PRODUCT INFORMATION

Scientific Overview: AvailOm®

(Omega-3 Polyunsaturated Fatty Acid L-Lysine Complex)

EVONIK
Leading Beyond Chemistry

AvailOm® is a novel solid form of omega-3 polyunsaturated fatty acids consisting of a complex of the omega-3 with the natural amino acid L-lysine. The new compound has a high content of the key omega-3 polyunsaturated long chain fatty acids EPA and DHA. The powder form of the product allows it to be incorporated into a wide variety of applications, such as tablets, capsules and functional foods. AvailOm® is rapidly dissociated in the stomach into the omega-3 free fatty acids and L-lysine, and it is therefore highly bioavailable. Human trials have shown that omega-3 free fatty acids have a bioavailability 50 % higher than the triglycerides and 3 to 5 times higher than the ethyl esters. This effect is particularly pronounced when the omega-3 fatty acids are consumed as part of a low fat diet. AvailOm® has all the same clinical effects as other forms of omega-3 fatty acids, with applications in the areas of cardiovascular health, cognitive health, inflammatory disease, and as an adjuvant in cancer therapy.

Introduction to omega-3 fatty acids

Omega-3 polyunsaturated fatty acids are naturally occurring fatty acids found particularly in fish oil, and have been extensively investigated for their health benefits. The two main omega-3 fatty acids found in fish oil are 5,8,11,14,17-eicosapentaenoic acid (*all Z-*) (EPA, C20:5n-3), and 4,7,10,13,16,19-docosahexaenoic acid (*all Z-*), (DHA, C22:6n-3) (Figure 1). The term omega-3 refers to the position of the first double bond in the alkyl chain.

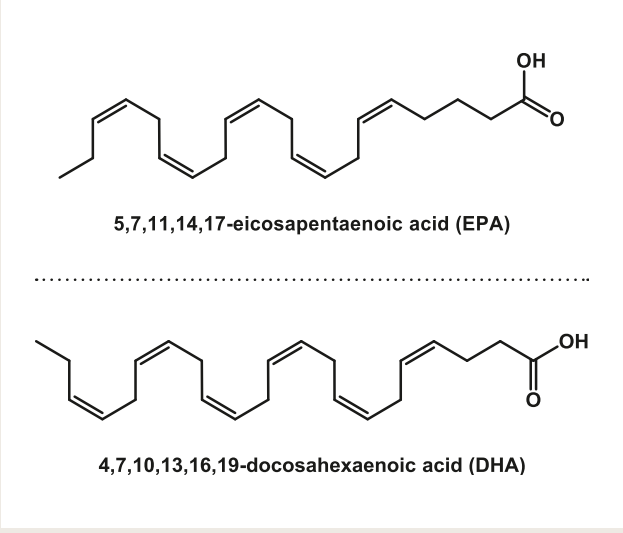


Figure 1. Structures of the principal omega-3 fatty acids

Crude fish oil is refined in several stages to produce omega-3 products for human consumption (Figure 2). The refining process involves neutralization to remove free fatty acids, winterization to remove phospholipids, and steam treatment to remove odorous compounds[1,2]. The refined fish oil contains a mixture of fatty acids in the form of triglycerides (TAG). The approximate composition of omega-3 products in the refined fish oil is ca. 18 % EPA and ca. 12 % DHA, so each triglyceride will on average contain one omega-3 fatty acid side chain.

Chemical trans-esterification of the triglycerides to the ethyl ester form of the omega-3 fatty acids is carried out by treatment with ethanol under base catalysis, followed by high vacuum distillation to give a mixture of fatty acid ethyl esters (EE). The omega-3 content in the product can be increased to > 60 % by this refining process[1,2].

The omega-3 ethyl esters can be further trans-esterified by an enzymatic process using *Candida antarctica* lipase, or chemically via the free fatty acid, to give a mixture of tri-, di- and mono-glyceride esters[1,3,4]. This product is called re-esterified triglyceride (rTG) and contains a similar high proportion of omega-3 fatty acids as the ethyl esters. However, the omega-3 fatty acid chains are now in all three side chain positions of the glycerol, whereas the original fish oil triglyceride has the omega-3 side chain mainly at the 2-position[3,4].

Hydrolysis of the omega-3 ethyl esters gives the omega-3 free fatty acids (FFA), but these are unstable and easily oxidized, so they are not used as a commercial form of dietary omega-3. AvailOm® is a new stabilized form of omega-3, as the omega-3 fatty acid is stabilized as a complex with L-lysine.

Fish oil
(mainly Triglycerides, TAG)

Trans-esterification (ethanol)

Omega-3 Ethyl Esters
(EE)

Enzymatic trans-esterification (glycerol)

Hydrolysis

Re-esterified Omega-3 Triglycerides
(rTG)

Omega-3 Free Fatty Acids
(FFA)

Figure 2. Process for refining omega-3 fatty acids

Several other processes have been developed for isolation and purification of the omega-3 products from fish oil, including supercritical extraction, chromatography, and complexation of the free fatty acids with urea. These methods are described in comprehensive reviews[2,5,6]. Omega-3 fatty acids have also been isolated from krill oil, which has a different composition, being about 40–50 % phospholipids, 30–40 % triglycerides, and the remainder free fatty acids[7]. Antarctic krill oil from *Euphausia superba* contains about 13 % EPA and 8 % DHA.

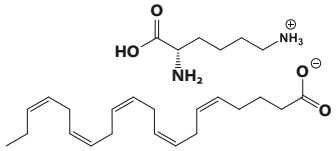
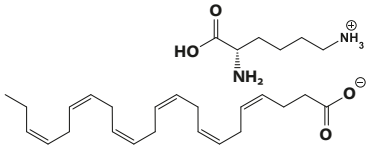
Properties of AvailOm®

AvailOm® is a novel solid form of omega-3 polyunsaturated fatty acids in the form of a compound with the natural amino acid L-lysine. By making a solid form of omega-3, Evonik has produced a product which is easy to handle, and can be readily formulated, e. g. into tablets (Figure 3).

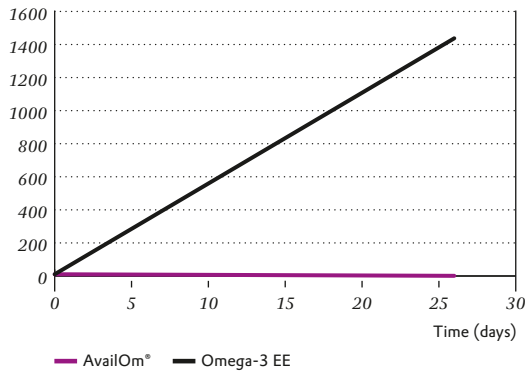
Figure 3. AvailOm® allows omega-3 oil to be compressed into tablets

The principal omega-3 polyunsaturated fatty acids present in AvailOm® are EPA and DHA, and the content of EPA+DHA is ≥ 45 %. The content of L-lysine is ≥ 30 %. Details of the principal constituents of AvailOm® are given in Table 1. The balance of the composition of AvailOm® consists of lysine salts of other fatty acids, and the exact composition, as well as the ratio of EPA to DHA, will depend on the acid composition of the starting omega-3 oil[3] used for the manufacture of AvailOm®. AvailOm® is manufactured by Evonik using a patented process, which can be adapted for oils with different ratios of EPA and DHA for use in a wide variety of applications.

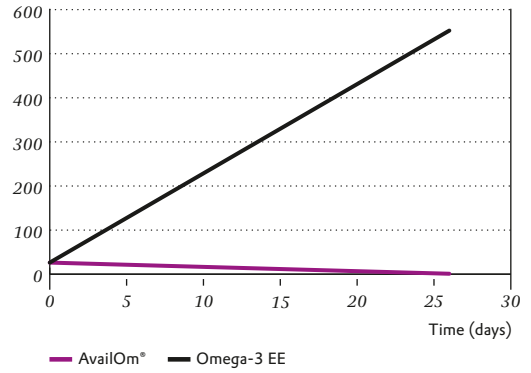
Table 1. AvailOm®: Principal Components.

Name	5,8,11,14,17-Eicosapentaenoic acid (*all Z-*), compound with L-lysine	4,7,10,13,16,19-Docosahexaenoic acid (*all Z-*), compound with L-lysine
Formula	 $C_{26}H_{44}N_2O_4$	 $C_{28}H_{46}N_2O_4$
Molecular weight	448.65 g/mol	474.69 g/mol
Appearance	Free flowing beige to yellowish powder	

Anisidine Value (AV)



Peroxide Value (PV)



Iodine number

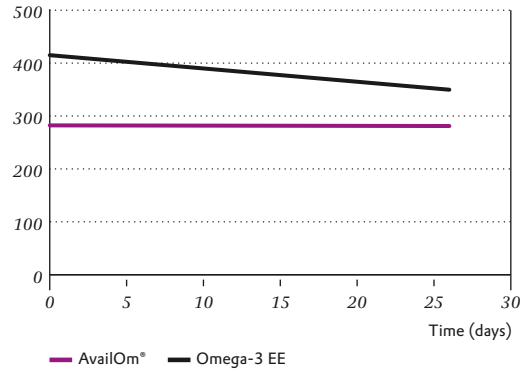
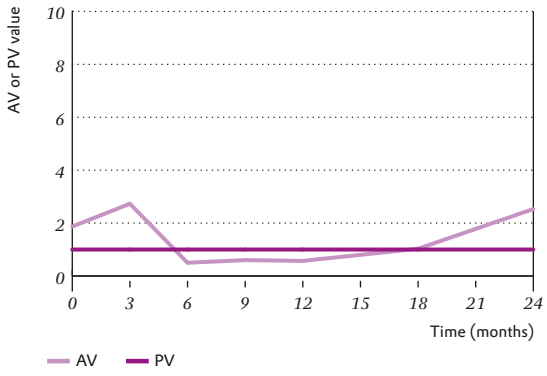
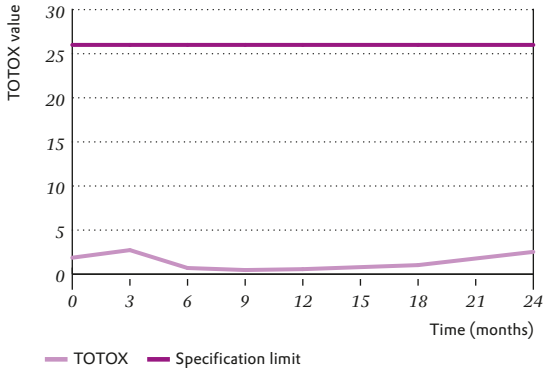


Figure 4. Accelerated storage stability data for AvailOm®

AV und PV stability values for AvailOm®



TOTOX stability value for AvailOm®



Assay of AvailOm® on storage

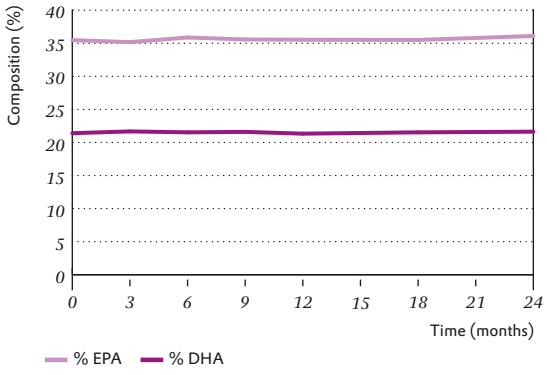


Figure 5. Long term storage stability data for AvailOm®

The formation of a solid form of omega-3 fatty acid as a compound with lysine gives the omega-3 complex a higher degree of stability with respect to oxidative degradation, which can give an omega-3 product a rancid smell, and lead to "fishy burps" after ingestion. Figure 4 shows the results of an accelerated storage test (50 °C, open container), comparing AvailOm® with a commercial omega-3 fatty acid ethyl ester. The indicators of the presence of oxidation products, namely anisidine value and peroxide value, remain close to zero, while the iodine number, an indication of the degree of unsaturation in the fatty acid, remains constant[8].

The same increased stability of the lysine complex AvailOm® was found in long term stability trials conducted over 24 months at 25 °C and 60 % relative humidity. As shown in Figure 5, the anisidine value (AV), the peroxide value (PV), and the TOTOX value (2*PV + AV) all remain close to zero over this period, and the TOTOX value is well within the specification limits for the product. Figure 5 also shows the storage stability of AvailOm® (25 °C, 60 % relative humidity) with respect to the HPLC assays of the principal fatty acid components EPA and DHA[8]. The stability of AvailOm® is superior to that of other forms of omega-3 polyunsaturated fatty acids, including the triglycerides, ethyl esters, free fatty acids and inorganic fatty acid salts (e. g. sodium, potassium, calcium and magnesium).

Although AvailOm® is currently manufactured as a complex of omega-3 polyunsaturated fatty acids with L-lysine, similar complexes can be formed with other basic amino acids, and these also show improved physical form and stability. Such suitable basic amino acids include L-arginine and L-ornithine, which can be used to add tailored properties to the omega-3 complex.

Evonik has completed dissolution studies to show that the omega-3 fatty acid lysine complex AvailOm® is completely dissociated in the gastric fluid of the stomach to give the individual components EPA, DHA and L-lysine[8]. The safety of the product AvailOm® is based on the safety of the components EPA, DHA and lysine, which all occur endogenously in the diet, and have been assessed as safe by the regulatory authorities (up to a total intake of 5 g EPA+DHA / day)[9]. A 14 day repeated dose toxicity study on AvailOm® in rats demonstrated no adverse effects up to 5 % omega-3 fatty acid lysine complex in the diet, equivalent to 4400 mg / kg body weight / day[8].

Formulation options for AvailOm®

As AvailOm® is a novel solid form of omega-3 fatty acids, there are many opportunities for new formulations, and for the incorporation of AvailOm® into functional foods. AvailOm® can be directly compressed into tablets, using standard excipients and tableting equipment. Tablets can also be made with combinations of omega-3 and other nutrients, for example various vitamins. AvailOm® can also be filled into hard capsules. In addition, AvailOm® can be incorporated as a powder into new functional foods, where the rapid bioavailability of the omega-3 and the lack of a fish-oil aftertaste can be advantageous. When formulated into tablets and capsules for immediate release, AvailOm® is released in the stomach, and the omega-3 free fatty acids are absorbed in the small intestine. If required to remove all occurrence of "fishy burps", which can be a negative property of omega-3 products for consumers, enteric formulations are also possible, where the omega-3 free fatty acids are released in the small intestine. In this case, rapid absorption of the free fatty acids is also possible, as there is no need for ester hydrolysis before absorption.

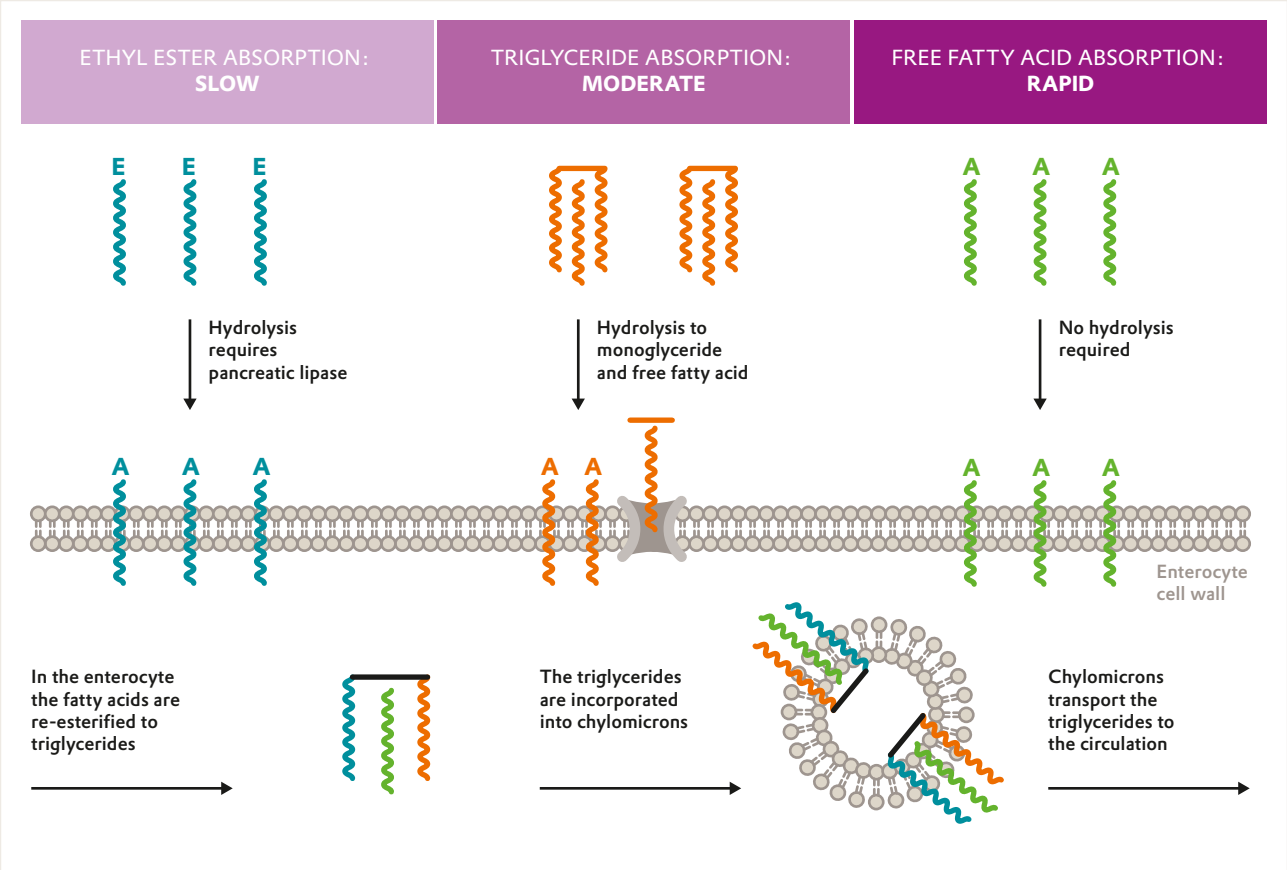


Figure 6. Comparison of the mechanism of absorption of different forms of omega-3 products

Physiology, metabolism and absorption of AvailOm®

The absorption of omega-3 fatty acids by the enterocytes in the gut lumen is well understood and has been extensively reviewed[4,10]. A simplified version of the metabolic pathway, showing the hydrolysis and absorption of three forms of omega-3; the triglycerides (as present in fish oil), the ethyl esters and the free fatty acids, is presented in Figure 6. AvailOm®, as a compound containing a free fatty acid combined with an amino acid, has been shown to be rapidly hydrolyzed under the strongly acid conditions present in the stomach, to give the omega-3 free fatty acids and L-lysine hydrochloride[8]. For the purposes of this discussion, therefore, AvailOm® will be considered to be equivalent to the free fatty acids.

Dietary fatty acids and their esters, as well as those taken orally as supplements, are converted into an emulsion by churning in the stomach, and transported in this form into the small intestine. In order to be absorbed through the wall of the enterocytes in the small intestine, the omega-3 polyunsaturated fatty acid products must be converted into a suitable form. The triglycerides found in fish oil cannot be directly absorbed by the enterocytes, so must first be hydrolyzed by the action of pancreatic lipase. This removes the fatty acids in the 1- and 3-positions, giving free fatty acid and the 2-monoglyceride, which can be absorbed through the enterocyte cell wall. The omega-3 fatty acid ethyl esters, on the other hand, require an additional pancreatic enzyme, bile salt-dependent pancreatic lipase, for hydrolysis before they can be absorbed by the enterocytes. This is a slower process, which explains the lower bioavailability of the ethyl esters compared with other forms of omega-3. AvailOm®, after rapid dissociation into free fatty acid and lysine, can be directly absorbed by the enterocytes, giving it a much higher level of bioavailability. It has been found that the efficiency of absorption of omega-3 fatty acids is also dependent on the diet; a high fat diet taken together with the omega-3 supplement increases the production of pancreatic lipase, so that all types of omega-3 products exhibit a higher availability. On the other hand, a low fat diet reduces the bioavailability of products requiring pancreatic lipase for hydrolysis, particularly the ethyl esters[10].

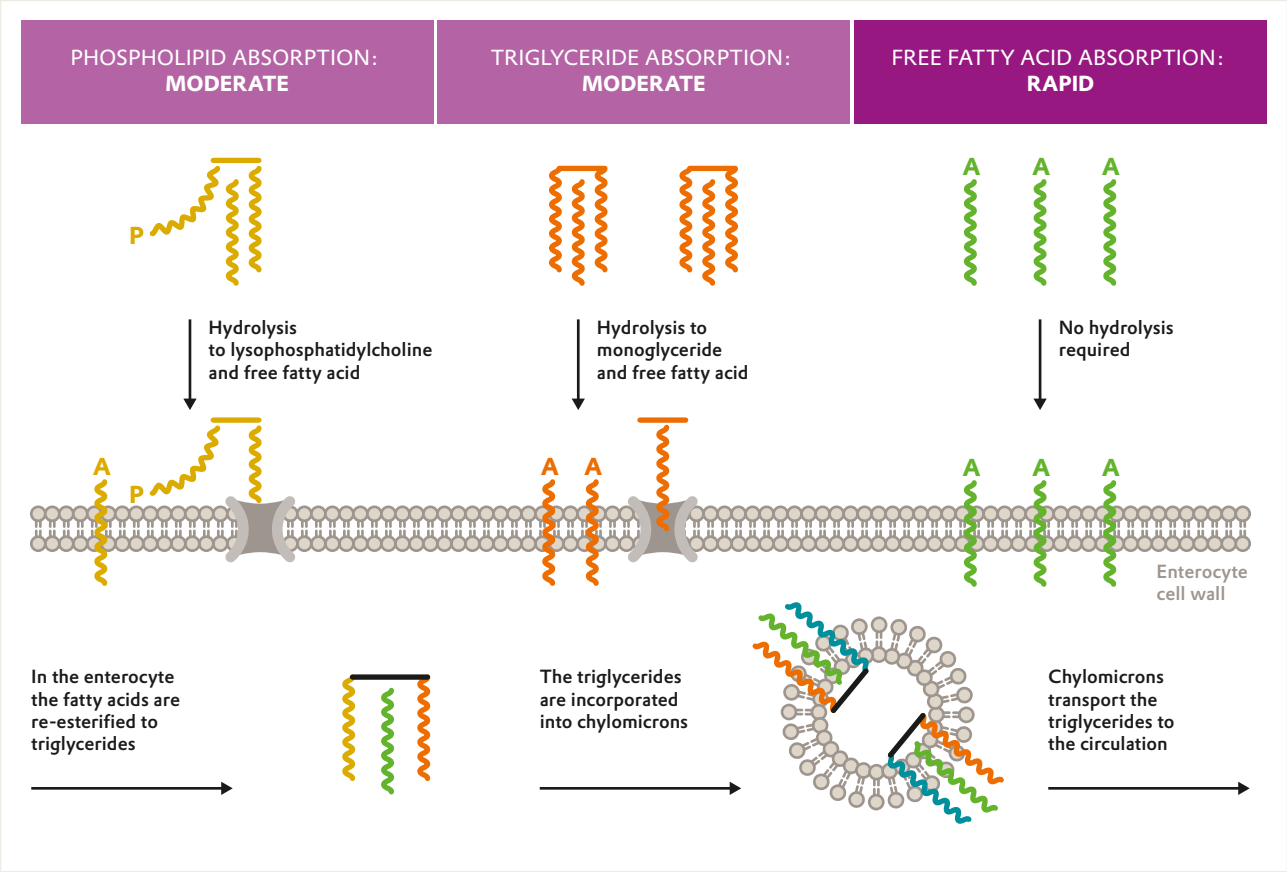


Figure 7. Comparison of the absorption of the main omega-3 products from krill oil and from fish oil

Once absorbed into the enterocytes in the gut, the further metabolism of the omega-3 fatty acids is the same, and is independent of the source of the omega-3. The fatty acids are re-esterified to triglycerides, which are then incorporated into chylomicrons, which is the form that the triglycerides are transported into the general circulation. The omega-3 fatty acids are transported in the blood to the target tissues where they are incorporated into cell membranes, for example, in heart muscle, in the brain and nervous system and in the retina[4]. They are responsible for several cellular functions including cell membrane structure and fluidity, and cell-to-cell interaction and signaling.

Compared with fish oil, krill oil has a different make-up of its fatty acids. Although some of the fatty acids are present as triglycerides, as in fish oil, about 40 % of the total fatty acids have been found to be in phospholipids, the most common of which is phosphatidylcholine, and about 20 % of the EPA and DHA have been observed to be present as free fatty acids[11,12]. In the small intestine, the phospholipids are hydrolyzed by pancreatic lipases at the 2-position to give a free fatty acid and lyso-phosphatidylcholine, which can be absorbed by the enterocytes as part of mixed micelles (Figure 7)[11]. Phospholipids are seen to be essential for the formation of mixed micelles and, because of their increased hydrophilicity, may increase the binding of digestive enzymes and the rate of hydrolysis of other lipids. AvailOm® is made from material derived from fish oil rather than krill oil, and does not contain phospholipids. However the process used for manufacture of AvailOm® from fish oil would also be applicable to krill oil as an alternative raw material.

Bioavailability of the different forms of omega-3

Bioavailability studies on the various forms of omega-3 fatty acids have been conducted both in animals and in humans. A review by Ghasemifard[13] summarizes the results of animal studies, while a review by Schubert[4] together with the Ghasemifard review[13] describe the various human trials which have been published. Compared with the extensive work that has been performed in humans, the animal studies are not good predictors of the bioavailability of the various forms of omega-3 fatty acids.

The reviews on bioavailability[4,13] describe 18 and 17 human studies, respectively, with the earliest dating from 1987. Many of these studies look at differences between the types of fish oil used, or compare the ethyl ester and triglyceride forms only. Six of the human trials also include the omega-3 free fatty acid in the comparison, and four of these provided sufficient data to be considered in more detail.

The first such study is by El Boustani[14], which compares different forms of EPA (Figure 8). These are the triglyceride (TAG), the ethyl ester (EE), the free fatty acid (FFA) and the arginine salt (Arg). This is the only human trial which compares an omega-3 free fatty acid with the amino acid salt of the same fatty acid. The trial was performed with a small group of 24 subjects. As shown in Figure 8, the absorption peaks at 3 – 5 hours after ingestion of a single dose of the omega-3 product. The curves for the free acid and the arginine salt are roughly similar, demonstrating that the arginine salt is rapidly dissociated in the body and is absorbed in the same way as the free fatty acid. The bioavailability of the free fatty acid and the arginine salt is 30–35 % above that of the triglycerides, and 3 times that of the ethyl ester, which is absorbed very sluggishly.

The second study is by Lawson[15], who compared the absorption of EPA as the triglyceride, the ethyl ester and the free fatty acid. There were 8 subjects in each group, who received single doses of the omega-3 product, and were monitored over 8 hours. Again the maximum absorption was reached after 5 hours (Figure 8). The free fatty acid was shown to have the highest bioavailability, being 3.1 times that of the ethyl ester and 40 % higher than that of the triglyceride fish oil.

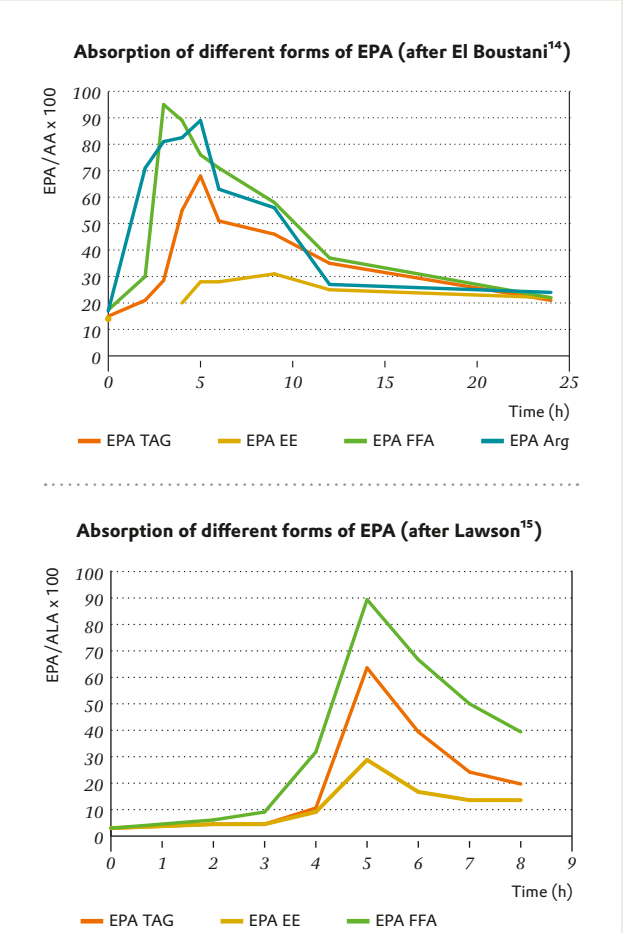


Figure 8. Bioavailability trials of different forms of omega-3 in humans[14,15].

In a third study, Beckermann[16] compared triglyceride, ethyl ester and the free fatty acid. The study involved 8 adult females, who all consumed a low fat diet together with a single dose of omega-3. The peak absorption of both EPA and DHA for the free fatty acid was more than twice that of the ethyl ester, and was also considerably higher than that of the triglyceride (Figure 9). Peak absorption was reached in about 6 hours. To get a better picture of the overall bioavailability, the authors also calculated the areas under the curves in Figure 9 to determine the total amount of omega-3 absorbed. For both EPA and DHA, this showed that the total bioavailability of the omega-3 taken as free fatty acid was >4 times higher than that of the ethyl ester and 80 % higher than that of the triglyceride.

The final trial was conducted as a study of the effect of two pharmaceutical forms of omega-3 on hypertriglyceridemia in a group of 54 overweight men and women[10]. The products tested were pharmaceutical grade omega-3 containing both EPA and DHA either in the form of the ethyl ester (Lovaza®) and the free fatty acid (Epanova®). The omega-3 product was given as a single 4 g dose, and the subjects were monitored over 24 hours. The trial was performed with the subjects on either a low fat or a high fat diet during the 24 hours of the study. As this was a four-way crossover trial, all the participants were subjected to each product/diet in turn. The results for the low fat diet and for the high fat diet are shown in Figure 10.

The charts show a clear effect of diet on the absorption of omega-3. The peak absorption rate is reached after 5 hours, in line with other studies. In each case the maximum absorption rate of the free fatty acid is higher than that of the ethyl ester. For the low fat diet, the peak absorption of the free fatty acid is 5 times that of the ethyl ester, while for the high fat diet, the peak absorption is 50 % higher. In both cases the peak absorption was also higher for the high fat diet. For the free fatty acid, the peak absorption was 2.5 times higher than with the low fat diet, while for the ethyl ester, the peak absorption was 10 times higher in the high fat diet. The total amount of omega-3 absorbed was calculated from the area under the curves. For the high fat diet, the free fatty acid had a bioavailability 30 % higher than the ethyl ester, while for the low fat diet, the bioavailability of the free fatty acid was 4 times higher than that of the ethyl ester.

The results from the Beckermann and Davidson studies can be explained by the more rapid absorption of the free fatty acid from the gut. The ethyl ester requires the provision of pancreatic lipases for hydrolysis before absorption, and these are produced in larger quantities in conjunction with a high fat meal, so that more ethyl ester is hydrolyzed and absorbed. In the case of the low fat diet, more of the omega-3 ethyl ester is excreted before hydrolysis and absorption. It is interesting, however, that the provision of a high fat diet also enhances the absorption of the free fatty acid, both the peak amount and also the total absorption over 24 hours (60 % higher total absorption of free fatty acid when accompanied by a high fat diet). As omega-3 supplements are often consumed together with a low fat diet in order to reduce triglyceride and cholesterol levels, or as part of a weight loss program, then the results presented here regarding the improved omega-3 absorption of the free fatty acid in conjunction with a low fat diet are particularly important.

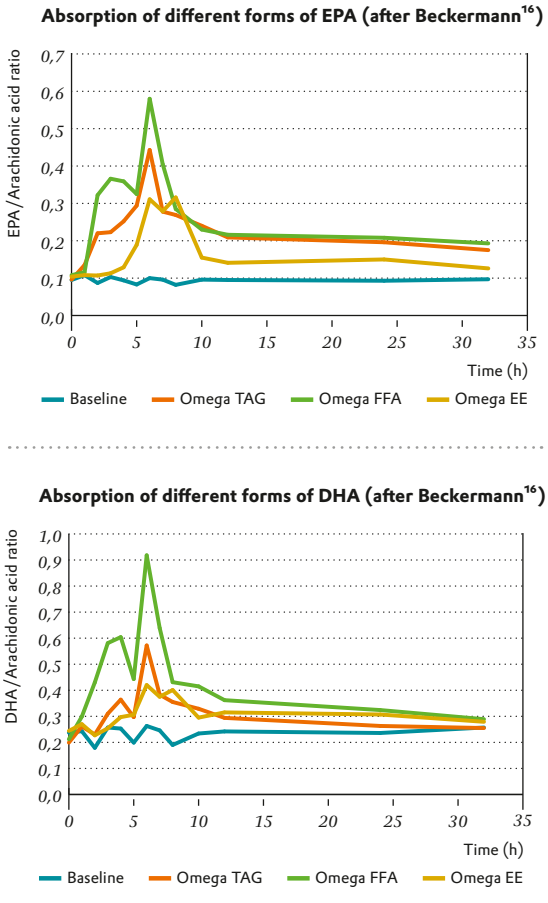


Figure 9. Bioavailability of different forms of EPA and DHA[16]

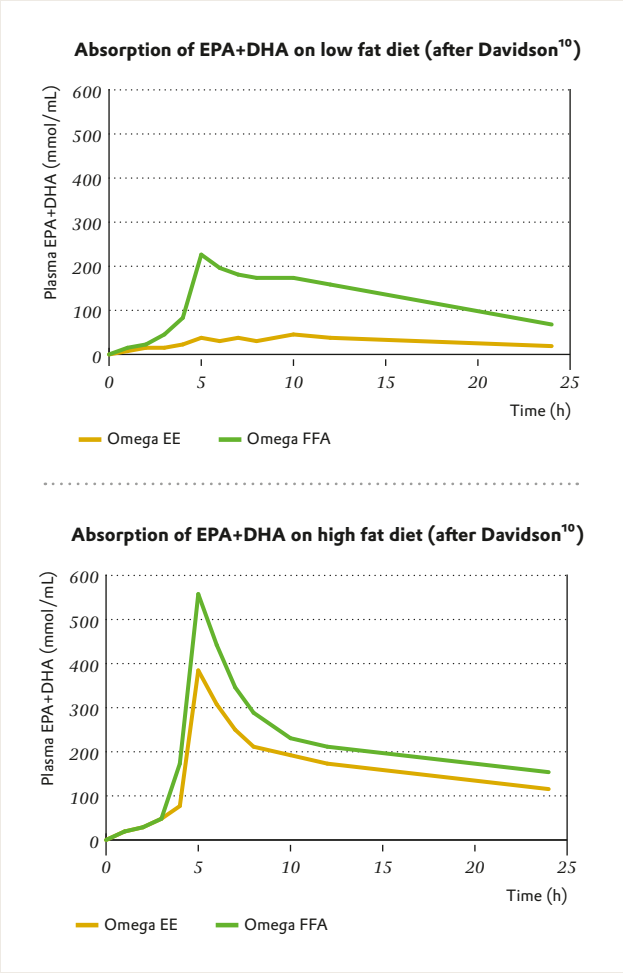


Figure 10. Differential absorption of different forms of omega-3 as a function of diet[10]

The authors of the study also reported on a phase 2b open label clinical trial of the free fatty acid product, compared with literature results already published on the ethyl ester product (52 weeks at 4 g omega-3 product / day). In both the ethyl ester and free fatty acid cases, the EPA level in blood plasma had stabilized by week 16. In the free fatty acid trial group the EPA levels increased 351 % from baseline, compared with an increase of 163 % from baseline in the published ethyl ester trial data[14].

Studies conducted with krill oil:

No human studies have been reported where the bioavailability of krill oil has been compared with that of the free fatty acid. However several studies have been published where krill oil has been compared with triglycerides and ethyl ester derived from fish oil. Schuchardt[11] gave a group of 12 men either refined omega-3 triglycerides, omega-3 ethyl ester or krill oil (each containing 2 g total omega-3 fatty acids) and followed the absorption by measuring the increase in EPA and DHA in plasma phospholipids over 72 hours (see Figure 11). The absorption peaked later than in the trials reported above, but this could be because the measurements were made on the phospholipids in plasma.

The results showed that the absorption of krill oil was more efficient than the triglycerides which in turn was more efficient than the ethyl ester. This study could only give a general ranking, because of the large error bars in the data.

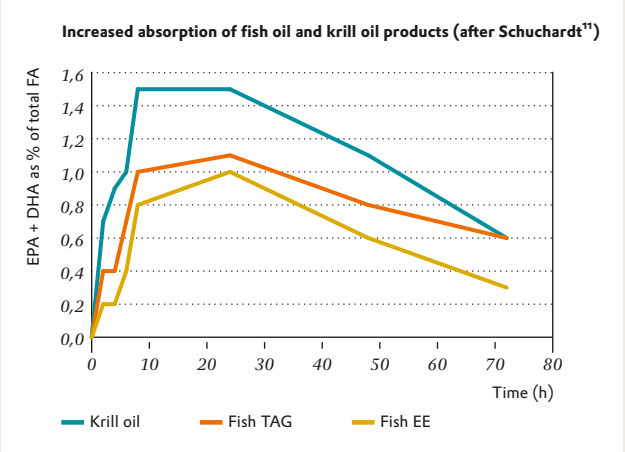


Figure 11. Comparison of fish oil and krill oil omega-3 absorption[11].

A larger scale study was reported by Yurko-Mauro[17], who performed a repeated dose trial with 66 subjects over 28 days. The participants received 1.3 g / day EPA + DHA, either in the form of fish oil triglycerides, fish oil ethyl ester, or krill oil. After 28 days the mean plasma levels of EPA + DHA were in the order krill oil > triglycerides > ethyl ester, but the authors did not consider the difference to be statistically significant. In addition the authors point out that the relative levels of triglycerides and phospholipids in krill oil can vary widely, depending on the source and the diet of the krill (phytoplankton or zooplankton). It should also be noted that krill oil contains less EPA and DHA than fish oil, and therefore the dose has to be higher to achieve the same intake of omega-3 fatty acids. No studies have been performed to compare krill oil with free omega-3 fatty acids or with amino acid complexes such as AvailOm®. However the data available suggest that AvailOm® and free fatty acids will both have a much higher level of availability than krill oil, up to 3 – 5 times higher on the basis of the human study results presented above. In addition, AvailOm® contains a much higher level of omega-3 fatty acids compared with krill oil.

Applications of AvailOm® and omega-3 fatty acids:

Numerous trials have been reported on the health effects of omega-3 fatty acids and fish oils containing omega-3 fatty acids. Details of individual studies can be found in recent reviews[18,19]. Some of the areas where there is clear evidence of a positive effect are discussed below. Only some of these effects have been acknowledged by the European Food Standards Agency (EFSA) and nine health claims for the omega-3 fatty acids EPA and DHA have been approved. Other health claims for additional proposed effects have been submitted to EFSA but have been rejected.

Approved EFSA Health Claims for omega-3 fatty acids:

- DHA contributes to the maintenance of normal vision[20,21].
- DHA contributes to the maintenance of the normal brain function[20,21].
- EPA and DHA contributes to the normal function of the heart[21,22].
- DHA contributes to the maintenance of normal blood triglycerides level[20].
- DHA and EPA contributes to the maintenance of normal blood pressure[22].
- DHA and EPA contributes to the maintenance of normal blood triglycerides level[22].
- Docosahexaenoic acid (DHA) maternal intake contributes to the normal development of the eye of the foetus and breastfed infants[23]
- Docosahexaenoic acid (DHA) maternal intake contributes to the normal brain development of the foetus and breastfed infants[23]
- Docosahexaenoic acid (DHA) intake contributes to the normal visual development of infants up to 12 months of age[23]

These claims may be used only for foods which contain a certain minimum amount of DHA or EPA and DHA. The conditions of use of each claim are laid down in Regulations (EU) No 432/2012 and No 440/2011.

Qualified FDA Health Claim for omega-3 fatty acids:

- Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of [Name of the food] provides [ ] gram of EPA and DHA omega-3 fatty acids[24].

See www.fda.gov for conditions of use for qualified health claims for EPA and DHA.

Recommended dietary intake of omega-3 fatty acids:

EFSA and the United Nations Food and Agriculture organization (FAO) have recommended minimum dietary intake for the omega-3 fatty acids EPA and DHA. For adults the recommendation is a minimum of 0.25 g/day EPA+DHA. For pregnant females, an additional 0.1 – 0.2 g/day DHA is recommended[19,25.26].

EFSA has also considered a maximum daily intake for omega-3 fatty acids[27]. It was decided that there was insufficient information to recommend a maximum daily intake, but found that consumption of EPA + DHA up to 5 g/day, EPA alone up to 1.8 g/day and DHA alone up to 1 g/day had not produced adverse health effects in reported trials[27]. Similar recommendations have been made by the Global Organization for EPA and DHA Omega 3s (GOED). They recommend 0.5 g/day EPA + DHA for the general population, 0.7 – 1.0 g/day for pregnant or lactating women, and >1 g/day for high risk groups (e.g. with high blood pressure)[28]. The American Heart Association recommends 1 g/day EPA + DHA for those with a history of heart disease, while the FDA recommends that supplements should not exceed 2 g/day EPA + DHA[24].

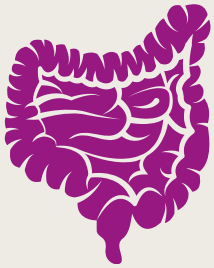
Effects on cardiovascular health:

The effects of omega-3 fatty acids in both preventing cardiovascular disease, and in reducing the severity of effects in people who already have cardiovascular disease, have been extensively reported, and meta-analyses have aggregated data from multiple studies including more than 400,000 participants. The main protective effect of the omega-3 fatty acids is via reduction of plasma triglycerides, and trials have shown particular efficacy in reducing high levels of dyslipidemia. Additional effects of omega-3 fatty acids have been found to be a reduction in blood pressure and a reduction in inflammation[18]. These are all risk factors for atherosclerosis. In people who already have a history of cardiovascular disease, there is some evidence of a protective effect (measured in terms of a reduced incidence of death from myocardial infarction), but other trials have failed to reproduce these results. The protective effect of omega-3 fatty acids here are believed to be a lower heart rate and reduced incidence of heart arrhythmia, an anti-inflammatory effect and an anti-thrombotic effect[18,29]. Related to the effects on cardiovascular health is the action of omega-3 fatty acids in the prevention and treatment of obesity and metabolic syndrome[29]. Obesity is associated with an increased risk of developing hypertension, insulin-resistance and dyslipidemia. The consumption of omega-3 fatty acids has been shown to have an effect on reducing insulin-resistance and triglyceride levels, but the evidence of an effect on insulin sensitivity is not convincing.

Effects on cognitive health:

The main omega-3 fatty acid found in the brain and in the retina of the eye is DHA. DHA is important for neurotransmission and neuronal membrane stability[18]. It is required for the rapid brain growth which occurs in later pregnancy and in the first year of life, and is transmitted to the infant via the placenta and breast milk. Supplementation of DHA has been recommended for women during pregnancy and breastfeeding, although the evidence for improved cognitive development in the infant is not conclusive.

There is increasing evidence that omega-3 fatty acids, and particularly DHA, are essential for maintaining a healthy brain throughout life[18,30,31]. Animal and human studies have indicated that omega-3 fatty acids may protect against brain aging by reducing neuronal inflammation, oxidative damage and vascular aging[31]. Inflammation, mitochondrial dysfunction and oxidative damage are also factors in both cognitive decline and Parkinson's disease. There have been no clinical trials for omega-3 fatty acid for Parkinson's, but positive effects have been found in trials to improve memory and learning in cognitively healthy subjects and those with a mild cognitive impairment[30]. Low levels of omega-3 fatty acids are found in children with attention deficit/hyperactivity disorder (ADHD). A review of 25 studies on the effect of supplements of omega-3 fatty acids on ADHD concluded that they had a positive effect on the condition, particularly in patients with mild forms of the condition[32]. The effect of omega-3 supplementation on other mental disorders has also been reported. Omega-3 fatty acids, and in this case particularly EPA, have been shown to have a positive effect on major depressive disorder, other types of depression, and bipolar disorder[33,34]. The omega-3 supplements may act as an adjuvant when given alongside conventional anti-depressant medication. The use of DHA has also been recommended for use in the treatment of mild traumatic brain injury (concussion)[35].



Effects on inflammatory disease:

As well as an anti-inflammatory effect in cardiovascular disease, where chronic low-grade inflammation is a contributory factor, omega-3 fatty acids have been applied in a wide range of other conditions where inflammation is the main response. These include rheumatoid arthritis, inflammatory bowel disease and asthma, among others. EPA and DHA in particular have been shown to influence inflammatory processes such as leukocyte migration and the production of inflammatory cytokines. This is in contrast to the omega-6 fatty acid arachidonic acid, which is the precursor for pro-inflammatory eicosanoids[18]. The effect of omega-3 fatty acids has been most studied in rheumatoid arthritis. The omega-3 compounds EPA and DHA decrease the arachidonic acid content of cells involved in immune responses, and also are precursors for the anti-inflammatory and inflammation-resolving compounds known as resolvins. A review of human studies has shown a consistent but modest benefit of omega-3 fatty acids with respect to joint swelling and pain, duration of morning stiffness and the use of non-steroidal anti-inflammatory drugs[36]. A related inflammatory condition is systemic lupus erythematosus, where some reduction of symptoms has been observed after regular supplementation with omega-3 fatty acids[37].

As an adjuvant in cancer therapy:

A number of human trials have been conducted where omega-3 fatty acids have been used as an adjuvant to conventional chemotherapy[18,38,39]. These have been based on the knowledge of the anti-inflammatory properties of the omega-3 fatty acids, and mechanisms have been proposed by which the omega-3 compounds can affect tumor cell proliferation, invasion and metastasis[39]. Long term dietary studies on populations who consume a fish-rich diet have found a lower incidence of cancer, particularly those cancers which are linked to inflammation[38]. As well as direct effects on the cancer treatment, such as lower remission rates, and a better tolerance of chemotherapy, which have been observed using either DHA, EPA, or a mixed omega-3 fatty acid product, improvements have been observed in other areas. The level of weight loss (cachexia) observed with some cancers, can be reduced or, in some cases, an increase in weight was observed. In some of the trials, patients reported a better quality of life, including less fatigue, a reduction of pain or a reduction in nausea/vomiting[38,39].

References

1. Ciriminna R, Meneguzzo F, Delisi R, Pagliaro M, Enhancing and improving the extraction of omega-3 from fish oil, *Sustainable Chemistry and Pharmacy*, 2017, **5**, 54

2. Sahena F, Zaidul ISM, Jinap S, Saari N, Jahurul HA, Abbas KA, Norulaini NA, PUFAs in Fish: extraction, fractionation, importance in health, *Comprehensive Reviews in Food Science and Food Safety*, 2009, **8**, 59

3. Dyerberg J, Madsen P, Møller JM, Aardestrup I, Schmidt EB, Bioavailability of marine n-3 fatty acid formulations, *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 2010, **83**, 137

4. Schuchardt JP, Hahn A, Bioavailability of long-chain omega-3 fatty acids, *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 2013, **89**, 1

5. Shahidi F, Wanasundara UN, Omega-3 fatty acid concentrates: nutritional aspects and production technologies, *Trends in Food Science & Technology* 1998, **9**, 230

6. Rubio-Rodríguez N, Beltrán S, Jaime I, de Diego SM, Sanz MT, Carballido JR, Production of omega-3 fatty acid concentrates: A review, *Innovative Food Science and Emerging Technologies,* 2010, **11**, 1

7. Tou JC, Jaczynski J, Chen Y-C, Krill for human consumption: Nutritional value and potential health benefits, *Nutrition Reviews*, 2007, **65**, 63

8. Evonik Industries AG, unpublished results

9. EFSA, Scientific Opinion, *EFSA Journal*, 2012, **10**, 2815

10. Davidson MH, Johnson J, Rooney MW, Kyle ML, Kling DF, A novel omega-3 fatty acid formulation has dramatically improved bioavailability during a low-fat diet compared with omega-3-acid ethyl esters: The ECLIPSE (Epanova® compared to Lovaza® in a pharmacokinetic single-dose evaluation) study, *Journal of Clinical Lipidology*, 2012, **6**, 573

11. Schuchardt JP, Schneider I, Meyer H, Neubronner J, von Schacky C, Hahn A, Incorporation of EPA and DHA into plasma phospholipids in response to different omega-3 fatty acid formulations – a comparative bioavailability study of fish oil vs. krill oil, *Lipids in Health and Disease*, 2011, **10**, 145

12. Burri L, Hoem N, Banni S, Berge K, Marine omega-3 phospholipids: metabolism and biological activities, *International Journal of Molecular Sciences*, 2012, **13**, 15401

13. Ghasemifard S, Turchini GM, Sinclair AJ, Omega-3 long chain fatty acid "bioavailability": a review of evidence and methodological considerations, *Progress in Lipid Research*, 2014, **56**, 92

14. El Boustani S, Colette C, Monnier L, Descomps B, Craste de Paulet A, Mendy F, Enteral absorption in man of eicosapentaenoic acid in different chemical forms, *Lipids*, 1987, **22**, 711

15. Lawson LD, Hughes BG, Human absorption of fish oil fatty acids as triacylglycerols, free acids, or ethyl esters, *Biochemical and Biophysical Research Communications*, 1988, **152**, 328

16. Beckermann B, Beneke M, Seitz I, Vergleich der Bioverfügbarkeit von Eicosapentaensäure und Docosahexaensäure aus Triglyceriden, freien Fettsäuren und Ethylestern bei Probanden, *Arzneimittel Forschung*, 1990, **40**, 700

17. Yurko-Mauro K, Kralovec J, Bailey-Hall E, Smeberg V, Stark JG, Salem Jr N, Similar eicosapentaenoic acid and docosapentaenoic acid plasma levels achieved with fish oil or krill oil in a randomized double-blind four-week bioavailability study, *Lipids in Health and Disease*, 2015, **14**, 99

18. Calder PC, Very long chain omega-3 (n-3) fatty acids and human health, *European Journal of Lipid Science and Technology*, 2014, **116**, 1280

19. Calder PC, Omega 3: The good oil, *Nutrition Bulletin*, 2017, 42, 132

20. EFSA, Scientific Opinion, *EFSA Journal*, 2010, **8**, 1734

21. EFSA, Scientific Opinion, *EFSA Journal*, 2011, **9**, 2078

22. EFSA, Scientific Opinion, *EFSA Journal*, 2010, **8**, 1796

23. *Official Journal of the European Union*, L 119/4, 07.05.2011

24. FDA, Guidance for Industry: A Food Labelling Guide (12. Appendix D: Qualified Health Claims), 2013

25. **New #25:** EFSA, Scientific opinion on dietary reference values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids and cholesterol. EFSA Journal, 2010, 8, 1461.

26. **New #26:** FAO-WHO, Fats and Fatty Acids in Human Nutrition. Rome: FAO Food and nutrition paper # 91. Report of an expert consultation. FAO Food Nutr Pap 2010:91:1-166

27. EFSA, Scientific Opinion, *EFSA Journal*, 2012, **10**, 2817

28. GOED, Intake recommendations, www.goedomega3.com/industry

29. Lorente-Cebrían S, Costa AGV, Navas-Carretero S, Zabala M, Martinez JA, Moreno-Aliaga MJ, Role of omega-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases: a review of the evidence, *Journal of Physiological Biochemistry*, 2012, **69**, 633

30. Denis I, Potier B, Heberden C, Vancassel S, Omega-3 polyunsaturated fatty acids and brain aging, *Current Opinion in Clinical Nutrition*, 2015, **18**, 139

31. Dyall SC, Long-chain omega-3 fatty acids and the brain: a review of the independent and shared effects of EPA, DPA and DHA, *Frontiers in Aging Neuroscience*, 2015, **7**, 52

32. Königs A, Kiliaan AJ, Critical appraisal of omega-3 fatty acids in attention-deficit/hyperactivity disorder treatment, *Neuropsychiatric Disease and Treatment*, 2016, **12**, 1869

33. Martins JG, EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials, *Journal of the American College of Nutrition*, 2009, **28**, 525

34. Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, Drago F, Caraci F, Role of omega-3 fatty acids in the treatment of depressive disorders: A comprehensive meta-analysis of randomized clinical trials, *PLoS ONE*, 2014, **9**, e96905

35. Bailes JE, Patel V, The potential for DHA to mitigate mild traumatic brain injury, *Military Medicine*, 2014, **179**(11), S112

36. Miles EA, Calder PC, Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis, *British Journal of Nutrition*, 2012, **107**, S171

37. Curado Borges M, Moura Santos FdM, Weiss Telles R, Davisson Correira MIT, Duarte Lanna CC, Polyunsaturated omega-3 fatty acids and systemic lupus erythematosus: what do we know? *Revista Brasiliera de Reumatologia*, 2014, **54**, 459

38. Vaughan VC, Hassing M-R, Lewandowski PA, Marine polyunsaturated fatty acids and cancer therapy, *British Journal of Cancer*, 2013, **108**, 486

39. Merendino N, Constantini L, Manzi L, Molinari R, D'Eliseo D, Velotti F, Dietary omega-3 polyunsaturated fatty acid DHA: A potential adjuvant in the treatment of cancer, *BioMed Research International*, 2013, 310186

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