Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Krill Oil

Evidence Summary

Krill oil contains lower DHA/EPA levels compared to fish oil but may be potentially more bioavailable. Promising for preventing/improving CVD and arthritis, but shortened lifespan in mice raises concerns.

Neuroprotective Benefit: The evidence is limited and mixed on whether DHA/EPA from krill oil is more beneficial than DHA/EPA from other sources.

Aging and related health concerns: There is potential cardiovascular protection and improvement in arthritis, but the shortened lifespan and increased bleeding in rodent studies dampen enthusiasm.

Safety: Although no serious side effects have been reported in short-term clinical trials, rodent studies have shown shortened lifespan and increased bleeding.

What is it? Krill oil is oil that is derived from krill, the small semi-transparent crustaceans that feed on planktons; krill are at the bottom of the food chain. Krill oil contains DHA and EPA like fish oil, but the DHA and EPA in krill oil are mostly in the form of phospholipids (phosphatidylcholine) rather than triglycerides [1], which presumably make the DHA and EPA more bioavailable. Phospholipids are not found in fish, plant, or algal-based oil products. Another benefit of krill oil over fish oil is that it contains astaxanthin, a carotenoid that increases the "longevity gene" (FOXO3). Krill oil has been used in people with high blood pressure, stroke, osteoarthritis, depression, and premenstrual syndrome.

Neuroprotective Benefit: The evidence is limited and mixed on whether DHA/EPA from krill oil is more beneficial than DHA/EPA from other sources.

Types of evidence:

- 1 randomized clinical trial in healthy elderly
- Several studies on bioavailability
- Numerous laboratory studies
- Several reviews

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? Only one study has been carried out in men. In a double-blind randomized controlled trial, 45 healthy elderly received oil capsules containing krill oil (n-3 PUFAs in phosphatidylcholine), sardine oil (n-3 PUFAs in triglycerides), or medium chain triglycerides (MCTs; placebo) for 12 weeks [2]. Subjects underwent working memory testing and changes in oxyhemoglobin and event-related potentials were measured. Although no results were reported on the effect of supplements on working memory, per se, they noted that those who received krill oil had greater changes in oxyhemoglobin concentration and event-related potentials (decrease in P300 latency) in the prefrontal cortex during working memory tasks compared to those receiving MCTs. The results suggest that ingestion of krill oil increases prefrontal activation and may accelerate the rate of information processing. Although sardine oil contained the largest amounts of DHA and EPA, changes in oxyhemoglobin or event-related potentials were not significantly different from the placebo group. Further studies of larger sample sizes that also include women are needed to confirm these results.

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research: Studies in both humans and rodents have shown cognitive benefits with DHA and/or EPA (see ratings on DHA). In male and female rats, krill oil treatment (1.25% of daily ration of food, or 0.2 g/rat/day via oral gavage) for 7 weeks significantly improved cognitive function while also exerting anti-depressant effects [3]. These changes were accompanied by increased mRNA levels of the neurotrophic factor BDNF in the hippocampus.

The important remaining question is whether DHA and EPA from krill oil are more beneficial than those from other sources. A study in female rats compared the digestibility and brain deposition of DHA from different sources of fat, including krill oil, menhaden oil, salmon oil, tuna oil, flaxseed oil, and corn oil [4]. They found that although DHA content was 2-4 times higher in krill oil compared to other sources, digestibility and brain deposition was greater for salmon oil and tuna oil. Authors attributed the lower digestibility and brain deposition of krill oil DHA to the higher phospholipid composition of DHA. Phospholipids are generally thought to be more bioavailable, but this may only reflect its relative ease to get into the blood—it is possible that phospholipids are not as easily incorporated into the brain. Although krill oil is rich in the carotenoid astaxanthin, its presence did not alter levels of lipid oxidation or antioxidant defense enzymes.

Findings from the rodent study above counter the notion that DHA and EPA in phospholipid form are more bioavailable than those in triglyceride form. Studies in humans comparing the bioavailability of DHA and EPA from krill versus fish oil are limited and difficult to interpret as different amounts of each were used, intervention duration varied, and different study groups were included [5; 6]. For example, in an effort to normalize the amounts of EPA and DHA across different sources, some oils had to be diluted with other oils (e.g., corn oil), making the formulation unnatural [7; 8; 9].

Despite these issues, some studies suggest that bioavailability from krill oil is higher than that from fish oil. For example, a double-blind crossover study in 12 healthy adults showed that a single dose of 1,680 mg of EPA+DHA produced higher bioavailability when it was provided in krill oil compared to two different types of fish oil (re-esterified triacylglyceride or ethyl esters) [10]. However, due to high variability across subjects, there were no statistically significant differences across groups receiving krill oil and two types of fish oil. One interesting property of krill oil is that it contains a fair amount of EPA and DHA as free fatty acids (21% of EPA and 22% of DHA), which may have contributed to their higher plasma levels. The two types of fish oil did not contain any free fatty acids. However, a limitation to this study is that they measured plasma phospholipid content of EPA and DHA, which is not representative of tissue (brain) levels. When supplements are compared without accounting for the different doses of

EPA and DHA, concentrated triglyceride fish oil (650 mg EPA, 450 mg DHA) was more effective in raising blood levels of omega-3 compared to krill oil (150 mg EPA, 90 mg DHA) in an open-label study in 35 healthy subjects [6].

Perhaps the most well-designed double-blind randomized controlled trial was the one that tested the bioavailability of fish oil in ethyl ester form, fish oil in triglyceride form, and krill oil, while controlling for the amounts of EPA and DHA in each formulation [11]. Similar plasma and red blood cell levels of EPA and DHA were achieved across krill oil and fish oil products after 4 weeks of supplementation, indicating comparable oral bioavailability regardless of formulation. However, this study too showed that the means for EPA and DHA were 10-20% higher in people who took krill oil compared to the two types of fish oil.

In a single-blind study, bioavailability of low phospholipid krill oil was compared with high phospholipid krill oil [12]. There were no significant differences between low and high phospholipid krill oil treatments on plasma levels of EPA, DHA, and total n-3 PUFA. But the high phospholipid krill oil increased the red blood cell concentration of EPA (by 69%) and total n-3 PUFA (by 118%) to a significantly greater extent than low phospholipid krill oil (by 43% and 30%, respectively). These results suggest that high phospholipid content promotes longer-term absorption as well as tissue absorption.

In a rodent study, the effects of phosphatidylserine from krill and soy oil were compared [13]. Compared to untreated aged rats, treatment of phosphatidylserine from krill oil (20 mg/kg) improved spatial memory and prevented the loss of hippocampal cholinergic neurons. Interestingly, comparable benefits were obtained with phosphatidylserine from soy oil.

APOE4 interactions: Unknown.

Aging and related health concerns: There is potential cardiovascular protection and improvement in arthritis, but the shortened lifespan and increased bleeding in rodent studies dampen enthusiasm.

Types of evidence:

- 9 clinical trials: 1 on knee joint pain, 3 in people with hyperlipidemia, 2 in overweight/obese people, 1 in diabetics, 1 in cardiovascular or arthritis, and 1 in healthy adults
- 2 open-label trials in healthy adults
- Numerous laboratory studies

Cardiovascular: BENEFIT/MIXED. In a double-blind randomized controlled trial of 47 patients with type 2 diabetes, krill oil treatment (1000 mg/day) for 4 weeks improved endothelial function [14]. A total of 34 subjects completed an open-label study with an additional 17 week-supplementation period. These subjects had a statistically significant improvement in endothelial function and blood HDL levels.

In a randomized controlled trial of 120 people with hyperlipidemia, krill oil (1-3 g/day) was significantly more effective than fish oil (3g/day) in reducing LDL (32-39% reduction with krill oil vs 5% reduction with fish oil) [15]. HDL increased in both the krill oil and fish oil groups. However, the evidence on cholesterol is mixed and a large double-blind randomized controlled trial in 300 people with high triglyceride levels showed no improvement in triglyceride levels, total cholesterol, LDL, or HDL after 12 weeks of krill oil treatment (0.5-4 g/day) [16]. In a double-blind randomized controlled trial of 25 people with moderate hypertriglyceremia, both krill oil and esterified omega-3 oil lowered triglyceride levels [17]. Krill oil, but not esterified omega-3 formulation, also increased HDL cholesterol.

An open-label study in 17 healthy young adults showed that krill oil (832.5 mg of EPA and DHA/day) for 28 days significantly decreased levels of plasma triacylglycerol (linked to atherosclerosis) and large very-low density lipoprotein (VLDL; causes buildup of cholesterol) [16].

Arthritis: BENEFIT. In a double-blind randomized controlled trial of 50 people with mild knee joint pain, krill oil (2 g/day) for 30 days significantly mitigated pain and stiffness compared to placebo [18]. In a larger double-blind randomized controlled trial that included 90 patients with cardiovascular disease or rheumatoid- or osteoarthritis (criteria was high C-reactive protein [CRP] levels), Neptune krill oil treatment (300 mg/day) for 30 days significantly inhibited inflammation and reduced arthritic symptoms compared to placebo [19]. Krill oil reduced CRP levels by 30.9% after 30 days and reduced pain scores and stiffness scores by 28.9% and 20.3%, respectively.

Inflammation: MIXED. Krill oil reduced inflammation in people with arthritis [19]. But in a randomized controlled trial in 37 healthy adults performing exercise, krill oil (2 g/day) for 6 weeks did not modify exercise performance and resulted in increased levels of a few inflammatory markers (IL-2 and natural killer cell cytotoxic activity) 3 hours post-exercise , though other markers of inflammation were unchanged (IL-6, IL-4, IL-10, IL-17, IFN-γ, TBARs) [20]. In a mouse model of inflammation (induced by lipopolysaccharide), FlexPro MD, a mixture of krill oil, astaxanthin, and hyaluronic acid (relieves joint pain in humans) significantly lowered levels of proinflammatory cytokines (IL-6, TNF-α, IL-1β) and elevated levels of anti-inflammatory cytokine IL-10 [21].

Diabetes: HARM/MIXED. In a double-blind randomized controlled trial of 47 overweight men, supplementation with a krill-salmon oil supplement (88% krill, 12% salmon; containing 230 mg EPA plus 154 mg DHA per day) for 8 weeks was associated with a 14% *reduction* in insulin sensitivity compared to controls receiving canola oil [22]. However, a commentary on this study authored by a manufacturer of krill oil suggested that the effect on insulin sensitivity was small and the method of analysis was not appropriate. Also, the author reported that the krill-salmon oil blend did not have the fatty acid composition typical of krill oils in the US Pharmacopeia-National Formulary [23]. In a different double-blind randomized controlled trial of 47 patients with type 2 diabetes, krill oil treatment (1000 mg/day) for 4 weeks did not affect glucose levels or glucose control (HbA1c) [14].

Lifespan: HARM/MIXED IN PRECLINICAL MODELS. In long-lived male mice (B6C3F1 strain), diet supplemented with krill oil (1.17 g/kg diet) or fish oil (Lovaza, 4.40 g/kg diet) started at 12 months of age significantly shortened lifespan by 6.6% compared to controls, and a trend was also seen for shortened median lifespan, by 4.7% and 9.8%, respectively [24]. Doses were picked based on those recommended for human use. This negative effect on lifespan was not due to increased levels of fat/calories in the diet, as equivalent volumes of soybean oil were removed from the control diet to replace with krill or fish oil. It is also unlikely that the effect on lifespan was due to toxins (e.g., mercury, PCB) in the oils, as Lovaza is a highly purified prescription drug with very low levels of these toxins. Lovaza and krill oil significantly increased lung tumors by 4.1-fold (8/35) and 8.2-fold (16/36), respectively (2/36 in control). Fish and krill oil also increased hemorrhage in the peritoneal cavity by 3.9-fold (15/35) and 3.1-fold (12/35), respectively (4/36 in control). The anticoagulant effects of dietary marine oils likely contributed to the hemorrhage and early mortality. Krill oil modestly increased bilirubin, triglycerides, and blood glucose levels, but these were not likely related to the observed increased mortality.

In contrast, treatment with astaxanthin, a carotenoid contained in krill oil, extended mean lifespan by 16-30% in wild-type and long-lived mutant *C. elegans* [25]. Treatment was started from pre-reproductive stage and resulted in protection of mitochondria and nuclei. Authors suggest that astaxanthin lengthens lifespan by activating the insulin/IGF1 signaling based on the fact that no extension of lifespan was observed in nematodes lacking DAF-16 which targets this pathway. If this is the mechanism of lifespan extension, it is unlikely to apply to humans, as higher IGF1 signaling or levels are associated with shorter lifespan and increased risks of some cancers in humans [26; 27].

Safety: Although no serious side effects have been reported in short-term clinical trials, rodent studies have shown shortened lifespan and increased bleeding.

Types of evidence:

- 8 clinical trials
- 1 study testing oxidation levels in 171 omega-3 supplements
- 1 study testing levels of organic pollutants in 11 fish or krill oil
- Numerous laboratory studies

Clinical trials: None of the clinical trials testing krill oil have reported serious adverse events [2; 8; 12; 16; 17; 22; 28]. There were also no effects on creatinine (kidney function) or liver transaminases (liver function) [17]. Side effects reported with krill oil included high incidence of eructation ("fishy burps"), mild gastrointestinal symptoms, increased bowel frequency, soft stool, flatulence, mild hypertension, taste change, heart burn, and localized pimples [8; 16; 22]. But gastrointestinal symptoms and bowel frequency changes also occurred in controls taking canola oil, so these effects are probably not specific to krill oil [22].

Rodent lifespan studies: As mentioned above, a study in mice showed that krill oil (1.17 g/kg diet) or fish oil (Lovaza, 4.40 g/kg diet) significantly shortened lifespan by 6.6% and this effect was attributed to increased incidences of lung tumors and hemorrhage in the peritoneal cavity [24]. In another study, rats fed krill oil had increased liver weight gain (per unit body weight) compared to those fed flaxseed oil or corn oil, though the increase in liver weight was less than those fed salmon oil or tuna oil [4]. Although the increase in liver weight appears alarming, this is likely due to the deposition of omega-3 fatty acids in the liver as opposed to triglycerides deposits, which are associated with fatty liver disease.

Oxidation: In a laboratory study that tested oxidation levels for 171 over-the-counter n-3 PUFA supplements, 50% of test products exceeded the voluntary recommended levels [29]. Another 18% of the products approached these limits within 1-3 years before expiration. Although only a few krill oil supplements were analyzed, they had significantly higher secondary oxidation levels (60+ mEq/kg of anisidine) compared to plant-based products and more than 3 times the recommended safety limit for anisidine (<20 mEq/kg). With regards to oxidation, encapsulated products without flavor additives had lower levels of oxidation compared to bulk oils and flavored products.

Pollutants: In a toxicology study comparing 11 products that included 2 krill oil, 3 enriched fish oil, 3 formulations, and 3 budget-grade fish oil, none of the products exceeded the chemical guideline

threshold for persistent organic pollutants (POP) [30]. Krill oil products were ranked as intermediate in terms of their levels of POP contamitants compared to other seafood oil products/formulations.

Drug interactions: Krill oil may interact with estrogens (birth control pills or hormone replacement), blood thinners (e.g., warfarin), aspirin and other NSAIDs, beta-blockers (e.g., atenolol, carvedilol, etc.), diuretics (e.g., chlorothiazide), and orlistat for weight loss [31]. Krill oil should not be used if you are allergic to fish, shrimp, or any other type of seafood.

Sources and dosing: Doses of krill oil in clinical studies ranged from 300-2000 mg per day. Aside from the higher phospholipid content, krill oil manufacturers claim several advantages of krill oil over fish oil, including lower contaminants such as mercury and the absence of a fishy aftertaste. However, because fish oil typically contains significantly higher amounts of EPA and DHA than krill oil, the slightly higher bioavailability of krill oil may not be enough to warrant taking krill oil over fish oil. Due to some concerns with oxidation, higher dietary intake of fresh seafood rich in EPA/DHA may be more beneficial than seafood oils in capsules.

Research underway: There are 2 ongoing clinical trials testing krill oil. One double-blind randomized controlled trial is testing if supplementation with krill oil concentrate improves cognitive test scores in people who have entered the US Army Infantry Basic Officer Leaders Course (NCT02908932). This trial will test whether krill oil improves psychological resiliency, navigation, rule-making, marksmanship, attention, and information processing speed. This trial is scheduled to be completed in March 2018. The other double-blind randomized controlled trial is testing whether krill oil capsules improve learning, cognition, and behavior in healthy adolescents (14-15 years old) with low omega-3 index (NCT02240264)[32]. Although this study was scheduled to be completed last year, the study is still ongoing.

Search terms:

Pubmed, Google: Krill oil

- + cognitive, + dementia, + clinical trial, + safety, + meta-anaysis, + life span

Clinicaltrials.gov, Examine.com, Labdoor.com: Krill oil

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