

Microalgae – A healthy solution for EPA and DHA.

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Why choose Algae derived Omega-3s?

Omega-3s are a type of polyunsaturated healthy fats (or PUFAs) that are critically important for optimal human nutrition. Of the seven Omega-3s fats present in nature, the two most important are Eicosapentaenoic acid (or EPA) and docosahexaenoic acid (or DHA). For centuries, the primary source of EPA and DHA Omega-3 in the diet was from marine sources like whole fatty fish or fish liver oils. Today, most people around the world aren't getting enough EPA and DHA in their diet (Panchal et al. 2021), leading to the growing demand for food supplements derived from fish oils. As the **consumer market for Omega-3 fats has grown to over \$47 Billion per year** (GOED report 2022), demand for Omega-3s from plant sources has increased. Demand for plant-based alternatives to animal-derived sources of nutrients appeals in particular to the Millennial and Gen Z generations. Their focus on making sustainable and climate-conscious choices that support life above and below water has contributed to the growing demand for microalgae derived Omega-3s.

Health and Wellness of PUFAS

The two most important Omega-3 PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Another common Omega-3 PUFA is alpha-linolenic acid (ALA). This short-chain Omega-3 is found in flax, walnuts, chia and other terrestrial plants but is not associated with the same health benefits as EPA and DHA. The human body can convert ALA to other long chain PUFA but the process is slow and inefficient. Stearidonic acid (SDA) is another, albeit less common, fatty acid that is found in some plants, such as echium. SDA can be converted to longer chain fatty acid more effectively than ALA can but both plant-sourced **ALA and SDA are much less effective for improving human nutrition than consuming pre-formed EPA and DHA directly.** *Figure 1.*

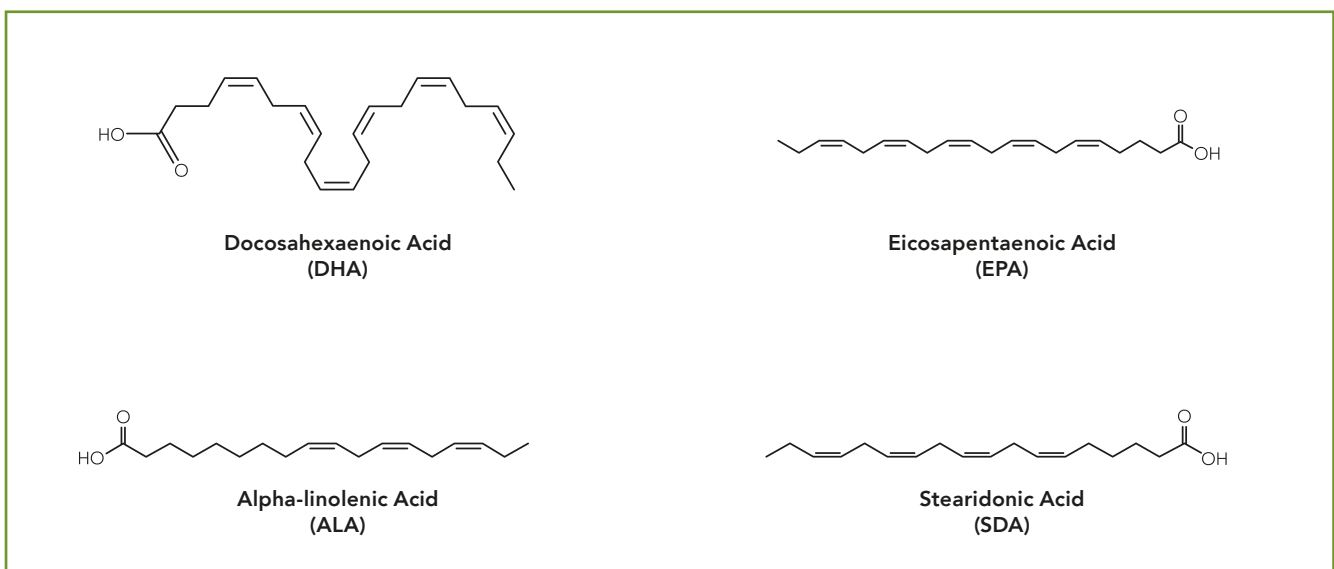


Figure 1: Chemical structure of Omega-3 fatty acids. Stearidonic Acid (SDA), Eicosapentaenoic Acid (EPA), Docosahexaenoic Acid (DHA) and Alpha-linolenic Acid (ALA).

Over 5000 double-blind placebo controlled clinical studies have been published on the health benefits of EPA and DHA (GOED Clinical Study Database). Scientific interest in EPA and DHA started in the 1970's when Danish scientists noticed that the Inuit population of Greenland had much lower incidence of cardiovascular disease and diabetes mellitus than were seen in mainland Caucasian Danes (Bang et al. 1971). When the blood of the Greenland Inuit was analyzed, much lower levels of plasma triglycerides were found despite consuming a very high fat diet contributing as much as 50% of total calories to their diet. This counter-intuitive finding was because the fat being consumed was primarily from whales, seals and fatty fish, all of which are rich sources of EPA and DHA. The authors speculated that this could be linked to their lower levels of heart disease and diabetes. This article took the scientific community by storm and led to a flurry of research on the health benefits of EPA and DHA over the next 50 years.



Learn about the history of Omega-3 directly from Dr. Jorn Dyerberg, who is considered to be the 'Father of Omega-3 science' in this video: <https://vimeo.com/773291575>

Research on EPA and DHA Omega-3 continues with over 50,000 peer-reviewed papers published to date exploring many health outcomes. A study of 20,000 women found that EPA and DHA supplementation during **pregnancy** has been shown to reduce the risk of early pre-term birth and low birth weight (Middleton et al. 2018). DHA is found in high concentrations in the **brain** and **retina** as a key structural lipid and is crucial to the development of healthy brains and eyes in infants (Koletzko et al). Regular consumption of EPA and DHA remains important for adults seeking to maintain **cognitive function**. (Yurko-Mauro et al. 2015). Omega-3 fatty acids can be beneficial for **eye health** in adults as well. Studies have shown that high intakes of EPA and DHA are associated with lower risks of age-related macular degeneration and dry eye syndrome (McCusker et al. 2016).

The relationship between EPA and DHA intake and **cardiovascular disease** has been extensively studied (Calder 2021). These fatty acids are effective at lowering the risk of cardiovascular disease by reducing blood serum triglyceride levels and increasing HDL cholesterol. EPA and DHA can also decrease blood pressure, lower heart rate and decrease platelet aggregation (Calder et al. 2021).

One of the most important roles that omega-3 fatty acids play in the human body is modulation of inflammation. EPA and DHA are metabolized in vivo into specialized mediator compounds called **E-series resolvins and D-series resolvins and protectins**. These have **anti-inflammatory and inflammation resolving properties**. *Figure 2*.

In addition, consuming EPA and DHA prevents the formation of pro-inflammatory mediators that are derived from other fatty acids. Research shows that this could be beneficial in managing symptoms of diseases and conditions associated with inflammation, such as **rheumatoid arthritis, asthma, obesity, atherosclerosis** and **cardiovascular events** (Calder 2010).

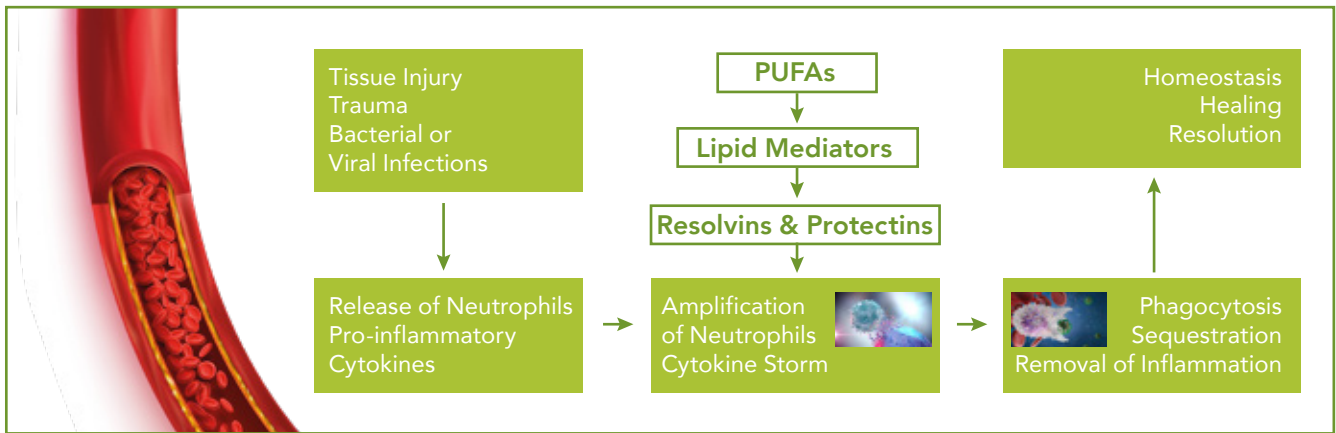


Figure 2: Shortened acute inflammatory response using lipid mediators

Because of their many health benefits, the popularity of dietary supplements containing EPA and DHA has steadily grown. Fish oils and cod liver oils have historically been the primary source of these fatty acids. **Increased demand for long-chain Omega-3s over the coming decades, indicate that historical marine sources may not be able to support the global need for Omega-3 EPA and DHA.** Scientists have speculated that changes in water temperatures could cause the amount of EPA available from the world's oceans to decrease up to 28% in some regions while the amount of available DHA could plummet by up to 58% (Holm et al. 2022, Columbo et al. 2019). *Figure 3.*

Even though fisheries supplying marine-based Omega-3s are managed sustainably, it is clear that **alternate sources of EPA and DHA are needed ensure that the global nutritional needs can be met well into the future.**

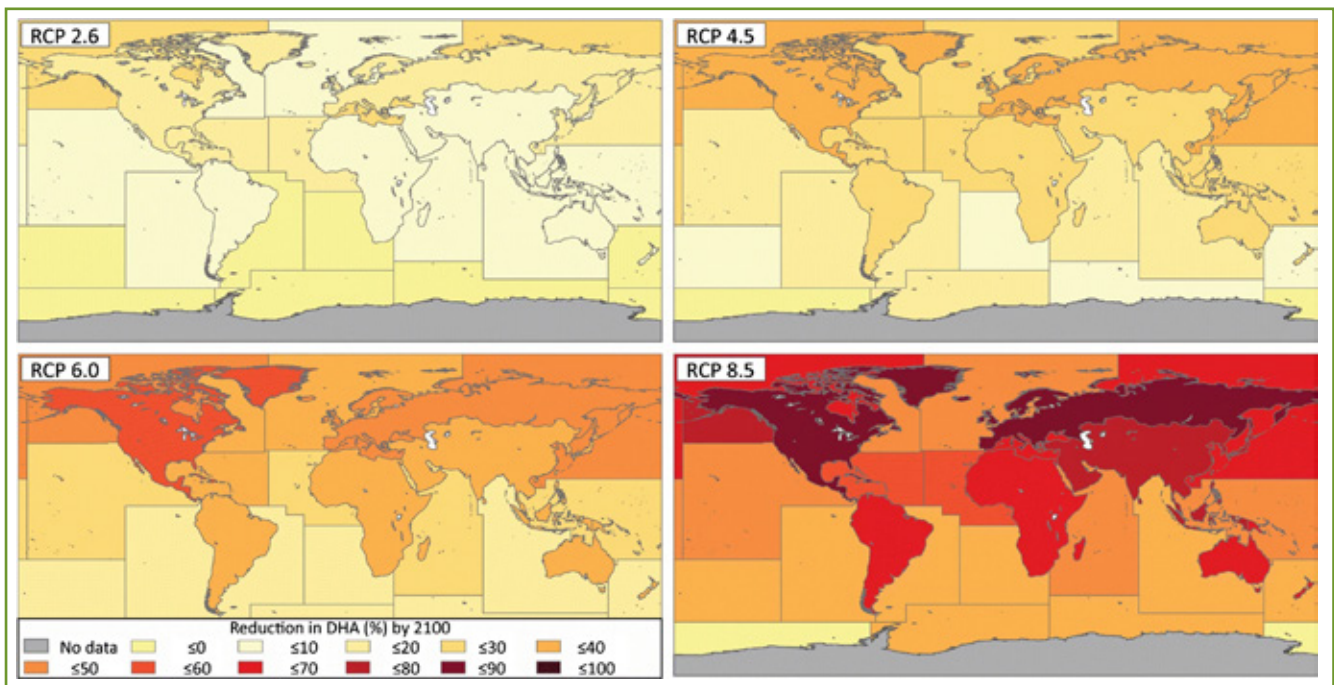


Figure 3: Projected declines in global DHA availability for human consumption as a result of global warming

Colombo, S.M., Rodgers, T.F.M., Diamond, M.L., et al. Projected declines in global DHA availability for human consumption as a result of global warming. *Ambio* 49, 865–880 (2020). <https://doi.org/10.1007/s13280-019-01234-6>

What are Microalgae?

Microalgae are microscopic organisms that grow in oceanic and freshwater environments. There are thousands of different types of microalgae that all have different characteristics.

Phytoplankton, a type of microalgae, is the foundation of the marine food web. It is consumed by zooplankton, bivalves and other filter feeders. These creatures are in turn consumed by small fish and crustaceans. The cycle of predation continues into larger fish, marine mammals, and seabirds. At each stage, EPA and DHA Omega-3s are important for all species in the marine food web.

Some species of microalgae contain a large proportion of lipids within their single-cell bodies. Often, these oils are rich in Omega-3s as EPA and DHA are carried up the food chain and become concentrated in larger predators. Fatty fish like tuna, mackerel, salmon, sardines and anchovies contain high levels of EPA and DHA but do not produce these fatty acids themselves. **Microalgae is the origin of EPA and DHA in the marine food web.** This has led scientists to develop methods of isolating unique strains of microalgae and cultivating on a commercial scale to support specialized fats for dietary supplements, foods and aquaculture.

Science of Microalgae

Scientists around the world have been working to cultivate microalgae to create a sustainable source of EPA and DHA. This has involved screening of thousands of different strains of algae, all sourced from different marine environments. Manipulation of growing conditions for microalgae (acidity, temperature, energy source) can change the amount and types of fats that algae produce. Microalgae is composed primarily of proteins, lipids and carbohydrates such as starch, sugars and other polysaccharides. Adjusting growth parameters to change the lipid content of microalgae also alters amounts of these other compounds as well. Microalgae use the lipids they produce as energy reserves. The lipids stored in the cell wall are primarily phospholipid and glycolipids while the lipids in the body of the cell are mainly triglycerides.

Figure 4.

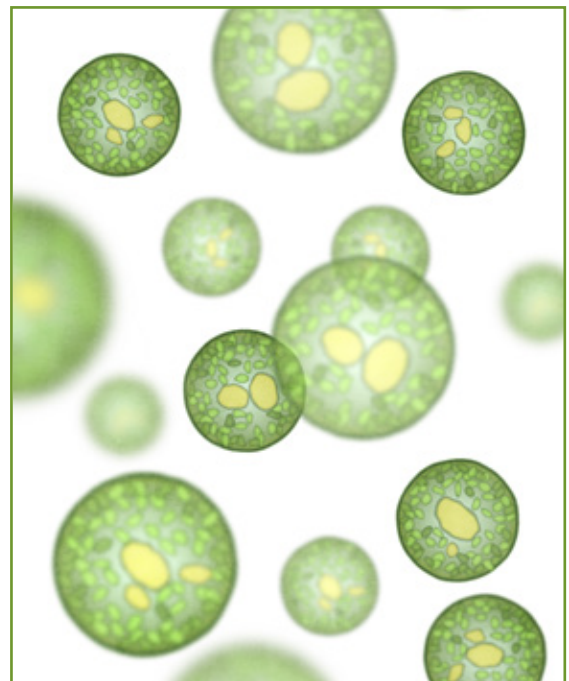


Figure 4: Single-cell algae with lipid droplets. Illustration of microalgae under the microscope, isolated on white.

Some types of algae, like **Nannochloropsis sp.**, are autotrophic. This algae requires sunlight to grow and are often grown outdoors in large open raceway ponds. They can also be grown indoors in tubes that are exposed to sunlight, but this is very capital intensive. Autotrophic algae obtain the carbon that they need from atmospheric carbon dioxide or from carbon dioxide sources. Photosynthetic algae store the bulk of their lipids in their cell walls. These are primarily phospholipid and glycolipids. The result is an oil product that is very viscous and is dark in color due to the presence of chlorophyll and other plant pigments. The oil derived from *Nannochloropsis* tend to be enriched in EPA and typically contains between 3% and 30% of this healthy PUFA. *Figure 5.*

Other species, like **Schizochytrium sp.**, are heterotrophic and grow best in the dark. Commercially, this is accomplished using large closed tanks. This type of algae needs a carbohydrate source to grow, typically sugar or starch. These algae grow through fermentation, similar to the production of corn ethanol. The oil produced by heterotrophic algae tend to be stored in the body in the cell and are mainly triglycerides. These oils typically have reddish pigment due to presence of carotenoids and tend to be free-flowing and light in color. **Oils from these species can contain up to 60% DHA, an amount that far surpasses the amount of DHA found in fish oil**, even in rich sources like tuna. When algae are grown in a closed system, the growth conditions can be tightly controlled which ensures a consistent product that has not been exposed to environmental contamination. *Figure 6*

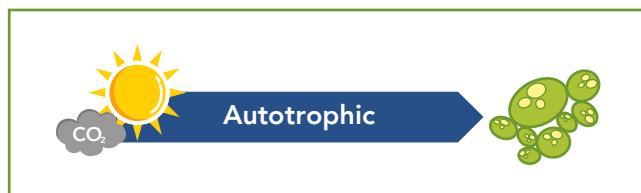


Figure 5: Autotrophic microalgae are cultivated in large raceway open ponds, or in closed photo-bioreactors, using sunlight and carbon dioxide (CO₂)



Figure 6: Heterotrophic microalgae are grown in large fermenter tanks using sugar or starch, similar to corn ethanol fermentation.

Microalgae Harvest and Extraction

Once the algae have finished growing, the lipids from the microalgae cells must be extracted. The first step in this process is to harvest the algae. Typically, this involves removing as much water as possible from the algae, through filtering, centrifuging or drying, to create a thick paste of microalgae biomass. The next step is to physically break the algae cells to release the oil. There are many different ways that this can be done. Some popular methods include use of high frequency sound waves (ultrasound) to lyse cells, the use of high pressures to rupture the cells, and using food-grade enzymes to degrade cell walls. Once the cells have been ruptured, different techniques can be used to separate the oil from the rest of the cell material. This is often done using ethanol and water combined with centrifugation. While solvents like hexane may still be used by some growers, this is becoming less and less common. Highly polar oils, like those from *Nannochloropsis sp.* are more challenging to refine and may have to undergo additional steps to convert them into a free-flowing oil.

The oil harvested from the algae is then subjected to further processing. These processes are very similar to those used for vegetable or fish oils and usually involves physical refining, concentration, distillation and deodorization. This ensures that the algal oil is stable and free of sediment, organic matter, and oxidation products. Algal oils that contain triglycerides, such as those from *Schizochytrium* sp. often undergo a process called winterization. This involves cooling the oil down to low temperatures and filtering out the saturated fats that crystallize of the oil. This helps to ensure that the refined oil remains clear and free of oily sediment when stored in the refrigerator.

Advantages of Algae versus Fish

Algae oil can be grown on land, providing a controlled and sustainable source of EPA and DHA Omega-3 fats to support global nutrition. **Concerns about future supply or impact of climate changes on the oceans and marine ecosystems can be mitigated through responsible cultivation of microalgae.** The potential for exposure to persistent environmental contaminants is also greatly reduced with the controlled manufacturing environment for microalgae-based lipids. In addition, algal oil is a beneficial way for vegetarians and vegans to supplement their **plant-based diets** to obtain adequate amounts of EPA and DHA Omega-3s. The addition of algal oils to the dietary supplement market provides an opportunity for these populations to ethically increase the amounts of these important fatty acids in their diets.

Who Makes Alga3™?

Lipids produced from sp. *Schizochytrium* were originally produced to supplement infant nutrition products and have gained widespread incorporation as a key source of docosahexaenoic acid (DHA) in infant formula. While algal oils containing 40-50% DHA are readily available, there has been no commercially relevant source of algal-based eicosapentaenoic acid (EPA) available on the marketplace – until now.

KD Pharma Group™ a leading contract development (CDMO) and research organization active in Omega-3 API manufacturing launched **Alga3™** EPA and DHA ingredients into the nutritional market in fall 2021. Produced by KD Nutra®, the nutritional products division of KD Pharma Group™, **Alga3™ is the world's first 100% Vegan Omega-3 ingredient that can truly match Omega-3 content and EPA/DHA ratio of common fish oil concentrates.** Concentrations for EPA or DHA of up to **95%** total or combined are available in many common EPA/DHA ratios. *Figure 7.*

Alga3™ builds upon KD Pharma Group's decades of experience in purifying and concentrating fish-based EPA and DHA lipids to the highest levels (95%+) required for API pharmaceuticals. Algal crude lipids from skilled growers around the world are brought into the KD Pharma Group's factories in Norway, UK and Germany where the crude EPA and DHA lipids are carefully separated from non-omega fats and concentrated to the highest levels in the industry, all within a cGMP manufacturing quality system in Germany.

If a finished dosage form (FDF) product is desired, **100% vegetarian capsules** can be produced at the KD Nutra® world-class encapsulation facility in Miami, USA which is NSF-certified and Australian TGA approved. If liquid delivery solutions are required, KD Nutra® can also provide algal oil in **turnkey liquid oil** or emulsion formulations, delivering a broad range of custom nutritional solutions to support brand-holders around the world.

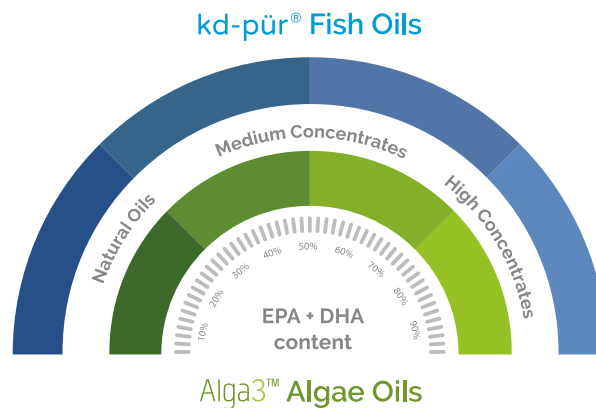
A unique aspect of KD Nutra's refining and concentration process for Alga3™ ingredients is that the lipids are concentrated and purified without the use of harmful solvents like methanol or hexane. **KD Nutra® has a proprietary solvent-less process to concentrate EPA and DHA to >95% purities in the finished products.**

After concentration, the lipids are re-formed into the natural triglyceride form using a gentle enzymatic process. Algal oils are treated with natural clay and carbon absorbents, then deodorized to remove unwanted flavors and odors, and finally protected against oxidation with non-GMO natural mixed tocopherols (vitamin E), rosemary extract, and ascorbyl palmitate. The resulting product is a 100% vegetarian EPA+DHA concentrated lipid available in the same range of concentrations as fish oil. *Figure 8.*



Figure 7: Ultra-potent algal EPA+DHA turnkey solutions from KD Nutra®.

Figure 8:
Think of any fish oil concentrate, KD Nutra® can make it vegan!



Alga3™ Environmentally friendly

As increased demand for Omega-3s grow beyond what marine sources can provide, Alga3™ EPA/DHA concentrates from microalgae offer supplement brands a viable option to shift their supply to a plant-based supply without compromising Omega-3 content. In an increasingly demanding market for DHA and EPA supplements, Alga3™ provide an option that can help communicate **a brand's commitment to sustainability** to a new generation of cause-conscious consumers.

With the controlled cultivation and processing of Alga3™, consumers can have confidence in the quality and purity of the product they consume. Concerns about persistent organic pollutants like PCBs, Dioxins, or microplastics are non-existent in Alga3™ because of the highly controlled processing environment. Use of Alga3™ can also support a brand's commitment to sustainable products by positively supporting several **UN Sustainable Development Goals**, namely Goal 3 - Good Health/Wellbeing, Goal 12 - Responsible Consumption & Production, Goal 13 - Climate Action, and Goal 14 - Life Below Water.

Outlook of Microalgae derived PUFAs

Market reports on algae Omega-3 ingredients indicate a steady growth at a CAGR of 11.90% during the forecast period of 2020 – 2025 (Mordor Intelligence 2021). The strong market growth is caused by the increasing demand for infant formulas worldwide because DHA and EPA are essential for infant brain development and immunity. China is the world's largest consumers of infant formula products, due to the high numbers of births in the country. Other countries are following this trend. Novel delivery methods, enhancements of taste profiles, and improved bioavailability will allow for great market opportunities of micro-algae PUFAs in the functional food and beverage, dietary supplements, pharmaceuticals, and animal nutrition markets. *Figure 9.*

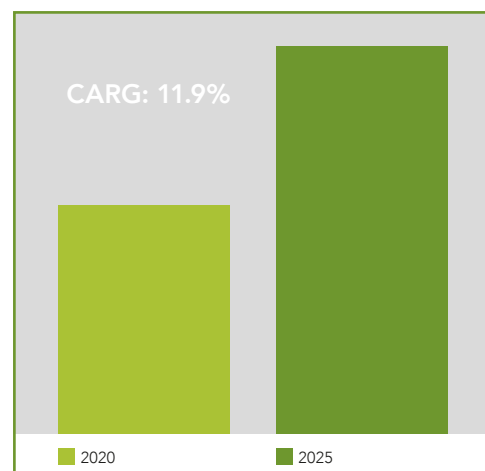


Figure 9: The global algae Omega-3 ingredients market
Source: Mordor Intelligence

About the Authors:



Dr. Andrea Holmes, Chief Science Officer at KD Pharma Group

Andrea joined the KD Pharma Group in June 2022, bringing over 25 years of academic, research, chemical, and cannabis business experience. Throughout the years, she conducted research on warfare detection sensors for the Department of Defense, automated imaging methods of colorimetric molecules, false positive drug test results, cannabis testing methods, nanotechnology designed for the inhibition of hospital acquired bacterial infections. Most recently, she has focused on the organic synthesis of minor cannabinoids and explored niche markets in the growing cannabis industry.



Dr. Jenna Ritter, for KD Pharma

Dr. Jenna Ritter has over 15 years of experience in the natural health products industry. She is an expert in the development of Omega-3 products in various dosage formats (liquids, capsules, emulsions). She has extensive experience in sensory evaluation of Omega-3 oils, lipid chemistry, including evaluation of natural antioxidants.



Dan Wiley, Vice President of Special Projects, KD Pharma Group

Dan joined the KD Pharma Group in September 2021, with over 20 years of specialty chemical and dietary supplement management expertise. He has broad operational, engineering, and commercial expertise, has built processing plants, and successfully launched many new products into the market. He currently serves as VP Special Projects for the KD Pharma Group where he leads commercialization of KD's emerging business units.

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