides to where they are needed.