A SPECIAL ALL-DIGITAL ISSUE

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Omega-3 INSIGHTS

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VEGETARIAN Long-Chain OMEGA-3s

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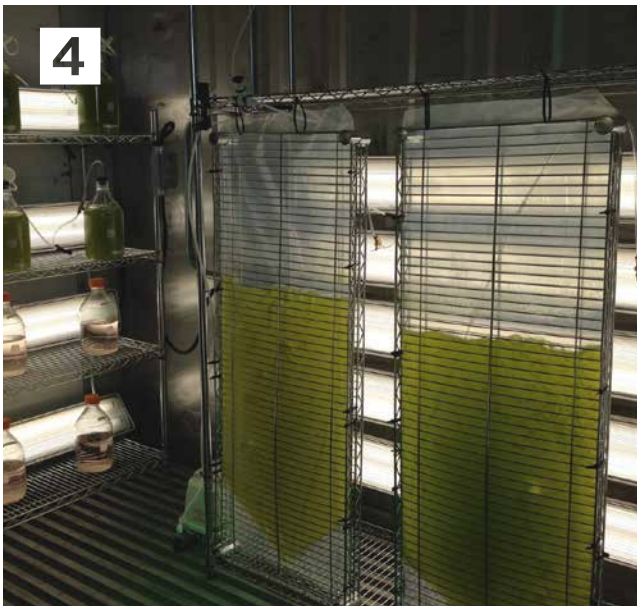

Opportunities in the Omega-3 Market

When looking at the positive science around the health benefits of long-chain omega-3s, it seems obvious to many of us that the nutrients should be a priority—in food or supplement form—for everyone. However, very few folks around the world actually get enough long-chain omega-3s. Perhaps people aren't aware of how omega-3s could benefit their health, or perhaps they have other reasons for bypassing the current choices on the market.

For example, it's estimated that more than 15 million U.S. adults are vegetarian or vegan, avoiding consumption of any animal products—including the fish and krill that make up the majority of long-chain omega-3 offerings on the market. Others may have concerns about sustainability (regardless of whether grounded in science, since perception is reality), or questions about the persistence of environmental toxins in these ingredients.

Fortunately, there are emerging options beyond the previous concept of consuming lots of short-chain omega-3 and hoping the conversion rate is high enough. Instead, companies are looking at different types of algae and fungi, as well as different plant sources that may deliver longer-chain omega-3s from their own breeding or possibly through genetic modification. As the industry looks to promote good health on a global scale from consumption of omega-3s, more options are a positive thing, and can only better support long-term wellness for millions of people around the world.

If you have additional thoughts on where the new opportunities may lie, don't hesitate to reach out and share those with us.

Best regards,

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VEGETARIAN SOURCES of EPA and DHA

by Adam Ismail

The market for vegetarian sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is still in its infancy, which is appropriate because today the market for these sources is primarily in infant formulas. While many products remain in the research and development (R&D) pipeline, the high cost of existing vegetarian sources has limited the market to applications such as infant formula, where the cost of competitive products is still high, and very high values are achieved for the underlying omega-3. Dietary supplements are the largest market for EPA and DHA omega-3 oils; but, in that category, fish oil remains a low-cost source of supply. This has forced many of the new vegetarian sources to rethink their business models in order to bring products to market faster and generate positive cash flow.

Single-Cell Organisms

There are five genus of algae producing the majority of vegetarian long-chain omega-3s today: *Schizochytrium, Crypthecodinium, Euglena, Nannochloropsis* and *Phaeodactylum* algae. In addition, there are a couple fungal species being used to produce omega-3s, including *Ulkenia* and *Yarrowia*. Of these, *Schizochytrium* and *Crypthecodinium* are probably the most well-known because they are the primary source of DHA in infant formula, and are also used in foods and supplements in smaller volumes. The Global Organization for EPA and DHA Omega-3s (GOED) estimates these two sources supply about 1,400 metric tons of oil, more than 98 percent of the global market. The supply chain used to be much more concentrated just a few years ago, but now there are multiple manufacturers producing these oils in the United States, China, Sweden and India.

GOED estimates *Schizochytrium* and *Crypthecodinium* algae supply more than 98 percent of the global market for vegetarian omega-3 oils.

Algal oils tend to have higher production costs and cost structures than other types of omega-3 oils, so it is important to understand how the various types of algae are produced. *Schizochytrium* and *Crypthecodinium* are produced in large fermentation tanks and use carbohydrates as a source of energy to feed the algae. Once the algae reaches its optimal concentration in the tanks, the oil is extracted from the biomass

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and refined. The oil yielded is standard triglyceride oil, similar to that found in fish oils, but it typically has between 40 and 45 percent DHA content. By contrast, the closest competitor to algal oils in infant formulas is tuna oil, with 21 to 28 percent DHA.

Schizochytrium has the potential to be optimized in many ways. In fact, a couple of suppliers, such as DSM and Source Omega, now offer varieties with more substantial levels of EPA, and some even make oils with more than 50 percent DHA. These specialty products are generally achieved by making small changes to the fermentation process, or incenting the organisms to flip their existing genetic circuitry "on" or "off" at opportune times during manufacturing.

Euglena is another algal source of omega-3 that has been used for more than a decade in Japan. The intellectual property (IP) is more or less controlled by a single company, appropriately named Euglena Co., which uses the algae to make consumer products for sale in Japan and China, so it is lesser known than other forms. However, this approach generates $41 million in revenue per year for Euglena, making it a significant source. *Euglena* grows through photosynthesis and relies on carbon dioxide as a source of energy, so it is produced in open-air systems rather than inside fermentation tanks.

Euglena is mostly being produced as a dried biomass for direct consumption, similar to a chlorella powder. The high digestibility of its cell wall allows it to be sold as a powder in drink mixes, powder capsules, or as an ingredient blended with other foods, rather than as an oil. While the genus produces EPA and DHA naturally, it also absorbs other fatty acids readily, so enriched *Euglena* is commercially available with up to 50 percent DHA and 20 percent EPA in its own natural state. However, by avoiding extraction and refining of the oil, the biomass also supplies phospholipids and other nutrients that have unique commercial value.

Nannochloropsis is the genus of algae that is probably the most active in terms of current R&D activity. There is already one commercial source of *Nannochloropsis* oil, from Qualitas Health. Part of what makes *Nannochloropsis* unique is it is a robust organism that can be made in a variety of production systems, but can also yield a variety of products. Qualitas staked out its area with oil that is rich in EPA, at approximately 25 percent of the oil content, but uniquely supplies it as glycolipids and phospholipids.

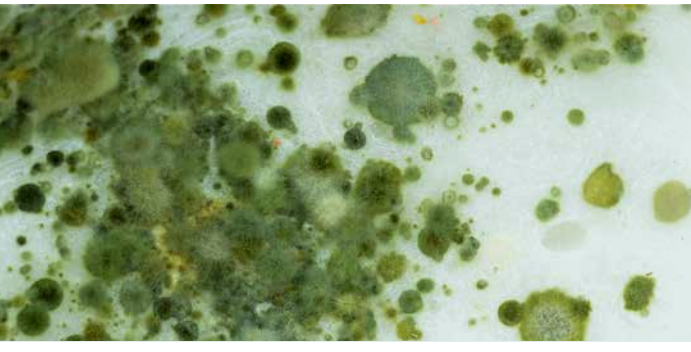
Other companies are working to bring *Nannochloropsis* to market on both open-air racetrack production systems as well as photobioreactor systems. Both use sunlight and carbon dioxide as fuel sources, but the main difference is the racetrack systems are comprised of large ponds that circulate the water around a track, while photobioreactors usually consist of large bags or clear

pipes in a closed system that allow sunlight in to feed the algae. No system is uniformly better than another, but each manufacturer utilizes the system that helps them achieve whatever production goals they have set. For instance, companies aiming for much density of biomass in the oil may feel a closed system helps reduce risk of contamination that can destroy a batch, while those looking to produce larger volumes of biomass may simply require the larger racetrack ponds.

In addition, *Nannochloropsis* can produce standard triglyceride oils, and some companies are flirting with EPA content between 50 to 70 percent naturally in their products. Many companies are exploring ways to produce DHA in *Nannochloropsis* algae as well, but it appears that will be second- or third-generation technology, if it is possible.

Ulkenia and *Phaeodactylum* are currently minor sources of omega-3s, produced solely by Simris Alg in Sweden. *Ulkenia* was more popular as a source of DHA in infant formulas in the past, produced by Nutrinova and later acquired by Lonza. It used to be grown exclusively in fermentation tanks, but Simris Alg has started producing it in photobioreactors to utilize photosynthesis. Similarly, the company is also producing EPA from *Phaeodactylum* algae in similar systems. Both algae strains yield triglyceride oils, but Simris Alg is commercializing its own supplements at this point rather than selling the oils, using a strategy to capture more of the downstream margin.

Fungi, like algae, are single-celled organisms, but they generally differ in that their cell membrane typically contains more chitosan and they generally do not utilize photosynthesis. *Ulkenia* is actually considered a fungus by some



Fungi, like algae, are single-celled organisms, but they generally differ in that their cell membrane typically contains more chitosan and they do not utilize photosynthesis.

researchers but others classify it as algae instead. Regardless, in most infant formulas, DHA is paired with arachidonic acid (ARA), an omega-6 fatty acid that is important in brain development. The primary source of ARA today is *M. Alpina*, a fungus grown in closed fermentation systems. Since we know this fungal method of producing fatty acids is clearly well-established, it begs the question about whether fatty acids such as EPA and DHA can be produced in fungi.

One key business strategy that many new algal companies are exploring was pioneered by *Schizochytrium* manufacturer Omega Tech in the 1990s, when it

used intermediate products to enrich animal feed with sources of DHA. Most new entrants are not focusing their entry strategies on gaining a foothold in infant formula, so as they are trying to bring their R&D projects into the market, this strategy of getting value from intermediate products is proving very attractive.

The largest consumer of fish oil in the world is not the omega-3 industry; it is actually the aquaculture industry. Farmed fish are fed a combination of oil and protein, which are essentially the same materials from which algal biomass is comprised. As fish oil prices have risen in recent years, fish feed has replaced much of the fish oil it used with vegetable oils; but, as a result, the amount of EPA and DHA accumulating in fish tissues has been falling—and omega-6 levels have been increasing due to the reliance on vegetable oils. This is largely seen as unattractive for human health, and the salmon industry has been experimenting with ways to economically produce fish with better health profiles.

Dupont pioneered the use of a yeast fungus, *Y. Lipolytica*, to produce an oil that contained nearly 70 percent EPA in its native triglyceride form. The oil was originally used in the supplement industry, but was pulled off the market temporarily to redevelop the manufacturing process. However, in the meantime, the company continued to make a biomass product that has successfully been used to enrich salmon feed with EPA and to produce a farmed salmon—sold under the Verlasso brand name—high in omega-3s, similar to a wild salmon.

Many of the *Nannochloropsis* entrants are pursuing a similar strategy and are undergoing feed trials at companies that make fish feed for aquaculture. However, it is quite difficult to successfully advance through feed trials, as there is ample competition. At a recent industry event, feed manufacturer EWOS noted it runs more than 400 feed trials on new ingredients and additives to its feed per year, and generally only one or two are considered successful enough to change the composition of feed.

Plant Sources

For many companies, the Holy Grail is being able to produce EPA and DHA in a plant that is already commercially used as an oilseed because there is proven demand. After all, oilseeds are already used in a wide variety of processed foods and animal feeds, so there is opportunity to take a product that is already inexpensive and widely used to make the food chain better. However, except for a couple of examples in weeds such as purslane, plants do not produce significant quantities of EPA and DHA, and certainly not in the existing sources of oilseed commodities.

This means plants must be genetically modified in order to convert the fatty acids they already produce into EPA and DHA. There are a number of

companies and research institutions working in this area, mostly utilizing genes from algae that are responsible for converting various fatty acids. These companies have been full of promise, and they appear to have made significant headway in the past year. Rothamsted Research Institute in the U.K. and CSIRO in Australia both announced they have performed successful crop trials this year with camelina and canola, respectively. In the past, the industry consistently heard these crops were just five to 10 years away from being commercialized, but the goal seemed somewhat elusive. Now that successful crop tests have been conducted, the companies basically just have to start planting and regrowing the plants to generate enough seed to start planting the crops at commercial scales. This affords them a few years to scale up while they are pursuing regulatory approvals for their products.

The hope for these types of companies is that they will be able to deliver EPA and DHA levels in quantities similar to fish, but achieve the economics of typical oilseeds, in which the oil and protein fractions sell for much lower prices than fish oil and fishmeal today. This makes markets such as animal and aquaculture feed very attractive, but human nutrition markets are also clamoring for low-cost vegetarian sources of supply. It will be interesting to watch how these companies navigate the genetically modified organism (GMO) area to bring a healthful product to market.

Companies pursuing these crops hope to deliver EPA and DHA levels similar to fish, while achieving the economics of typical oilseeds, in which the oil and protein fractions sell for much lower prices.

Five years ago, there were really only two types of vegetarian long-chain omega-3 oils, but the market has now seen a small explosion of new entrants producing those same types of oils—along with new entrants making oils from the *Nannochloropsis*, *Phaeodactylum* and *Yarrowia* single-celled organisms. It also appears EPA and DHA oils from oilseed crops are not far behind. All of this means it does finally seem like we are entering the renaissance of the vegetarian EPA/DHA market. ❑

Adam Ismail has served as the first executive director at Global Organization for EPA and DHA Omega-3s (GOED) for more than eight years and oversees all organizational development for new and existing members. Since being named executive director in March 2007, Ismail has led GOED to experience a seven-fold growth in its membership and budget, worked on the founding of an international learning consortium based at Purdue University, and spearheaded overturning a ban on fish oil imports in Europe. With more than 10 years in the natural health and nutraceutical industries, Ismail's previous experience includes product development for Cargill Inc.'s omega-3 line and several years as a senior consultant for both Health Strategy Consulting and Health Business Partners. He holds an MBA from the University of Navarra's IESE Business School (Barcelona, Spain) and a bachelor's degree from Boston University's School of Management.

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Vegetarian Omegas: The Importance of SDA

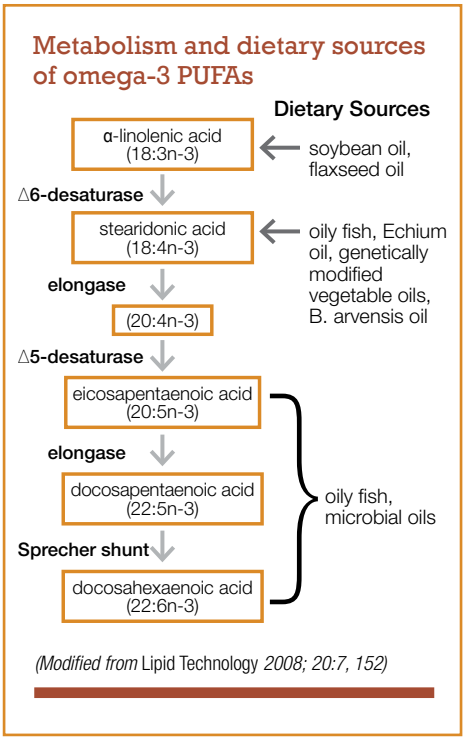
by Greg Cumberford

Stearidonic acid (SDA), a long-chain omega-3 fatty acid (C18:4) with a range of health benefits, could be a game-changer in supplements and foods because it offers a truly clean label, vegan, traceable and highly scalable pathway to meeting omega-3 recommended daily intakes.

SDA in Omega-3 Metabolism

Significant dietary SDA is commercially available only from vascular plant origins, although it occurs naturally at low levels (0.5 to 2 percent typically) in edible oily fish. Metabolically, SDA is synthesized by humans from dietary alpha-linolenic acid (ALA, C18:3), a more widely abundant omega-3 found in some seed and nut oils such as flax and chia. ALA is converted into SDA by delta-six desaturase (Δ6D), an enzyme originating in the liver. While critical to the synthesis of very long-chain omega-3s, this enzymatic conversion is particularly inefficient in humans. SDA is then further converted to the widely studied and well-known omega-3 eicosapentaenoic acid (EPA, C20:5). Human cell membranes require the highly unsaturated fatty acids to be incorporated as phospholipids in order to maintain proper fluidity, porosity and integrity, and to serve as reservoirs of anti-inflammatory response mediators. While SDA is itself a product of ALA metabolism, direct dietary SDA intake offers a much more efficient way to synthesize EPA from non-marine sources. (See Figure 1.)

Figure 1



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As such, SDA has been dubbed a "pro-EPA" omega-3 fatty acid because it bypasses the Δ6D rate-limiting step in humans that causes plant-derived ALA sources to convert poorly to the more elongated omega-3 fatty acids EPA, docosapentaenoic acid (DPA, C22:5) and docosahexaenoic acid (DHA, C22:6). Clinical studies have shown while SDA does not convert to DHA to any significant degree, SDA converts to EPA in tissues and circulating cells up to five times more efficiently than ALA. Further, since SDA is less unsaturated than EPA and DHA, it is more stable, less prone to oxidation, and therefore more amenable to use a wide variety of food and beverage applications where resulting "fishy" off-flavors present challenges to palatability and consumer acceptance.

SDA Commercial Supply and Sustainability

SDA came to prominent awareness in the U.S. natural products industry due to developmental work announced by Monsanto and Solae of a genetically modified (GM) SDA-enriched soya oil in 2008 to 2010. The Monsanto product, whose commercialization rights are now owned by DSM, does not yet appear to be commercially available for human consumption. Recently, Nature's Crops International gained regulatory approvals in the United States and EU for refined *Buglossoides arvensis* seed oil (tradename: Ahiflower), which has the highest SDA content from a single non-GM plant source.

Figure 2

Commercially available oilseed sources of SDA are as follows:

Oilseed Source	SDA Level
	up to 2%
	2.5-4.5%
	12-14%
	18-20%

In 2013, the Global Organization for EPA and DHA Omega-3s (GOED) reported that in 12 industrialized countries, 220 million consumers had stopped taking marine-derived omega-3 supplements due to sustainability concerns. This is a large and expanding consumer market. More recently, in 2014 and 2015, one of the Peruvian anchoveta fisheries and the U.S. West Coast sardine fishery were closed due to plummeting fish stocks. This is significant because the Peruvian fishery is responsible for supplying about 70 percent of the world's omega-3 fish oil, as reported by GOED.

This event, though relatively short-lived, underscored the growing need for an "all-in" approach to supplying omega-3 fatty acids globally—from marine, algal and plant sources. Whether due to climate factors, unregulated overfishing in nearby waters, or changes in the reproductive ecology of wild anchovy and sardines, the resulting supply chain disruptions of available fish meals to aquaculture (salmon, shrimp, etc.) and for human dietary supplement uses portend a longer-term sustainable supply concern. While the Peruvian, Moroccan, U.S. West Coast and other anchovy and sardine fisheries subject to intermittent population collapses can recover with proper management, diverse new omega-3 nutritional sources are needed to address long-term demand, let alone respond to consumers who cannot or choose not to eat marine animal products.

Supply chain disruptions of available fish meals to aquaculture and for human dietary supplement uses portend a longer-term sustainable supply concern.

In an era of rapidly expanding middle-class affluence in countries such as China, Brazil and India (total combined population of 2.8 billion), and with returning growth in omega-3 product demand in North America after several years of negative publicity about a purported lack of health benefits of omega-3s, demand for high-quality, high-purity omega-3 nutrition will increase steadily for the foreseeable future.

A recent industry market research report shows the global demand for omega-3 supplements growing to $4.48 billion by 2020 with a 13.1 percent annual growth rate. This means SDA, a readily scalable and sustainable plant-based omega-3 source which does not rely on marine fisheries, nor on more costly algal or microbial omega-3 sources of EPA and DHA, will certainly help solve a global supply dilemma. SDA presents formulators, manufacturers and consumers an immediate alternative to current plant-derived omega 3s from flax and chia—increasing the overall effective omega-3 payload and hence reducing the total caloric intake and/or dosing.

SDA Clinical Science

SDA has its own emerging body of scientific and clinical research, supporting health benefits both aligned with and in some cases independent of omega-3 ALA, EPA and DHA findings. This is the case in topical and ingestible SDA

applications. Recent peer-reviewed published references include the following benefits or activities associated with SDA:

Anti-Aging: Topical SDA oil can increase dermal structural proteins and reduce fine lines and wrinkles, while inhibiting UV-induced inflammation.

Weight Control: SDA can suppress adipocyte (fat cell) differentiation.

Blood Glucose Control: SDA can suppress certain biomarkers associated with type 2 diabetes.

Healthy Inflammatory Response: Plant SDA oil decreases intestinal PGE2 sequestration and reduces endogenous production of COX-derived arachidonic acid metabolites.

Heart Health: Plant SDA oil sources decrease cholesterol blood fractions and triglycerides, benefiting people at risk for coronary heart disease (CHD) and cardiovascular disease (CVD).

Long-term prospective studies in humans investigating the specific health effects of SDA consumption have yet to be carried out and published. However, preliminary cell line, animal and human studies indicate SDA has beneficial effects on various biomarkers distinct from ALA and DHA. SDA is indeed a promising "pro-EPA" omega-3 alternative, especially for vegetarians or people choosing not to consume marine or algal omega-3 sources. In the natural products industry's efforts to respond to consumer concerns about the sustainability, traceability, purity and sensory appeal of omega-3 nutrition sources, SDA is truly a market-responsive omega-3 fatty acid. ❑

Greg Cumberford, a 25-year natural products industry executive, is vice president – strategic initiatives with Nature's Crops International.

OMEGA-3 CONTACTS

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