Krill oil – are there alternatives?

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Authors:
Clarissa Gödde, Institute for Alternative and Sustainable Nutrition
Dr. Markus Keller, Fachhochschule des Mittelstands (University of Applied Sciences)

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AA	Arachidonic acid
AAP	American Academy of Pediatrics
AFFSA	French Agency for Food, Environmental and Occupational Health and Safety
AHA	American Heart Association
ALA	α-linolenic acid
AND	Academy of Nutrition and Dietetics
CVD	Cardiovascular disease(s)
DDT	Dichlorodiphenyltrichloroethane
DHA	Docosahexaenoic acid
EE	Ethyl ester
EFSA	European Food Safety Authority
EPA	Eicosapentaenoic acid
EU	European Union
FAO	The Food and Agriculture Organization of the United Nations
FFA	Free fatty acid
GL	Glycolipid
GMO	Genetically modified organism
GOED	Global Organization for EPA and DHA Omega-3s
HDL	High-density lipoprotein
ISSFAL	International Society for the Study of Fatty Acids and Lipids
LA	Linoleic acid
LC n-3 PUFA	Long chain omega-3 polyunsaturated fatty acid
LDL	Low-density lipoprotein
n-6 PUFA	Omega-6 polyunsaturated fatty acid
PCB	Polychlorinated biphenyl

PL	Phospholipid
SCAN	Scientific Advisory Committee on Nutrition
TAG	Triacylglycerol
VITAL	Vitamin D and Omega-3 Trial
WHO	World Health Organization

INTRODUCTION

Krill are shrimp-like marine crustaceans of the order *Euphausiacea*. Krill oil is primarily obtained from Antarctic krill *(Euphausia superba)*. Due to its high content of the long chain omega-3 polyunsaturated fatty acids (LC n-3 PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) krill oil is widely used as a LC n-3 PUFA supplement, in addition to LC n-3 PUFA supplements derived from fish or microalgae. In contrast to terrestrial plants, marine microalgae are not only able to synthesize LC n-3 PUFAs, but are the main primary producers of these fatty acids in the marine environment.[3] Thus, by trophic upgrading EPA and DHA accumulate along the marine food chain in krill and fish. In krill oil EPA and DHA occur in phospholipid (PL) and free fatty acid (FFA) form, while in fish oil they are predominantly present in triacylglycerol (TAG) form. Based on these biochemical variations a review has discussed a higher bioavailability of EPA and DHA from krill oil than fish oil, but concluded the available human studies are inconclusive[4].

1 PHYSIOLOGICAL ROLE OF LC N-3 PUFAS

While saturated fatty acids predominantly are utilized to provide and store energy, PUFAs, like EPA and DHA, have structural and regulatory functions. Thus, they determine the fluidity of bio-membranes, alter the inflammatory capacity of tissue hormones and influence cellular signalling pathways and gene expression.[5] High concentrations of DHA are especially found in brain tissue and the retina. There is scientific evidence that a PUFA-rich diet is associated with a reduced risk for cardiovascular diseases (CVD)[6], inflammatory conditions, like arthritis[7], and neurodegenerative diseases[8]. It is well known that DHA is essential for the neurological and visual development of infants.[9] The health effects of LC n-3 PUFAs are discussed in detail in chapter 3.

EPA and DHA are considered as conditionally essential for humans because they can be synthesized from the essential fatty acid α-linolenic acid (ALA).[10] However, the conversion of ALA to EPA and DHA in the human body is limited by the set of enzymes responsible for elongation and desaturation, which they share with the omega-6 fatty acids (n-6 PUFA), i. e. the conversion of linoleic acid (LA) to arachidonic acid (AA). Modern human nutrition is rich in n-6 PUFAs like LA, therefore, the conversion of ALA into long chain n-3 PUFAs is very low

(ALA to EPA ~8-12 %; ALA to DHA < 1 %). Women seem to have higher conversions rates (ALA to EPA up to 21 %; ALA to DHA up to 9 %) than men (ALA to EPA 0.3-8 %; ALA to DHA < 1 %).[5] The International Society for the Study of Fatty Acids and Lipids (ISSFAL) concluded that the conversion of ALA to DHA in infants amounts to 1 % and is "considerably lower" in adults.[11]

2 RECOMMENDED INTAKE OF LONG CHAIN OMEGA-3 FATTY ACIDS

Many international and national authorities and scientific organizations have published recommendations for the daily intake of n-3 PUFAs. The World Health Organization (WHO) proposes a n-3 PUFA (all forms combined) intake of 1-2 % of the total energy intake.[12] The Food and Agriculture Organization (FAO) and the European Food Safety Authority (EFSA) assess a minimum dietary requirement/adequate intake for ALA of 0.5 % of total energy to be sufficient to prevent deficiency symptoms in adults.[13,14] Recommendations for the combined intake of EPA and DHA for the general adult population mostly vary between 250 mg/day (EFSA[13]) and 500 mg/day (ISSFAL[15]) (**Table 1**). These recommendations are mainly based on considerations concerning cardiovascular health. Due to insufficient data, it is not possible to derive an average requirement for EPA and/or DHA. To date, LC n-3 PUFA deficiency symptoms are not known.[13] In addition, the majority of international and national organizations recommend a minimum intake of 200 mg DHA per day for pregnant and lactating women, taking into account the role of LC n-3 PUFAs in visual and cognitive development of the infants.[16]

Table 2: Recommendations of international and national authorities and scientific organizations for the n-3 PUFA intake of adults

Region	Organization	Target Population	Recommendation
Global	Food and Agriculture Organization of the United Nations (FAO)[14]	General adult population	0.5-0.6 % ALA of total dietary energy 250 mg EPA+DHA/day
		Pregnant and lactating women	300 mg EPA+DHA/day, of which ≥ 200 mg/day should be DHA

	International Society for the Study of Fatty Acids and Lipids (ISSFAL)[17]	General adult population	≥ 500 mg EPA+DHA/day
USA	Academy of Nutrition and Dietetics (AND)[18]	General adult population	500 mg EPA+DHA/day
	American Heart Association (AHA)[19]	General adult population	500 mg EPA+DHA/day
	American Academy of Pediatrics (AAP)[20]	Pregnant and lactating women	200-300 mg DHA/day
Canada	Dietitians of Canada[21]	General adult population	300-450 mg EPA+ DHA/day
Australia & New Zealand	Department of Health & Ageing, National Health & Medical Research Council[22]	General adult population	Men: 160 mg EPA+DPA+DHA/day Women: 90 mg EPA+DPA+DHA/day
Europe	European Food Safety Authority (EFSA)[13]	General adult population	0.5 % ALA of total dietary energy 250 mg EPA+DHA/day
		Pregnant and lactating women	Additional 100-200 mg DHA/day
United Kingdom	Scientific Advisory Committee on Nutrition (SACN)[23]	General adult population	450 mg EPA+DHA/day
Germany, Austria, Switzerland	German Nutrition Society, Austrian Nutrition Society and	General adult population	0.5 % ALA of total dietary energy
		Pregnant and lactating women	≥ 200 mg DHA/day

	Swiss Society for Nutrition[24]		
France	French Agency for Food, Environmental and Occupational Health and Safety (AFFSA)[25]	General adult population	250 mg DHA/day 500 mg EPA+DHA/day
		Pregnant and lactating women	250 mg DHA/day 500 mg EPA+DHA/day

3 EFFECTS OF LC N-3 PUFAS ON HUMAN HEALTH

There is growing evidence that EPA and DHA have positive effects on several health outcomes. Especially the improvement of cardiovascular health is convincing (see below). Most studies which explore the association between LC n-3 PUFAs and health outcomes concentrate on secondary prevention (e. g. patients after a first cardiovascular event). Primary prevention trials in the general population are currently rare, raising the question whether healthy individuals would benefit from a higher LC n-3 PUFA intake. For example, vegetarians and especially vegans tend to have low blood levels of EPA and DHA, due to the absence of LC n-3 PUFAs in plant foods.[26] However, vegetarians and vegans show a good long term health with a reduced prevalence for obesity and hypertension[27] (both are established cardiovascular risk factors), and a lower risk for ischaemic heart disease.[28] These positive outcomes can be explained to a great extent by the health-promoting food choices of vegetarians and vegans, e. g. higher consumption of vegetables, fruit and whole grain products, and no consumption of red meat and meat products, but also by an overall healthier lifestyle. It is unclear if and to what extend vegetarians and vegans benefit from an improved LC n-3 PUFA status, e. g. in a further decrease of CVD risk.[29] The ongoing VITAL (VITamin D and OmegA-3 TriaL) trial aims to investigate the potential effects of a marine LC n-3 PUFA supplementation on the primary prevention of cancer and cardiovascular disease in a multi-ethnic population of 20.000 men (> 50 years old) and women (> 55 years old) in the USA.[30]

3.1 Cardiovascular diseases

The influence of LC n-3 PUFAs on health outcomes, especially CVD, has been extensively studied. The story began in the 1970s, when Danish researchers had been informed that the Greenland Eskimos had a low prevalence of coronary heart diseases (CHD). Their diet was rich in seal blubber and fish and therefore in LC n-3 PUFAs, which led the researchers to the suggestion that this so called "Eskimo diet" was a key factor in the alleged low CHD incidence (meanwhile, the "Eskimo diet theory" has been disproven: most studies conducted during the last 40 years found that the Greenland Eskimos, as well as Canadian and Alaskan Inuit, have CHD as often as the non-Eskimo populations).[31,32]

Nevertheless, subsequent studies found that EPA and DHA decrease elevated TAG levels[33], reduce hypertension[34] and exert other cardioprotective functions[35], like reduction of platelet aggregation. In line with these findings, epidemiological studies reported an association between high intakes and blood levels of LC n-3 PUFAs, and (slightly) reduced cardiovascular events.[6,36] However, in recent trials low dose LC n-3 PUFA supplementation in addition to state-of-the-art therapy did not reduce the rate of cardiovascular events.[37] This is supported by a recent systematic review of clinical trials which concluded that LC n-3 PUFA supplementation does not seem to show any benefit for the treatment of CVD or associated complications. Nevertheless, it also stated that a supplementation of ≥ 1 g LC n-3 PUFAs per day (through supplements or marine products) reduces cardiovascular risk factors and therefore can be recommended to improve cardiovascular health.[38] A most recent meta-analysis (10 trials) found no support for the recommendation to use approximately 1 g LC n-3 PUFAs per day in people with a history of CHD for the prevention of cardiovascular events.[39]

3.2 Inflammatory diseases

LC n-3 PUFAs influence inflammatory cells, for instance by changing the fatty acid composition of their membranes and by altering the eicosanoid-pattern. The regulatory potential of LC n-3 PUFAs with regard to inflammatory processes suggests that a supplementation may be beneficial in inflammatory diseases, e. g. rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, psoriasis, and asthma.[40] Studies confirm this assumption for rheumatoid arthritis[41], but are not consistent for

inflammatory bowel disease[42] and asthma[40]. For the majority of inflammatory conditions evidence is not sufficient.[40] Besides the absolute amount of LC n-3 PUFA intake the n-6:n-3 PUFA ratio seems important. An increased n-6:n-3 PUFA ratio was found to act pro-inflammatory and pro-thrombotic (by the primary formation of n-6 series eicosanoids, like prostaglandin E_2 and thromboxane A_2) and, therefore, promote inflammatory diseases.[43]

3.3 Neurological development and degeneration

PUFAs are crucial for brain functioning, including brain development and cognitive function. DHA, which makes up about 40 % of brain PUFAs, for example increases in the grey matter and retina PL during early development.[44,45] Some studies report that DHA supplementation during gestation leads to higher cognitive outcomes and visual acuity in infants and children, whereas others could not find a difference in comparison to placebo controls.[44] A systematic review and meta-analysis concluded that cognitive outcomes had not been improved by DHA interventions and that the topic warrants further investigation.[46] The results concerning neurodegenerative disorders, like Alzheimer's disease and Parkinson's disease, are also inconclusive. Some, but not all, studies observed lower DHA concentrations in brain and/or liver tissue of individuals with Alzheimer's disease.[47] So far, intervention trials which support the hypothesis that LC n-3 PUFAs delay the progression of neurodegenerative diseases are lacking.

3.4 Other

A beneficial role of LC n-3 PUFAs in cancer[47] and diabetes[36] prevention is being discussed, but there is no sufficient evidence yet.

3.5 Health claims for EPA and DHA

Based on the scientific evidence the EFSA has approved several health claims for DHA and EPA which all focus on normal physiological functions:

- DHA and EPA contribute to the normal function of the heart (0.25 g per day)
- DHA and EPA contribute to the maintenance of normal blood pressure (3 g per day)

- DHA and EPA contribute to the maintenance of normal blood triglyceride levels (2 g per day)
- DHA contributes to maintenance of normal blood triglyceride levels (2 g per day in combination with EPA)
- DHA contributes to maintenance of normal brain function (0.25 g per day)
- DHA contributes to the maintenance of normal vision (0.25 g per day)
- DHA maternal intake contributes to the normal brain development of the foetus and breastfed infants (0.2 g DHA plus the daily recommended intake of omega-3 fatty acids (EPA+DHA for adults which is 0.25 g per day).
- DHA maternal intake contributes to the normal development of the eye of the foetus and breastfed infants (0.2 g DHA plus the daily recommended intake of omega-3 fatty acids (EPA+DHA) for adults which is 0.25 g per day).[48]

4 SOURCES OF N-3 PUFAS: KRILL AND PLANT-BASED ALTERNATIVES

4.1 Krill oil

Trials investigating the association between LC n-3 PUFA intake and health outcomes are typically conducted with fish oil supplements or an increased intake of fatty fish. Some of the supposed health-promoting effects of EPA and DHA have also been tested with supplements derived from krill oil. As expected, the intake of krill oil supplements increased plasma concentrations of EPA and DHA.[49,50] A systematic review and meta-analysis on the lipid-modifying effect of krill oil concluded that krill oil has a TAG and low-density lipoprotein (LDL) lowering effect, while it elevates high-density lipoprotein (HDL).[51] These modifications of blood lipids are known to be cardioprotective. Furthermore, one randomized, double-blind, cross-over trial found improved endothelial function in individuals with type 2 diabetes mellitus after krill oil supplementation.[52] In a randomized controlled trial krill oil intake for 30 days improved mild knee pain in patients.[53] Another randomized, double-blind, placebo controlled study indicates that krill oil intake (300 mg/day) reduces inflammation and arthritic symptoms.[54]

4.2 Plant-based LC n-3 PUFA sources

The rising recognition of LC n-3 PUFAs as beneficial to human health emphasizes the need for sustainable EPA and DHA sources, especially in consideration of the globally growing population. There is an increasing risk of excess harvesting of natural marine sources like oily fishes and krill. Furthermore, conventional supplements derived from fish oil or krill oil are not suitable for the growing population of vegetarians and vegans, for whom LC n-3 PUFAs are considered critical nutrients.[55] There are several alternative LC n-3 PUFA sources. The two most prominent are: 1. single-cell oils extracted from several microalgae, and 2. transgenic oilseeds and other plants (e. g. Camelina). Further options like EPA and DHA producing transgenic *Escherichia coli* and transgenic microalgae also are being explored.[56]

4.2.1 Microalgae oil

As discussed earlier, several microalgae, in contrast to terrestrial plants, are capable of de-novo synthesis of LC n-3 PUFAs and therefore are rich in EPA and DHA. Almost at the bottom of the marine food chain, microalgae supply those fatty acids for marine animals like fish and krill. In photoautotrophic microalgae (e. g. *Nannochloropsis oculata*) EPA and DHA occur partly in form of glycolipids (GL), which are bound to chloroplast membranes.[57] Some species produce high amounts of EPA and only little DHA. Due to higher growth rates and easier handling, heterotrophic microalgae (e. g. *Schizochytrium sp.)* are currently being preferred as a source of EPA and DHA supplementation.[56] They contain EPA and DHA predominantly in TAG and PL form. One randomized, double blind, controlled trial with 93 hypertriglyceridaemic participants found the same TAG lowering effects for microalgae oil as for fish oil.[58]

Commercially available EPA and/or DHA containing oils derived from cultivated microalgae contain 10-95 % EPA and/or 20-45% DHA.[59] These oils usually are offered in form of non-gelatine gel capsules. Besides, there are several plant oils available that have been fortified with EPA and/or DHA of microalgal origin, e. g. linseed or olive oil with EPA/DHA.[60,61]

4.2.2 Transgenic land-based plant crops

Among other plants camelina *(Camelina sativa)* and canola *(Brassica napus L.)* are viewed as potential hosts for the introduction of microalgal genes to facilitate LC n-3 PUFA production.[62] In 2014 researchers produced a camelina oil with up to 24 % EPA and a second version with 11 % EPA and 8 % DHA.[63] **Table 2** shows examples of genetically modified plant oils. However, due to the low acceptance of genetically modified organisms (GMOs) in the public, especially in Europe, these oils are intended to be used in aquacultures.[62] Furthermore, risks regarding the long term usage of GMO for human nutrition are not assessed.[64] Currently, they are not available for human nutrition.

Table 2: Transgenic plants with EPA/DHA content[2]

Plant (company)	EPA/ DHA (g/ 100g)
Oil seeds (CSIRO)	5.0 g EPA 1.0 g DHA
Mustard (BASF)	15.0 g EPA 1.5 g DHA
Soya bean (Dupont)	20.0 g EPA 3.0 g DHA

4.3 Comparison of krill with microalgae oil

4.3.1 Bioavailability of microalgae oil versus krill oil

In general, the FFA form of LC n-3 PUFAs is considered to have the highest and the ethyl ester (EE) form the lowest bioavailability, while the PL and TAG form seem to have a medium bioavailability. The PL form appears to be better bioavailable than the TAG form, but conclusive evidence from human studies is missing.[4] Furthermore, there is no data available to rank fatty acids in GL form into this order. In theory, LC n-3 PUFAs derived from krill oil in FFA and PL form might have a higher bioavailability than from heterotrophic microalgae oil in TAG and PL form. Bioavailability of LC n-3 PUFAs from photoautotrophic microalgae cannot be estimated based on theoretical considerations. Studies to confirm these conclusions are rare.

So far, one trial compared the bioavailability of LC n-3 PUFAs (1.5 g EPA, no DHA) derived from the photoautotrophic microalgae *Nannochloropsis oculata* with LC n-3 PUFAs (1.0 g

EPA, 0.5 g DHA) derived from krill oil. After consumption of a single dose the increase of plasma concentrations of EPA was significantly higher with the microalgae supplement compared to the krill supplement. DHA plasma concentrations also increased with both supplements, but there was no difference between the microalgae and krill oil. In conclusion, the authors suggest a better EPA bioavailability from the algal oil supplement compared to the krill oil supplement, even taking in account the different EPA concentrations of the two oils. One possible explanation for the higher bioavailability might be the presence of GL in the microalgae oil.[65]

Numerous studies compared the LC n-3 PUFA bioavailability of krill oil and fish oil. One review suggests a higher bioavailability of EPA and DHA from krill oil than fish oil, but concludes that further studies are needed to confirm this assumption.[66] Studies comparing krill oil and microalgae oil, apart from the mentioned study, and microalgae oil and fish oil are not available.

4.3.2 Safety of microalgae oil versus krill oil

Persistent organic pollutants, like DDT (dichlorodiphenyltrichloroethane), chlordane and PCB (polychlorinated biphenyl), accumulate preferably in the marine ecosystem and are a major health concern for the public. A recent review compared the toxicological profile of available krill oil and fish oil supplements and ranked the krill oil supplements intermediate regarding the persistent organic pollutant content. Hexachlorocyclohexane, pentachlorobenzene, hexachlorobenzene and a variety of PBCs were found in both analysed krill oil products. DDT occurred in one product and chlordane was not found in the two krill oil supplements. All analysed products were, at their highest recommended dosage, far below the tolerable daily intake for all analysed pollutants.[67]

Microalgae are regarded as a non-polluted resource of LC n-3 PUFA supplements since they are cultured under controlled conditions.[56]

5 CONCLUSION

As evidence of the beneficial effects of LC n-3 PUFAs on human health increases and several international and national authorities and organizations recommend the dietary intake of EPA and DHA, the demand for LC n-3 PUFA supplements will rise in the future. In light of this development, the sustainability of LC n-3 PUFA sources should be taken into account. From a health point of view, fish, krill and microalgae are considered to be safe sources of EPA and DHA for human nutrition. Currently, microalgae seem to be the only sustainable and plant-based alternative to fish and krill oil, since transgenic terrestrial plants raise ecological questions and are not accepted for human nutrition by the public.

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