# Krill Phospholipid Omega-3s

- Healthy Cells, Healthy Tissues, Healthy Body





### **KRILL OIL: THE POWER OF 4**

By Lena Burri, Ph.D.

KRILL EXIST IN EVERY OCEAN AROUND THE GLOBE, representing the largest biomass on Earth. They are very small (about the size of a small paper clip) and have a shrimp-like appearance, with big black eyes and a reddish, semi-transparent shell (see Figure 1).

Antarctic krill (*Euphausia superba*) live in huge swarms and feed on microscopic algae in the icy cold waters of the Southern Ocean. They feed on marine algae that produce omega-3 fatty acids – eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) – accumulating these fatty acids in their eggs and body. Thus, these omega-3 fatty acids can be extracted in oil, carrying with them other beneficial components such as phospholipids, choline and astaxanthin. It is this powerful combination of elements that makes krill oil unique in the omega-3 market (*see Table 1*).

In krill oil the majority of the omega-3 fatty acids are bound to a particular type of fat called a phospholipid, whereas in other marine oils these omega-3 fatty acids are bound to other forms of fat – usually triglycerides or ethyl esters. This compositional difference is significant because it dictates how these fats are incorporated in tissues and used by the body.

When omega-3 fatty acids are delivered in triglyceride form some of the beneficial omega-3 fatty acids are burned as energy or stored in the body's fat reserves. As a result, the dosage must be large enough to compensate for that loss to ensure that sufficient amounts of these fatty acids are available at the cellular level. In contrast, phospholipids are immediately available to the cells because they are key components in all cell membranes.

Recent human clinical studies have shown that when compared with triglyceride omega-3 fatty acids, less phospholipid-bound omega-3 fatty acids are required to reach equal accumulation in the body's cells and organs. Additionally, due to the structure of the phospholipids themselves, they are able to mix with water unlike other fats (*see Figure 2, next page*). This means krill oil is dispersible in the stomach fluids.



"Antarctic krill (Euphausia superba) live in huge swarms and feed on microscopic algae in the icy cold waters of the Southern Ocean."

Krill Oil Ingredients	Characteristics		
1) Omega-3 Fatty Acids (EPA & DHA)	<ul> <li>A particular class of fatty acids that are the building blocks of fat</li> <li>Recognized health benefits documented in more than 20,000 publications</li> <li>Benefit the heart, joints, brain, skin, and eyes</li> </ul>		
2) Phospholipids	<ul> <li>A lipid consisting of a phosphate and glycerol group and two fatty acids</li> <li>The best delivery form of EPA and DHA</li> <li>Represent the building blocks of cell membranes</li> <li>Help improve the uptake and diges- tion of omega-3 fatty acids</li> </ul>		
3) Choline	<ul> <li>An essential nutrient</li> <li>A biochemical building block important for liver, heart, and cognitive health</li> </ul>		
4) Astaxanthin	<ul> <li>A carotenoid with potent antioxidant properties</li> <li>Protects the omega-3 fatty acids in krill oil from oxidation, keeping them naturally fresh and stable over time – i.e., a natural preservative</li> </ul>		







### ANTARCTIC KRILL, *Euphausia superba*

The unique properties of krill and the oil extracted from it depend on the ecosystem in which it lives, what it feeds on, and how it is harvested. Today, there are more than 80 different known krill species. Among these, Antarctic krill is the only kind that can be fished because it lives in large swarms and swims in open water.

Krill swarms can be as long as six kilometres (approx. 3 miles) in length and have a density of up to one million individuals per cubic meter (approx. 35 cubic feet) [1]. Antarctic krill are low on the food chain, so they don't consume and therefore accumulate heavy metals and contaminants to the degree that other marine species do (i.e., fish). Further, the relatively sparse commercial activity in the Southern Ocean significantly contributes to the purity of krill's environment.

*Euphausia superba* is the longest krill species with a maximum body length of six centimeters (approx. 2 ¼ inches) and a lifespan of five to six years. At first glance, krill look similar to shrimp, as both creatures have a hard,

protective external skeleton. But unlike shrimp, krill have external gills and extremely active digestive enzymes [2]. Krill get bigger by molting, periodically discarding their shell to allow growth while the new shell is still soft.

Krill never touch the ocean bottom like crabs and lobsters do. They constantly move up and down in the ocean, often in columns, searching for algae at night in shallow waters and hiding from predators by day in deep water. They are also filter-feeders, which means they feed by passing water through specialized filtering structures to extract algae. Krill's six front legs and stiff hairs on the inner side are responsible for collecting these microscopic algae from the water and transferring it to the mouth. Krill do not have the ability to build up large fat deposits, so they survive in the winter on algae that grows on the underside of pack ice. Besides serving as a food source, the ice also provides protection from predators and commercial harvesting, thus allowing enough time for the krill population to recover from the summer season when most harvesting activity takes place.

### 1) OMEGA-3 FATTY ACIDS

The omega-3 fatty acids EPA and DHA are polyunsaturated fatty acids that are crucial for maintaining and improving cellular health. They are referred to as polyunsaturated because they contain more than one double bond that is "unsaturated" with hydrogen atoms. Unsaturated fatty acids are grouped into different classes depending on the position of the first double bond from the methyl end of the fatty acid chain. Hence, omega-3 fatty acids have their first double bond at three carbon atoms and omega-6 fatty acids at six carbon atoms from their methyl end. (See Figure 3, next page) The

precursors for omega-3 fatty acids ( $\alpha$ -linolenic acid, ALA) and omega-6 fatty acids (linoleic acid, LA) are not manufactured by the human body and must be obtained through the diet. The human body can convert ALA into the longer-chain fatty acids, EPA and DHA, but only at a low rate [3-5]. EPA consists of 20 carbons and five double bonds and can be converted into DHA. DHA is the longest fatty acid chain, with 22 carbons and six double bonds. The main product of the omega-6 precursor LA is called arachidonic acid (AA) and consists of 20 carbons and four double bonds.



Both omega-3 and omega-6 fatty acids are needed for optimal health. For example, deficient states of the omega-6 fatty acid arachidonic acid are associated with abnormal liver pathology, reduced growth and reproductive failure, as well as skin and hair problems [6]. However, since the Western diet is abundant in omega-6 fatty acids and relatively deficient in omega-3 fatty acids, the balance between the two is highly disturbed [7,8].

The high prevalence of omega-6 fatty acids is directly related to the overconsumption of vegetable oils rich in these fatty acids, which are typically present in corn, sunflower seeds, cottonseed, and soybeans, as well as industrially produced meat. At the same time, the consumption of omega-3-rich fish has decreased markedly during the last several decades. Because of this fatty acid imbalance, most consumers are living in a state of chronic inflammation, which might help explain the rise in diseases such as asthma, coronary heart diseases, many forms of cancer, and neurodegenerative diseases such as Alzheimer's. It may also contribute to arthritis, allergies, obesity, depression, dyslexia, diabetes, hyperactivity, inflammatory disorders and even violent tendencies.

Today, the ratio between omega-6 and omega-3 fatty acids can be as high as 10-20:1, whereas historically it was as low as 1-2:1 [9]. Most recent recommendations call for a ratio of 5:1 [10]. (See Table 2)

Striking the right balance between omega-6 and omega-3 fatty acids is essential for health. This is because omega-6 fatty acids produce too many pro-inflammatory molecules that can lead to increased blood clotting, impaired immune response, and systemic inflammation. In addition, omega-6 and omega-3 fatty acids compete for the same enzymes to be converted into pro-inflammatory or anti-inflammatory hormones, respectively (*see Figure 4*).



• A minimum of 250 mg of marine omega-3 fatty acids (EPA/DHA) should be supplemented



#### FIGURE 3: Omega-3 & Omega-6 Chemistry



#### FIGURE 4: The Importance of Balancing Omega-6 & Omega-3 Fatty Acids





# The Omega-3 Index: A New Measure of Health & Disease

An important predictor of health and disease is the amount of omega-3 fatty acids incorporated into cells, tissues and organs. While it would be impossible to routinely take tissue biopsies from the body's organs just to check the omega-3 fatty acid content, red blood cells are constantly being rebuilt and are readily accessible. Based on this premise, researchers developed the Omega-3 Index as a way to measure omega-3 status [11].

The Omega-3 Index is defined as the combined EPA and DHA concentration as a percentage of total fatty acids in red blood cells, which correlates well with the amount of EPA and DHA in other tissues [12,13]. In fact, studies show that there is a linear correlation between the content of Omega-3 fatty acids in phospholipids of red blood cells and the content of omega-3 fatty acids in the heart [14]. This means that by measuring the Omega-3 Index in red blood cells, we can also determine the omega-3 fatty acids content in the heart [13]. In large, randomized intervention trials, increasing the intake of omega-3 fatty acids led to an increased Omega-3 Index and reduction of sudden cardiac death, fatal and non-fatal myocardial infarctions, and improved survival and symptoms in congestive heart failure, and other cardiovascular diseases [15].

Theoretically, the Omega-3 Index represents a person's overall EPA and DHA status because red blood cells



have a phospholipid membrane and incorporate omega-3 fatty acids into their membrane as other tissues do. For example, if there are 64 fatty acids in the red blood cell membranes and three are omega-3 fatty acids, then the Omega-3 Index is 3/64 or 4.6%. An Omega-3 Index below 4% is associated with an increased risk for cardiovascular diseases, whereas an Omega-3 index above 4% reduces the risk for heart disease. Similarly, a study investigating patients with stable coronary artery disease found that those with an Omega-3 Index above 4% had a 27% lower risk of death, compared to those with an Omega-3 Index below 4% [16].

Based on numerous investigations of cardiovascular risk, the ideal range for the Omega-3 Index lies somewhere between 8% and 12% [15] (*see Figure 5*). At values above 11%, however, studies indicate no further benefit in terms of risk reduction [15].

Beyond cardiovascular disease, a low Omega-3 Index has also been correlated with an increased risk for the development of depression [17,18], cognitive decline [19], sleep apnea [20], and osteoporosis [21]. Overall, the health impact of omega-3 fatty acids is substantial, and can be divided into six segments, including heart disease, central nervous system/behavior, metabolic disorder, immune function, cancer, and others (see Table 3).

TABLE 3: Omega-3 H	lealth Benefit Categorie	'S			
	Omega-3 Fatty Acids				
Heart Disease	Central Nervous System	Metabolic Disorders	Immune Function	Cancer	Other
<ul> <li>Angina pectoris</li> <li>Arrhythmia</li> <li>Arterial Fibrillation</li> <li>Atherosclerosis</li> <li>Congestive heart failure</li> <li>High blood pressure</li> <li>High cholesterol</li> <li>High triglycerides</li> <li>Post myocardial infarction</li> </ul>	<ul> <li>ADHD</li> <li>Agression</li> <li>Alzheimer's disease</li> <li>Bipolar disorder</li> <li>Dementia</li> <li>Depression</li> <li>Dyslexia</li> <li>Epilepsy</li> <li>Huntington's disease</li> <li>Learning disabilities</li> <li>Memory/Cognition</li> <li>Parkinson's disease</li> <li>Schizophrenia</li> <li>Stroke</li> </ul>	<ul> <li>Diabetes</li> <li>Fatty liver</li> <li>Obesity</li> <li>Weight loss / control</li> </ul>	<ul> <li>Allergy</li> <li>Arthritis / joint pain</li> <li>Asthma</li> <li>Back/neck pain</li> <li>Chronic bronchitis</li> <li>Cystic fibrosis</li> <li>Inflammation</li> <li>Inflammatory bowel syndrome</li> <li>Lupus</li> <li>Multiple Sclerosis</li> <li>Pancreatitis</li> <li>Periodontal disease</li> <li>Psoriasis</li> </ul>	<ul> <li>Breast cancer</li> <li>Cachexia</li> <li>Cancer (general)</li> <li>Cervial cancer</li> <li>Colon cancer</li> <li>Lung cancer</li> <li>Prostate cancer</li> </ul>	<ul> <li>Aging</li> <li>Athletics</li> <li>Bone mineral density</li> <li>Dry eye syndrome</li> <li>Eating disorders</li> <li>Eczema</li> <li>Emphysema</li> <li>Hearing loss due to age</li> <li>Infant development</li> <li>Low birth weight</li> <li>Low metabolism</li> <li>Menopause</li> <li>Menstrual cramps</li> <li>Osteroporosis</li> <li>Pregnancy</li> <li>Raynaud's disease</li> <li>Sperm fertility</li> <li>Substance abuse</li> <li>Sudden death</li> <li>Sunburn/burns</li> <li>Wrinkles</li> </ul>



### 2) THE POWER OF PHOSPHOLIPIDS

While triglycerides consist of three fatty acids bound to a glycerol backbone, phospholipids only have two fatty acids, which are bound to a phosphorus group that is further linked to a head group, such as choline (*see Figure 6*). The percentage of phospholipids in oil extracted from krill is typically 40-45%.

Omega-3 fatty acids in triglyceride form do not mix with the stomach contents and instead tend to float on the surface, creating reflux and an unpleasant aftertaste. Krill oil, on the other hand, immediately mixes with stomach fluids, reducing the chance of stomach discomfort and bad aftertaste, which is an advantage that is highly appealing to consumers.



According to a 2012 US consumer survey conducted by Discovery Research Group in partnership with Aker BioMarine, there are wide differences between the user experience with fish oil and krill oil. For this study, 705 supplement consumers generally interested in health and wellness were interviewed. Nearly 40% indicated that while they would like to take omega-3s, they would prefer something other than fish oil. When asked why, most respondents cited bad taste, bad aftertaste, fishy burps, bad smell, and large capsule size as the reasons. So for consumers who want to increase omega-3 fatty acids in their diet but do not tolerate fish oil well, krill oil is an ideal a alternative.

In addition to a superior user experience, studies have also shown that omega-3 fatty acids in phospholipid form result in better tissue accumulation when compared to the triglyceride form. In older rats, the incorporation of DHA was more than twice as high from phospholipids than from triglycerides in the brain, liver, and kidney. In the brain, DHA uptake was significantly higher in 11 out of 14 brain regions after phospholipid administration compared to triglyceride administration [22].

In a study with obese rats, researchers compared the effects of omega-3 fatty acids given a fish oil (omega-3 triglycerides) with krill oil (omega-3 phospholipids). Compared to fish oil, krill oil led to a significantly higher incorporation of the omega-3 EPA and DHA into tissue phospholipids [23]. In the heart, there was a 96% (EPA) and 42% (DHA) higher incorporation into the tissue of phospholipids after krill oil consumption compared to fish oil supplementation. Similar effects were observed in the liver, where the corresponding incorporation of EPA (+47%) and DHA (+13%) into phospholipids was higher after krill oil supplementation [23]. In another rat study, a significantly higher incorporation of DHA into rat brains after krill oil supplementation was also observed [24].

"Numerous studies in humans, such as the Framingham study, link low DHA levels in blood plasma to brain-related disorders like Alzheimer's disease."

Numerous studies in humans, such as the Framingham study, link low DHA levels in blood plasma to brain-related disorders like Alzheimer's disease, leading to the conclusion that DHA likely plays several protective roles in the brain [25,26]. Additionally, human studies have demonstrated that compared to triglycerides, phospholipids deliver DHA to red blood cells more efficiently [27].

In addition to the combined or complementary effects of omega-3 fatty acids bound to phospholipids, consumption of phospholipids and choline alone has



also been shown to have its own health advantages (see Table 4). Phospholipids containing choline (i.e., phosphatidylcholine) are especially important for brain and liver metabolism.

These studies performed with phospholipids did not include omega-3 fatty acids, thus indicating that these lipids have their own beneficial effects. However, other studies have demonstrated that phospholipid-bound omega-3 fatty acids yield superior effects on liver lipid and blood plasma lipid levels, when compared to phospholipids without omega-3 fatty acids [38,39].

Hence, a combination of both in one molecule seems to be the most efficient way of enhancing these health benefits.

#### TABLE 4: Health Benefits of Phosphatidylcholine

- Offsetting age-related changes [28]
- Reducing the effects of inflammatory diseases [29]
- Improving cognitive function [30]
- Improving plasma and liver lipid metabolism [31,32]
- Lowering plasma cholesterol and triglyceride levels [33]
- Increasing levels of HDL-cholesterol ("good" cholesterol) in humans [32]
- Lowering hepatic triglyceride levels [31]
- Protecting the liver against alcohol-related damage [34-36]
- Defending against liver fibrosis and alcoholinduced cirrhosis [37]

# **3) CHOLINE**

The fatty acid composition of the phospholipids in krill oil was recently described in two studies [40,41]. These found that the majority of EPA and DHA are contained in the phosphatidylcholine form [2,42]. Choline, the head-group of phospatidylcholine, is an essential human nutrient (see *Figure 7*).

In addition to being an important component of phospholipids, choline is also used by the body to produce acetylcholine, a neurotransmitter that is involved in neuronal networks associated with memory. This is important because aging decreases the availability of neurotransmitters like acetylcholine. Hence, it has been hypothesized by some researchers that supplementation of choline-containing compounds, such as phosphatidylcholine, might stimulate the production of acetylcholine and confer a possible beneficial impact on the central nervous system [43].

"Choline supplementation is especially important for vegetarians, vegans and people who over-consume alcohol, since these groups are known to have an elevated risk of choline deficiency."



Choline supplementation is especially important for vegetarians, vegans and people who over-consume alcohol, since these groups are known to have an elevated risk of choline deficiency. Choline deficiency not only increases the risk of developing liver dysfunction [37,44,45], but it could also interfere with memory [46]. Supplementation with choline has been shown to impact brain function when given to rats either before birth or during the second week after birth [47-52]. The long-lasting effect of choline administration on rodent spatial memory function seems to involve changes in the hippocampus [53-55]. There is also some evidence to suggest a high intake of choline might reduce the risk of breast and colorectal cancers [56-58].





# 4) ASTAXANTHIN

Astaxanthin is the antioxidant carotenoid that gives krill oil its deep red color (see Figure 8).

Astaxanthin is a very potent antioxidant with antiinflammatory properties and the ability to cross the bloodbrain barrier [59,60]. It can neutralize free radicals, which are unstable molecules that can damage cells and increase the risk for age-related diseases, cancer, and heart disease. Astaxanthin has been associated with protecting lipids and low-density lipoproteins (LDL) from oxidation [61,62]. Furthermore, research suggests that it might be beneficial for cardiovascular health because it increases the "good" HDL-cholesterol and lowers triglyceride levels in both animals and humans [59,60,63-65].



## SUPERBA™ Krill Oil Studies

Since studies have demonstrated that increased blood levels of EPA and DHA promote human health and prevent disease, the accumulation of these omega-3 fatty acids in the blood is therefore very important. Recently, two human intervention studies investigated if the molecular form (phospholipid vs triglyceride) of omega-3 fatty acids is of importance for EPA and DHA levels detected in blood plasma [66,37].

In a randomized, double-blind, parallel clinical trial, 76 overweight and obese men and women received either Superba<sup>™</sup> krill oil, fish oil, or olive oil for one month [66]. The daily amount of EPA was similar in the krill oil and fish oil group, but the DHA quantity was approximately half as much in the krill oil group compared to the fish oil group. Nevertheless, after 4 weeks of supplementation the researchers found that the plasma EPA concentrations were higher in the krill oil group compared to the fish oil group, while the average DHA concentrations from krill were similar to the fish oil group.

Both sources of omega-3 fatty acids were safe and welltolerated and significantly increased EPA and DHA levels in plasma as compared to the control group. But most important, krill oil supplementation (2 gram/day) resulted in increased plasma EPA levels as well as equal increases in DHA, but at half the dose in comparison to fish oil. Overall, after dose adjustment, the total increase of EPA and DHA in the plasma of the subjects who received Superba<sup>™</sup> krill oil was 24% higher after 4 weeks compared to subjects who received fish oil.

Another study found that a lower dose of EPA and DHA



from phospholipids compared to a higher dose of omega-3 fatty acids from triglycerides resulted in equal levels of these fatty acids in plasma [67]. In this study, 113 subjects with normal or slightly increased total blood cholesterol and/or triglyceride levels were randomized into three groups and given Superba™ krill oil, fish oil, or a placebo for 7 weeks. The daily supplementation of total EPA and DHA was approximately 37% less in the krill oil group than in the fish oil group. The results showed that dietary omega-3 administration led to a similar increase of plasma omega-3 fatty acids in both the krill and fish oil groups compared to the control group. After adjustment of EPA and DHA levels in the daily dose given, the results from the krill oil group suggested an impressive 45% higher total EPA and DHA plasma level than in the fish oil group after 7 weeks of administration (*see Figure 9*).



Moreover, the subjects with the highest baseline values of triglycerides further benefited from krill oil supplementation and showed decreased plasma triglyceride levels. Additionally, the HDL-cholesterol/triglyceride ratio, a risk factor for heart disease, was significantly improved in participants after Superba<sup>™</sup> krill oil but not after fish oil treatment.

A more detailed analysis of the effect of krill oil on hyperlipidemia was investigated in a recent clinical trial (*unpublished*). This study evaluated Superba™ krill oil's ability to lower triglycerides without raising LDL cholesterol in 300 subjects with borderline-high or high triglyceride levels.

During the trial, patients received supplements with various amounts of krill oil (0.5, 1, 2 or 4 g/day) and the control group received placebo (olive oil). Krill oil reduced the level of circulating triglycerides significantly, compared to placebo, without impacting LDL levels. Thus, study authors concluded from their findings that krill oil is effective in reducing cardiovascular risk factors important in the treatment of dyslipidemia.

Other clinical and pre-clinical studies showing krill oil's wide variety of health benefits have been published and some are currently under further investigation (see Tables 6 & 7).

Area of study	Population characteristics	Treatment	Main findings	References
Cardiovascular	Dyslipidemia	КО	Improved blood lipids	[68]
Obesity	Normal to obese	КО	Changed endocannabinoid levels	[69]
Inflammation	Athletes	КО	Reduced arthritic symptoms	[70]
Exercise	Athletes	КО	Reduced oxidative damage	[71]
PMS	Women	КО	Reduced dysmenorrhea	[72]
Brain	Memory complaints	n-3 PS <sup>1</sup>	Improved word recall	[73]
Eye	ADHD children	n-3 PLs <sup>2</sup>	Improved attention	[74]
Bioavailability	Healthy	КО	Increased n-3 FA blood levels	[66,67,75]

FA, fatty acid; KO, krill oil; PLs, phospholipids; PMS, premenstrual syndrome; PS, phosphatidylserine

<sup>1</sup> n-3 PS synthesized from krill

<sup>2</sup> n-3 PLs isolated from KO

#### TABLE 7: Overview of Krill Oil Pre-Clinical Studies

Area of study	study Animal model Treatment Main findings		References	
Cardiovascular	Heart failure (r)	КО	Attenuated heart remodeling	[76]
Obesity	High fat diet (m)	n-3 PLs <sup>2</sup>	Improved metabolic profile	[77]
	High-fat diet (r)	КО	Decreased body weight	[78]
	High-fat diet (m)	КО	Reduced endocannabinoid biosynthesis	[79]
	High-fat diet (m)	КО	Decreased hepatic steatosis	[80]
	Genetic obesity (r)	КО	Decreased hepatic and heart lipids	[23]
Inflammation	TNF <b>α</b> overexpression (m)	КО	Increased hepatic β-oxidation	[81]
	Ulcerative colitis (r)	КО	Reduced oxidative stress	[82]
	Arthritis (m)	КО	Reduced arthritis scores	[83]
Brain	Healthy (r)	n-3 PLs <sup>1</sup>	Improved memory function	[84]
	Genetic obesity (r)	КО	Increased DHA level in brain	[24]
	Healthy (r)	n-3 PS <sup>2</sup>	Improved learning and memory	[85]
	Healthy (r)	КО	Enhanced learning and antidepressant-like effects	[86]
Bone	Growing females (r)	КО	Did not improve bone mass/architecture	[87]
Other	Healthy (r)	КО	Decreased hepatic lipogenesis	[88]
	Healthy (m)	КО	Beneficial hepatic gene regulation	[89]

2 Synthesized from KO





# Conclusion

Dietary intake of the marine omega-3 fatty acids EPA and DHA has been linked to many health benefits, from improved cardiovascular health and cognitive function, to reduced levels of inflammation. To that end, various organizations have established recommended daily intakes for EPA and DHA ranging from 160 mg (Australia, New Zealand) to > 1000mg (Japan, South Korea). Because typical Western diets fall short of these guidelines, dietary supplementation helps to make up the difference. Due to its inherent advantages — i.e., omega-3 fatty acids bound to phospholipids, naturally pure and stable, sourced sustainably — krill oil has enormous potential in serving the world's omega-3 health needs for years to come.

#### **ABOUT Lena Burri**

Lena Burri, Ph.D., has been involved in fundamental research and is together with co-authors credited with several original protein discoveries. She has published scientific articles in leading journals, and contributed book chapters, review articles and peer-reviewed manuscripts on subjects including omega-3 fatty acids. Lena earned a her Master of Science from the University of Basel (Switzerland) and her Ph.D. at the Ludwig Institute for Cancer Research (Switzerland). Her post-doctoral education included stays at Melbourne University (Australia), University of British Columbia (Canada) and University of Bergen (Norway). She now works as a scientific writer specializing in omega-3 phospholipids.

#### **ABOUT Aker BioMarine**

Aker BioMarine is an integrated biotechnology company dedicated to the sustainable harvest of krill and development of krill-derived biotech products. The company supplies biomarine ingredients through a completely transparent value chain. Aker BioMarine's Superba™ Krill products are provided with 100% traceability from the Antarctic sea to the end user. Only Aker's krill fishery has been awarded Marine Stewardship Council (MSC) certification.

#### ABOUT Superba<sup>TM</sup> Krill Phospholipid Omega-3s

Superba<sup>™</sup> Krill is a pure, natural source of health-promoting EPA & DHA omega-3 fatty acids and the naturally occurring antioxidant astaxanthin. The uniqueness of Superba<sup>™</sup> Krill is that the omega-3 fatty acids are provided in phospholipid form. In vitro, in vivo and human clinical research has demonstrated the safety and efficacy of Superba<sup>™</sup> Krill.





# References

- Hamner WM, Hamner PP, Strand SW, Gilmer RW: Behavior of Antarctic Krill, Euphausia superba: Chemoreception, Feeding, Schooling, and Molting. Science 1983, 220:433-435.
- Tou JC, Jaczynski J, Chen YC: Krill for human consumption: nutritional value and potential health benefits. Nutr Rev 2007, 65:63-77.
- Moore SA, Hurt E, Yoder E, Sprecher H, Spector AA: Docosahexaenoic acid synthesis in human skin fibroblasts involves peroxisomal retroconversion of tetracosahexaenoic acid. J Lipid Res 1995, 36:2433-2443.
- Sprecher H, Chen Q, Yin FQ: Regulation of the biosynthesis of 22:5n-6 and 22:6n-3: a complex intracellular process. Lipids 1999, 34 Suppl:S153-156.
- Voss A, Reinhart M, Sankarappa S, Sprecher H: The metabolism of 7,10,13,16,19-docosapentaenoic acid to 4,7,10,13,16,19-docosahexaenoic acid in rat liver is independent of a 4-desaturase. J Biol Chem 1991, 266:19995-20000.
- Davis-Bruno K, Tassinari MS: Essential fatty acid supplementation of DHA and ARA and effects on neurodevelopment across animal species: a review of the literature. Birth Defects Res B Dev Reprod Toxicol 2011, 92:240-250.
- Hibbeln JR, Nieminen LR, Blasbalg TL, Riggs JA, Lands WE: Healthy intakes of n-3 and n-6 fatty acids: estimations considering worldwide diversity. Am J Clin Nutr 2006, 83:1483S-1493S.
- Simopoulos AP: The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med (Maywood) 2008, 233:674-688.
- Simopoulos AP: omega-3 fatty acids in health and disease and in growth and development. Am J Clin Nutr 1991, 54:438-463.
- Simopoulos AP: The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed Pharmacother 2002, 56:365-379.
- Harris WS, Von Schacky C: The omega-3 Index: a new risk factor for death from coronary heart disease? Prev Med 2004, 39:212-220.
- Arnold C, Markovic M, Blossey K, Wallukat G, Fischer R, Dechend R, Konkel A, von Schacky C, Luft FC, Muller DN, et al: Arachidonic acid-metabolizing cytochrome P450 enzymes are targets of {omega}-3 fatty acids. The Journal of biological chemistry 2010, 285:32720-32733.
- Harris WS, Sands SA, Windsor SL, Ali HA, Stevens TL, Magalski A, Porter CB, Borkon AM: omega-3 fatty acids in cardiac biopsies from heart transplantation patients: correlation with erythrocytes and response to supplementation. Circulation 2004, 110:1645-1649.
- Metcalf RG, Cleland LG, Gibson RA, Roberts-Thomson KC, Edwards JR, Sanders P, Stuklis R, James MJ, Young GD: Relation between blood and atrial fatty acids in patients undergoing cardiac bypass surgery. The American journal of clinical nutrition 2010, 91:528-534.
- von Schacky C: The omega-3 Index as a risk factor for cardiovascular diseases. Prostaglandins & other lipid mediators 2011.
- Pottala JV, Garg S, Cohen BE, Whooley MA, Harris WS: Blood eicosapentaenoic and docosahexaenoic acids predict all-cause mortality in patients with stable coronary heart disease: the Heart and Soul study. Circ Cardiovasc Qual Outcomes 2010, 3:406-412.
- Baghai TC, Varallo-Bedarida G, Dorn C, Hafner S, Schule C, Eser D, Rupprecht R, Bondy B, von Schacky C: Major depressive disorder is associated with cardiovascular risk factors and low omega-3 Index. J Clin Psychiatry 2011, 72:1242-1247.
- Lin PY, Huang SY, Su KP: A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. Biol Psychiatry 2010, 68:140-147.
   Tan ZS, Harris WS. Beiser AS. Au R. Himali JJ. Debette S. Pikula A. Decarli C. Wolf PA.
- Tan ZS, Harris WS, Beiser AS, Au R, Himali JJ, Debette S, Pikula A, Decarli C, Wolf PA, Vasan RS, et al: Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. Neurology 2012, 78:658-664.
- Ladesich JB, Pottala JV, Romaker A, Harris WS: Membrane level of omega-3 docosahexaenoic acid is associated with severity of obstructive sleep apnea. J Clin Sleep Med 2011, 7:391-396.
- Moon HJ, Kim TH, Byun DW, Park Y: Positive correlation between erythrocyte levels of n-3 polyunsaturated fatty acids and bone mass in postmenopausal Korean women with osteoporosis. Ann Nutr Metab 2012, 60:146-153.
- Graf BA, Duchateau GS, Patterson AB, Mitchell ES, van Bruggen P, Koek JH, Melville S, Verkade HJ: Age dependent incorporation of 14C-DHA into rat brain and body tissues after dosing various 14C-DHA-esters. Prostaglandins Leukot Essent Fatty Acids 2010, 83:89-96.
- Batetta B, Griinari M, Carta G, Murru E, Ligresti A, Cordeddu L, Giordano E, Sanna F, Bisogno T, Uda S, et al: Endocannabinoids may mediate the ability of (n-3) fatty acids to reduce ectopic fat and inflammatory mediators in obese Zucker rats. J Nutr 2009, 139:1495-1501.
- 24. Di Marzo V, Griinari M, Carta G, Murru E, Ligresti A, Cordeddu L, Giordano E, Bisogno T, Collu M, Batetta B, et al: Dietary krill oil increases docosahexaenoic acid and reduces 2-arachidonoylglycerol but not N-acylethanolamine levels in the brain of obese Zucker rats. Int Dairy J 2010, 20:231-235.
- Cole GM, Ma QL, Frautschy SA: Dietary fatty acids and the aging brain. Nutrition reviews 2010, 68 Suppl 2:S102-111.
- Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA: Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Archives of neurology 2006, 63:1545-1550.
- Lemaitre-Delaunay D, Pachiaudi C, Laville M, Pousin J, Armstrong M, Lagarde M: Blood compartmental metabolism of docosahexaenoic acid (DHA) in humans after ingestion of a single dose of [(13)C]DHA in phosphatidylcholine. J Lipid Res 1999, 40:1867-1874.
- Hung MC, Shibasaki K, Yoshida R, Sato M, Imaizumi K: Learning behaviour and cerebral protein kinase C, antioxidant status, lipid composition in senescence-accelerated mouse: influence of a phosphatidylcholine-vitamin B12 diet. Br J Nutr 2001, 86:163-171.
- Schneider H, Braun A, Fullekrug J, Stremmel W, Ehehalt R: Lipid based therapy for ulcerative colitis-modulation of intestinal mucus membrane phospholipids as a tool to influence



inflammation. Int J Mol Sci 2010, 11:4149-4164.

- Chung SY, Moriyama T, Uezu E, Uezu K, Hirata R, Yohena N, Masuda Y, Kokubu T, Yamamoto S: Administration of phosphatidylcholine increases brain acetylcholine concentration and improves memory in mice with dementia. J Nutr 1995, 125:1484-1489.
- Buang Y, Wang YM, Cha JY, Nagao K, Yanagita T: Dietary phosphatidylcholine alleviates fatty liver induced by orotic acid. Nutrition 2005, 21:867-873.
- O'Brien BC, Andrews VG: Influence of dietary egg and soybean phospholipids and triacylglycerols on human serum lipoproteins. Lipids 1993, 28:7-12.
- Čohn JS, Wat E, Kamili A, Tandy S: Dietary phospholipids, hepatic lipid metabolism and cardiovascular disease. Curr Opin Lipidol 2008, 19:257-262.
- 34. Lieber CS: New concepts of the pathogenesis of alcoholic liver disease lead to novel treatments. Curr Gastroenterol Rep 2004, 6:60-65.
- Lieber CS: Alcoholic fatty liver: its pathogenesis and mechanism of progression to inflammation and fibrosis. Alcohol 2004, 34:9-19.
- Turecky L, Kupcova V, Szantova M, Uhlikova E: Plasma lipid parameters in patients with alcoholic fatty liver after treatment with essential phospholipids. Bratisl Lek Listy 2003, 104:227-231.
- Lieber CS, Robins SJ, Li J, DeCarli LM, Mak KM, Fasulo JM, Leo MA: Phosphatidylcholine protects against fibrosis and cirrhosis in the baboon. Gastroenterology 1994, 106:152-159.
- Dasgupta S, Bhattacharyya DK: Dietary effect of eicosapentaenoic acid (EPA) containing soyphospholipid. J Oleo Sci 2007, 56:563-568.
- Shirouchi B, Nagao K, Inoue N, Ohkubo T, Hibino H, Yanagita T: Effect of dietary omega-3 phosphatidylcholine on obesity-related disorders in obese Otsuka Long-Evans Tokushima fatty rats. J Agric Food Chem 2007, 55:7170-7176.
- Le Grandois J, Marchioni E, Zhao M, Giuffrida F, Ennahar S, Bindler F: Investigation of natural phosphatidylcholine sources: separation and identification by liquid chromatographyelectrospray ionization-tandem mass spectrometry (LC-ESI-MS2) of molecular species. J Agric Food Chem 2009, 57:6014-6020.
- Winther B, Hoem N, Berge K, Reubsaet L: Elucidation of phosphatidylcholine composition in krill oil extracted from Euphausia superba. Lipids 2011, 46:25-36.
- 42. Phleger CF, Nelson MM, Mooney BD, Nichols PD: Interannual and between species comparison of the lipids, fatty acids and sterols of Antarctic krill from the US AMLR Elephant Island survey area. Comp Biochem Physiol B Biochem Mol Biol 2002, 131:733-747.
- McDaniel MA, Maier SF, Einstein GO: "Brain-specific" nutrients: a memory cure? Nutrition 2003, 19:957-975.
- 44. da Costa KA, Cochary EF, Blusztajn JK, Garner SC, Zeisel SH: Accumulation of 1,2-sndiradylglycerol with increased membrane-associated protein kinase C may be the mechanism for spontaneous hepatocarcinogenesis in choline-deficient rats. The Journal of biological chemistry 1993, 268:2100-2105.
- Zeisel SH, Da Costa KA, Franklin PD, Alexander EA, Lamont JT, Sheard NF, Beiser A: Choline, an essential nutrient for humans. The FASEB journal : official publication of the Federation of American Societies for Experimental Biology 1991, 5:2093-2098.
- Zeisel SH: Choline: needed for normal development of memory. J Am Coll Nutr 2000, 19:528S-531S.
- Loy R, Heyer D, Williams CL, Meck WH: Choline-induced spatial memory facilitation correlates with altered distribution and morphology of septal neurons. Adv Exp Med Biol 1991, 295:373-382.
- Meck WH, Williams CL: Perinatal choline supplementation increases the threshold for chunking in spatial memory. Neuroreport 1997, 8:3053-3059.
- Meck WH, Williams CL: Simultaneous temporal processing is sensitive to prenatal choline availability in mature and aged rats. Neuroreport 1997, 8:3045-3051.
- Meck WH, Williams CL: Characterization of the facilitative effects of perinatal choline supplementation on timing and temporal memory. Neuroreport 1997, 8:2831-2835.
- Tees RC: The influences of rearing environment and neonatal choline dietary supplementation on spatial learning and memory in adult rats. Behav Brain Res 1999, 105:173-188.
- Williams CL, Meck WH, Heyer DD, Loy R: Hypertrophy of basal forebrain neurons and enhanced visuospatial memory in perinatally choline-supplemented rats. Brain Res 1998, 794:225-238.
- Albright CD, Tsai AY, Friedrich CB, Mar MH, Zeisel SH: Choline availability alters embryonic development of the hippocampus and septum in the rat. Brain Res Dev Brain Res 1999, 113:13-20.
- Albright CD, Zeisel SH: Choline deficiency causes increased localization of transforming growth factor-beta1 signaling proteins and apoptosis in the rat liver. Pathobiology 1997, 65:264-270.
- Holmes-McNary MQ, Loy R, Mar MH, Albright CD, Zeisel SH: Apoptosis is induced by choline deficiency in fetal brain and in PC12 cells. Brain Res Dev Brain Res 1997, 101:9-16.
- 56. Lee JE, Giovannucci E, Fuchs CS, Willett WC, Zeisel SH, Cho E: Choline and betaine intake and the risk of colorectal cancer in men. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2010, 19:884-887.
- 57. Xu X, Gammon MD, Zeisel SH, Bradshaw PT, Wetmur JG, Teitelbaum SL, Neugut AI, Santella RM, Chen J: High intakes of choline and betaine reduce breast cancer mortality in a population-based study. The FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2009, 23:4022-4028.
- 58. Xu X, Gammon MD, Zeisel SH, Lee YL, Wetmur JG, Teitelbaum SL, Bradshaw PT, Neugut AI, Santella RM, Chen J: Choline metabolism and risk of breast cancer in a population-based study. The FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2008, 22:2045-2052.
- Fassett RG, Coombes JS: Astaxanthin: a potential therapeutic agent in cardiovascular disease. Mar Drugs 2011, 9:447-465.
- 60. Riccioni G, D'Orazio N, Franceschelli S, Speranza L: Marine carotenoids and cardiovascu-



lar risk markers. Mar Drugs 2011, 9:1166-1175.

- Iwamoto T, Hosoda K, Hirano R, Kurata H, Matsumoto A, Miki W, Kamiyama M, Itakura H, Yamamoto S, Kondo K: Inhibition of low-density lipoprotein oxidation by astaxanthin. J Atheroscler Thromb 2000, 7:216-222.
- Pashkow FJ, Watumull DG, Campbell CL: Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease. Am J Cardiol 2008, 101:58D-68D.
- Hussein G, Nakagawa T, Goto H, Shimada Y, Matsumoto K, Sankawa U, Watanabe H: Astaxanthin ameliorates features of metabolic syndrome in SHR/NDmcr-cp. Life Sci 2007, 80:522-529.
- Ikeuchi M, Koyama T, Takahashi J, Yazawa K: Effects of astaxanthin in obese mice fed a high-fat diet. Biosci Biotechnol Biochem 2007, 71:893-899.
- 65. Yoshida H, Yanai H, Ito K, Tomono Y, Koikeda T, Tsukahara H, Tada N: Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia. Atherosclerosis 2010, 209:520-523.
- 66. Maki KC, Reeves MS, Farmer M, Griinari M, Berge K, Vik H, Hubacher R, Rains TM: Krill oil supplementation increases plasma concentrations of eicosapentaenoic and docosahexaenoic acids in overweight and obese men and women. Nutr Res 2009, 29:609-615.
- 67. Ulven SM, Kirkhus B, Lamglait A, Basu S, Elind E, Haider T, Berge K, Vik H, Pedersen JI: Metabolic effects of krill oil are essentially similar to those of fish oil but at lower dose of EPA and DHA, in healthy volunteers. Lipids 2011, 46:37-46.
- Bunea R, El Farrah K, Deutsch L: Evaluation of the effects of Neptune Krill Oil on the clinical course of hyperlipidemia. Altern Med Rev 2004, 9:420-428.
- 69. Banni S, Carta G, Murru E, Cordeddu L, Giordano E, Sirigu AR, Berge K, Vik H, Maki KC, Di Marzo V, Griinari M: Krill oil significantly decreases 2-arachidonoylglycerol plasma levels in obese subjects. Nutr Metab (Lond) 2011, 8:7.
- Deutsch L: Evaluation of the effect of Neptune Krill Oil on chronic inflammation and arthritic symptoms. J Am Coll Nutr 2007, 26:39-48.
- Skarpańska-Stejnborn A, Pilaczyńska-Szcześniak L, Basta P, Foriasz J, Arlet J: Effects of Supplementation with Neptune Krill Oil (Euphasia Superba) on Selected Redox Parameters and ProiInflammatory Markers in Athletes during Exhaustive Exercise. J Human Kinetics 2010, 25:49-57.
- Sampalis F, Bunea R, Pelland MF, Kowalski O, Duguet N, Dupuis S: Evaluation of the effects of Neptune Krill Oil on the management of premenstrual syndrome and dysmenorrhea. Altern Med Rev 2003, 8:171-179.
- Richter Y, Herzog Y, Cohen T, Steinhart Y: The effect of phosphatidylserine-containing omega-3 fatty acids on memory abilities in subjects with subjective memory complaints: a pilot study. Clin Interv Aging 2010, 5:313-316.
- 74. Vaisman N, Kaysar N, Zaruk-Adasha Y, Pelled D, Brichon G, Zwingelstein G, Bodennec J: Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: effect of dietary n-3 fatty acids containing phospholipids. Am J Clin Nutr 2008, 87:1170-1180.
- 75. Schuchardt JP, Schneider I, Meyer H, Neubronner J, von Schacky C, Hahn A: Incorpora-

tion 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.

- Fosshaug LE, Berge RK, Beitnes JO, Berge K, Vik H, Aukrust P, Gullestad L, Vinge LE, Oie E: Krill oil attenuates left ventricular dilatation after myocardial infarction in rats. Lipids in health and disease 2011, 10:245.
- Higuchi T, Shirai N, Suzuki H: Effects of herring roe on plasma lipid, glucose, insulin and adiponectin levels, and hepatic lipid contents in mice. J Nutr Sci Vitaminol (Tokyo) 2008, 54:230-236.
- Ferramosca A, Conte A, Burri L, Berge K, De Nuccio F, Giudetti AM, Zara V: A krill oil supplemented diet suppresses hepatic steatosis in high-fat fed rats. PloS one 2012, 7:e38797.
- Piscitelli F, Carta G, Bisogno T, Murru E, Cordeddu L, Berge K, Tandy S, Cohn JS, Griinari M, Banni S, Di Marzo V: Effect of dietary krill oil supplementation on the endocannabinoidome of metabolically relevant tissues from high fat-fed mice. Nutrition & Metabolism 2011, 8:1-16.
- Tandy S, Chung RWS, Wat E, Kamili A, Berge K, Griinari M, Cohn JS: Dietary krill oil supplementation reduces hepatic steatosis, glycemia and hypercholesterolemia in high-fat fed mice. Journal of Agricultural and Food Chemistry 2009, 57:9339-9345.
- Vigerust NF, Bjorndal B, Bohov P, Brattelid T, Svardal A, Berge RK: Krill oil versus fish oil in modulation of inflammation and lipid metabolism in mice transgenic for TNF-alpha. Eur J Nutr 2012.
- Grimstad T, Bjorndal B, Cacabelos D, Aasprong OG, Janssen EA, Omdal R, Svardal A, Hausken T, Bohov P, Portero-Otin M, et al: Dietary supplementation of krill oil attenuates inflammation and oxidative stress in experimental ulcerative colitis in rats. Scandinavian journal of gastroenterology 2012, 47:49-58.
- Ierna M, Kerr A, Scales H, Berge K, Griinari M: Supplementation of diet with krill oil protects against experimental rheumatoid arthritis. BMC Musculoskelet Disord 2010, 11:136.
- Gamoh S: Krill-derived phospholipids rich in n-3 fatty acid improve spatial memory in adult rats. J Agric Sci 2011, 3:3-12.
- Lee B, Sur BJ, Han JJ, Shim I, Her S, Lee HJ, Hahm DH: Krill phosphatidylserine improves learning and memory in Morris water maze in aged rats. Prog Neuropsychopharmacol Biol Psychiatry 2010, 34:1085-1093.
- Wibrand K, Berge K, Messaoudi M, Duffaud A, Panja D, Bramham CR, Burri L: Enhanced cognitive function and antidepressant-like effects after krill oil supplementation in rats. Lipids in Health and Disease 2013, 12.
- Lukas R, Gigliotti JC, Smith BJ, Altman S, Tou JC: Consumtion of different sources of omega-3 polyunsaturated fatty acids by growing female rats affects long bone mass and microarchitecture. Bone 2011, 49:455-462.
- Ferramosca A, Conte L, Zara V: A krill oil supplemented diet reduces the activities of the mitochondrial tricarboxylate carrier and of the cytosolic lipogenic enzymes in rats. J Animal Phys and Animal Nutr 2011:1-12.
- Burri L, Berge K, Wibrand K, Berge RK, Barger JL: Differential effects of krill oil and fish oil on the hepatic transcriptome in mice. Frontiers in Nutrigenomics 2011, 2:1-8.

#### Aker BioMarine Antarctic AS Fjordallèen 16, 0115 Oslo, Norway post@akerbiomarine.com Phone: +47 24 13 00 00

#### USA Subsidiary:

Aker BioMarine Antarctic US, Inc. info.us@akerbiomarine.com Phone: +1 206 855 6736

#### Asia Contact:

info.asia@akerbiomarine.com Phone: +1 206 660 6756

#### Australasia Subsidiary:

Aker BioMarine Antarctic Australasia Pty Ltd info.anz@akerbiomarine.com Phone: +61 3 9999 1112

#### www.superbakrill.com

Superba™ Krill is a trademark of the Aker Group. © 2013 Aker BioMarine. All rights reserved.



