Benefits of optimal omega-3 intake and status
EXECUTIVE SUMMARY

With many positive health benefits, omega-3 long chain polyunsaturated fatty acids (PUFAs) are one of the most researched micronutrients in the world. Yet, in many regions around the globe, a high proportion of the adult population still does not have adequate omega-3 status and this could have a significant public health impact. This whitepaper draws on the latest clinical and market data to demonstrate the importance of omega-3s in supporting human health. Highlighting key studies, it explains the vital function of omega-3s in cardiovascular health and risk reduction. It then provides a summary of continued positive research into omega-3s and brain health, as well as emerging areas such as eye and liver health. In addition, the paper shares the findings of a new structured review to identify regions around the world considered most at risk of health issues due to low red blood cell (RBC) omega-3 fatty acid levels. This document explores the barriers to effective intake and the estimated healthcare costs of deficient omega-3 intake are also presented.

WHAT ARE OMEGA-3 FATTY ACIDS?

To date, more than 31,000 scientific papers have been published citing omega-3 PUFAs. The greatest proportion (circa 20%) focuses on heart health, while brain health makes up the second largest volume of research at around 12%. The benefits during pregnancy and infancy, as well as for overall eye health, complete the top four research topics. As studies continue to emerge in these and other areas of human health, scientists gain a deeper understanding of how essential it is to obtain adequate intake of omega-3 fatty acids in the daily diet.

Scientific research has focused primarily on two types of omega-3 fatty acids – eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Together with alpha-linolenic acid (ALA), EPA and DHA are recognized as the main omega-3 fatty acids. There are, however, important differences between the three:

- **ALA**: this shorter-chain fatty acid acts as a source of energy when it is catabolized via beta oxidation, and as a building block for EPA and DHA. The body cannot produce it, but the quantities required can typically be obtained in the diet from sources such as vegetable oils like soy and canola, as well as nuts (especially walnuts), chia, hemp and flax seeds (linseed).

- **EPA** and **DHA**: functionally the most important omega-3s, these long chain fatty acids may be synthesized by the metabolic conversion (elongation and desaturation) of ALA. In humans, this conversion happens in very limited amounts. Therefore, it is essential to obtain preformed EPA and DHA in the diet in order to achieve adequate blood and tissue levels to prevent a deficient state. Principally found in fatty fish, such as salmon, tuna, herring, sardine and anchovy, marine algae are also a rich vegetarian source of EPA and DHA.

- **Both EPA and DHA** are important for, and play a key role in, overall health. Due to their different chemical structures, each performs a unique, but complementary function in the body. The most marked distinction is that unlike EPA, DHA is also a structural component of every cell throughout the body – with significant quantities found in the heart, brain, nervous system, eyes and testes.

The ratio of omega-6:omega-3 fatty acids in the human diet has been studied to assess how much individuals consume of each. Omega-6 fats are found in foods such as corn (maize), canola (rapeseed) and soy(a) oils. Healthy ratios of omega-6 to omega-3 range from 1:1 to 2:1, with people consuming both fats in proportionally equal amounts. However, research suggests that modern eating habits have resulted in typical Western diets containing higher levels of omega-6 compared to omega-3, with ratios of between 10:1 and 20:1. Research shows that excessive levels of omega-6 PUFAs and a very high omega-6 to omega-3 ratio can promote the pathogenesis of many diseases, including cancer, cardiovascular disease (CVD), and inflammatory and autoimmune diseases. Meanwhile, increased levels of omega-3s (a low omega-6 to omega-3 ratio) can have suppressive effects. These findings indicate that there is a need for individuals to adapt their diets to address the imbalance of omega-6 to omega-3.
GLOBAL OMEGA-3 STATUS: EPA AND DHA

Despite the considerable research and supporting evidence of a range of positive health benefits associated with omega-3s, a new structured review indicates that adults in most regions of the world have a low to very low status of EPA and DHA.4

The first systematic review to examine blood levels of omega-3s (specifically EPA and DHA) on a global scale, the paper analyzed 298 studies to create a global map (figure 1) showing the levels of these two long chain fatty acids in the blood stream of healthy adults.

The review finds that consumption of EPA and DHA may be too low to have a preventative or positive action on cardiovascular and cognitive health in a number of regions worldwide. Those identified as having a low omega-3 status are believed to be at higher risk of chronic disease, such as CVD and cancer.

North, South and Central America, Central and Southern Europe, the Middle East, Southeast Asia and Africa are all classified as having very low EPA and DHA blood levels (<4%).5

Interestingly, the regions with indigenous populations or where Westernized food habits have not been adopted, such as The Sea of Japan and Scandinavia, are classified as having a high EPA and DHA (>8%) status.

It is anticipated that this unique data will not only be used to provide a better understanding of current levels of omega-3 PUFAs in the blood of healthy adults around the world, but also to help develop regulatory guidelines for intake on a national and global level.

Figure 1: The global omega-3 status map highlights many countries that have low to very low blood levels of EPA and DHA6
OMEGA-3S AND CARDIOVASCULAR HEALTH

Typically recommended by healthcare practitioners to address immune modulation, pain and inflammation, omega-3s play an important role in supporting overall health, as well as chronic disease management and prevention. Low levels of PUFAs in the bloodstream are associated with a high risk of a number of chronic diseases, such as heart disease, cancer, autoimmune disease, depression and diabetes. Omega-3 RBC blood testing can be conducted by healthcare practitioners to determine whether an individual is at low (>8%) or high (≤4%) risk of CVD.7

A recent meta-analysis suggests that insufficient omega-3 fatty acid intake and status may increase the risk of all-cause mortality.8 Published in Scientific Reports, this systematic review analyzed 11 prospective observational studies involving more than 31,000 deaths among 371,965 participants from general global populations. It sought to evaluate the associations of dietary or circulating long chain PUFAs – specifically EPA and DHA – with the risk of all-cause mortality, to address previously identified inconsistencies:

- Potentially eligible studies were identified following a literature search of PubMed and EMBASE databases using a defined search strategy.
- Seven studies measuring dietary intake of long chain PUFAs were selected (published between 2004 and 2015).
- Four studies measuring circulating long chain PUFAs were evaluated (published between 2008 and 2015).

The results of this extensive review found both dietary and circulating long chain omega-3 PUFAs to be significantly associated with reduced risk of all-cause mortality – with both EPA and DHA delivering similar results. In addition, while further, more detailed research is recommended, the overall analysis shows that a 1% increase in RBC levels of EPA and DHA may reduce the risk of all-cause mortality by as much as 20%.

OMEGA-3S AND CARDIOVASCULAR HEALTH

View from consumers

In a recent global consumer health concerns survey that interviewed 7,541 people across 10 countries, it was discovered that 61% of respondents are worried about their cardiac health. Two-thirds (66%) of the interviewees act to address their concerns, with 33% focusing on diet and nutrition and 14% taking supplements.9

Omega-3s are strongly associated with heart health benefits and cardiovascular risk reduction and there has been an extensive number of scientific papers devoted to the topic, which have primarily shown favorable results. For instance, a recently published longitudinal study showed a 26% reduction in CVD mortality among marine omega-3 supplement users compared to non-supplement users when taken over a 22-year period.10 The media, however, has given disproportionate coverage to some recent null studies, especially when compared to the magnitude of positive outcomes. The mixed messaging has resulted in confusion amongst both healthcare practitioners and consumers.

In particular, there have been concerns amongst clinicians regarding the impact of omega-3s on human health in specific circumstances. For example, there has been considerable debate concerning fish oil and bleeding since the 1980s – with some worried that fish oil supplements could potentially increase the risk of bleeding for both healthy people, as well as those undergoing surgery and/or on blood thinning medications. To address these concerns, a recent systematic review has evaluated the effects of omega-3s on bleeding risk from 52 publications, and looked to provide recommendations on whether it is necessary to discontinue fish oil supplementation prior to surgery, in conjunction with antithrombotic treatment.

The results showed that in the majority of studies, including healthy subjects, there was reduced platelet aggregation following fish oil intake, but this was not reflected in an increased bleeding risk during surgery. Fish oil supplementation before or immediately after surgery did not increase bleeding either during or following surgery in randomized controlled trials. In fact, two of the publications included in the review reported that patients exposed to fish oil had a reduced need for red blood cell transfusions during surgery. Based on this systematic review, discontinuation of fish oil supplementation in combination with antithrombotic treatment prior to surgery is no longer recommended.11,12
MECHANISM BEHIND THE WIDE-RANGING CARDIOVASCULAR BENEFITS

Recent research suggests that omega-3 fatty acids may reduce many risk factors associated with CVD, including blood pressure, vascular function, endothelial dysfunction, inflammation, platelet reactivity and thrombosis, plasma triglyceride concentrations, heart rate and heart rate variability. Several reviews have shown that omega-3 fatty acids may also reduce mortality in ‘at-risk’ patients, by providing a therapeutic benefit across many physiological parameters affecting the heart.

The exact mechanism by which omega-3 fatty acids exert these protective cardiovascular effects remains an area of active research. It is, however, known that, as an integral part of cell membranes throughout the body, omega-3s influence the function of cell receptors and cell-to-cell communication. As such, these fatty acids are the starting point for the production of hormone-like bioactive substances, called eicosanoids, that regulate many functions in the body including blood clotting, the contraction and relaxation of muscles and artery walls, and modulation of inflammatory pathways. Such effects have been linked to a reduction in CVD and strokes.

The vast body of research undertaken in recent years to fully explore the effects of adequate intake of EPA and DHA on cardiovascular health provides compelling evidence of the following health benefits:

- Omega-3 PUFA therapy holds promise for primary and secondary prevention of CVDs.15
- Epidemiological studies support the cardioprotective effects of EPA and DHA from fish and fish oils, particularly in the setting of primary prevention.16
- Higher circulating plasma and RBC levels of individual (EPA and DHA) and total omega-3 PUFAs are associated with lower mortality, especially from coronary heart disease (CHD), in older adults. This demonstrates the cardioprotective benefit of ensuring adequate dietary or supplemental intake of omega-3s.17
- A recent randomized clinical trial concluded that omega-3 fatty acids may reduce adverse remodeling after a heart attack. A dose of four grams of omega-3 fatty acids a day for six months resulted in a 5.8% reduction in left ventricular end-systolic volume index, a clinical marker that can predict patient outcome after a heart attack, when compared to a placebo.18

Did you know?
There are ongoing clinical trials that, it is hoped, will help to build the market for drug development in the cardiovascular space.13
A recent systematic review and meta-analysis examining the role that omega-3s can play when administered to patients in cardiac surgery has shown a number of positive results. Firstly, that omega-3s may be able to significantly reduce cardiac patients’ time spent in hospital and the incidence of postoperative atrial fibrillation (POAF), a major risk factor for cardiac death. Secondly, patients exposed to extra-corporeal circulation (ECC) seemed to particularly benefit from omega-3 therapy with a greater reduction in the incidence of POAF.20

A new meta-analysis, which aimed to determine the effect of EPA and DHA on CHD, and the association between intake and risk, has found that intake of EPA and DHA may reduce the risk of CHD in people with elevated blood levels of triglycerides or LDL-cholesterol. Results show a statistically significant 18% reduced risk of CHD in people with elevated blood levels of triglycerides or LDL-cholesterol. These results are consistent with earlier studies.21

Investigations into the mode of action of omega-3s in combination with other heart-related medications have also reported important results for cardiovascular health, demonstrating a potential synergistic effect. For example, statins are widely prescribed to help lower the level of low density (LDL) cholesterol in the blood and reduce the risk of CVD. A combination of EPA with statins has been shown to significantly decrease the incidence of coronary events by 19%.23

The findings of a new JAMA study, which aimed to estimate associations of intake of 10 specific dietary factors with mortality, due to heart disease, stroke, and type-2 diabetes (cardiometabolic mortality), among US adults have been published. Dietary factors were estimated to be associated with 48.6% of cardiometabolic deaths in men and 41.8% in women, with 7.8% linked to low intake of seafood omega-3 fats. The authors concluded that “these results should help identify priorities, guide public health planning, and inform strategies to alter dietary habits and improve health.”24

Approved claims in the EU

Formal recognition of the role of omega-3s in relation to cardiovascular health was given by the European Food Safety Authority (EFSA) in 2009 when it returned a positive opinion on EPA and DHA as contributing to “the maintenance of normal cardiac function.” Further consideration by EFSA led to three more detailed heart health claims.22

- EPA and DHA contribute to the normal function of the heart (based on a daily intake of 250 mg combined total).
- EPA and DHA contribute to the maintenance of normal blood pressure (based on a daily intake of 3 g).
- DHA contributes to the maintenance of normal blood triglyceride levels (based on a daily intake of 2 g).
- EPA and DHA contribute to the maintenance of normal blood triglyceride levels (based on a daily intake of 2 g combined total).

These claims have garnered further support from organizations such as the World Health Organisation (WHO), the Heart Foundation and the International Society for the Study of Fatty Acids and Lipids (ISSFAL), which also recommend a daily intake of 250-500mg/g EPA and DHA.
OMEGA-3S AND BRAIN HEALTH

View from consumers

Brain health is a globally prevalent issue that can affect people throughout all life stages. A recent survey shows that many consumers worldwide are currently concerned with their mental and emotional health or mental sharpness. 44% of the survey’s respondents indicated that they were worried about Alzheimer’s disease or the loss of memory.25

Omega-3s are a major and essential structural component of the brain. They are critical in supporting almost every area of brain function and development throughout every life stage, including brain development during infancy, attention and learning, cognitive health, memory support, and the reduction of depression symptoms.

Given this extensive involvement in vital physiological functions in the brain, the scientific community has turned its attention to learning more about omega-3s in this context. In light of social and healthcare issues raised by the increase in dementia and Alzheimer’s disease globally, studies to demonstrate the potential benefit of omega-3s could have profound public health implications.

Individuals of all ages, both with and without cognitive disorders, are target audiences for research:

• Omega-3 intake from fish sources is associated with a lower risk of cognitive impairment. Fish derived DHA intake is associated with a lower risk of dementia and Alzheimer’s disease, but without a linear dose-response relation.26
• High-dose DHA supplementation in apolipoprotein E ε4 allele (APOE4) carriers – a unique population that is at a significant risk for developing Alzheimer’s disease – before the onset of dementia can be a promising approach to decreasing the incidence of Alzheimer’s disease. The authors concluded that ”given the safety profile, availability, and affordability of DHA supplements, refining an omega-3 intervention in APOE4 carriers is warranted.”27
• Intake of DHA alone or in combination with EPA contributes to support memory health in older adults with mild memory complaints.28
• Individuals with a regular low intake of long chain omega-3 PUFAs, children with low literacy ability and who are under or malnourished, and older adults with Age Related Cognitive Decline (ARCD) or Mild Cognitive Impairment (MCI), may benefit the most from consuming long chain omega-3s, particularly DHA.29
• Evidence indicates that long chain omega-3 fatty acids exert a positive effect on brain functions in healthy older adults, by improving executive functioning abilities.30
• Fish oil intake may support memory health in MCI subjects; however further investigations are needed before definitive recommendations can be made.31
• 24-week supplementation with 900 mg/d DHA supports memory health in healthy older adults with ARCD.32
• DHA supplementation appears to offer a safe and effective way to improve reading and behavior in healthy, but underperforming children, from mainstream schools.33
• Omega-3 PUFA supplementation is more beneficial in individuals with Major Depressive Disorder (MDD) who take their daily supplement as an adjunct to anti-depressant medications, rather than either therapy alone.34

In addition, EFSA’s positive scientific opinion that a cause and effect relationship has been established between consumption of DHA and the contribution to normal brain development is a major boost; providing a major driver for further evidence-based studies.

Approved claims in the EU

The expert EFSA panel noted the well-established role of DHA in cognitive performance across all age groups, when it approved the following statement in 2010:

• DHA contributes to the maintenance of normal brain function.

From fetal development during pregnancy through infancy and early childhood, EFSA recognizes that DHA has a positive influence in early life:

• DHA maternal intake contributes to the normal brain development of the fetus and breastfed infants.25
• DHA maternal intake contributes to the normal development of the eye of the fetus and breastfed infants.25
• DHA intake contributes to the normal visual development of infants up to 12 months of age.25
The scope of research pertaining to omega-3s also encompasses a number of additional health platforms where initial positive findings are suggestive, but require further substantiation.

**Vision**

Many studies and an EFSA approved health claim have prompted further interest:

- **Lack of education:** the majority of consumers are aware of the health benefits of omega-3s.52
- **Conflicting communication about omega-3s:** Many studies and an EFSA approved health claim have prompted further interest:
  - Omega-3s may help protect adult eyes from age-related macular degeneration (AMD) and dry eye syndrome.39,40,41
  - In 2010, EFSA released its positive scientific opinion on the following health claim: “DHA contributes to the maintenance of healthy vision.”42

**Liver**

There is promising evidence that omega-3s may improve liver function:

- Omega-3s have been shown to reverse liver pathology without related weight loss.43,44
- Omega-3s are recommended for primary prevention of liver disease in individuals at high risk of developing non-alcoholic fatty liver disease (NAFLD). NAFLD is the most common chronic liver disorder in the Western world.45

**Eye health**

Eye health is an important issue that affects many people globally. A recent global survey examining consumer health concerns revealed that 70% of interviewees across 10 countries are worried about their eye health, including their eyesight.18

**PUBLIC HEALTH BENEFITS OF ADEQUATE OMEGA-3 INTAKE**

An equally thought-provoking, independent study, recently commissioned by Food Supplements Europe, looks at low omega-3 status from an economic perspective. It found that regular consumption of omega-3 supplements could save €12.9 billion a year in healthcare costs in the European Union alone:50

- The research tested the hypothesis that the potential heart health benefits gained from daily intake of omega-3 supplements among high risk individuals aged 55 and over, could lead to a reduction in the number of costly, CVD-attributed, medical events.
- The findings of the random-effects systematic review were aggregated and the expected relative risk reduction determined to create a theoretical scenario model. The model was then used to establish the difference in benefits and cost that EU healthcare policy makers could expect, if everyone in targeted populations with high CVD risk adopted a daily intake of omega-3.
- Overall, 24% of people aged 55 and over are considered to be at risk of experiencing a hospital event from CVD. The findings of the study indicate that this risk could be reduced by 4.9% through consumption of 1,000 mg a day of omega-3 EPA and DHA. This corresponds to more than 15 million fewer CVD-attributed events between now and 2020.

In the United States, a similar report from 2013 states that omega-3 supplementation at a preventative level of 1,000 mg a day has a saving potential in avoided CVD-attributed hospital costs of almost US$500 million a year – a US$3.9 billion cumulative healthcare cost saving from 2013 to 2020.51 In addition to cost savings, the report also suggests that the same dose could avoid just over one million CHD-related medical events each year, equating to a relative risk reduction of 6.9%.

There are several ongoing intervention studies worldwide on omega-3 intake, the results of which are due to be published throughout 2017 and into early 2018. The level of research that is currently underway demonstrates that academia and governments are investing in the science behind the benefits of omega-3s and its important role in human health. The findings of these studies can help to support future nutrition and public health agendas.

**Air pollution**

A number of publications have reported that omega-3 intake may help to protect against the adverse health risks associated with particulate air pollution in terms of:

- Lowering the risk of asthma incidents.46
- Reducing oxidative stress.47
- Reducing adverse effects on the heart and normalizing the blood lipid profile.48
- Normalizing heart rate variability.49

**OVERCOMING BARRIERS TO EFFECTIVE INTAKE**

A recent DSM survey of over 14,000 consumers across the world found that 64% of participants are aware of the health benefits of omega-3s.52 However, previous DSM research carried out amongst 11,000 consumers globally, identified a number of consumer barriers for entering or re-entering the omega-3 supplement category:53

- **Need for multiple dosage to achieve required intake.**
- **Capsule size.**
- **Fishy burp and taste.**
- **Inconsistent or unclear language on labels and packaging:** in the US, nearly one out of every two shoppers walk away from the omega-3 aisle without making a purchase due to price/promotion and complexity.54
- **Conflicting communication about omega-3 benefits in mainstream media.**

Continued research and core competence in innovation in the field of nutritional lipids, allows food manufacturers to create products that directly address these concerns, and are convenient as well as appealing to consumers.
How can adequate omega-3 levels be achieved globally?

Increasing consumer awareness of omega-3s does not appear to be translating yet to adequate daily consumption for the associated health benefits to be gained. Identified consumer barriers to beneficial intake need to be addressed. Therefore, there is an ongoing need to continue to raise awareness among healthcare practitioners, consumers and industry that there is a deficiency among a high proportion of healthy adult populations around the world. Education is an integral part of this strategy. It is important to communicate effectively the impact of low and very low blood levels of EPA and DHA — not only in terms of the potential health implications for the individual, but also the much wider issue of pressure on already stretched public healthcare expenditure. Beyond education, it is continuous research and innovation that will allow the creation of new products that overcome consumer barriers and contribute to effective intake.

Importantly, consumers need to be encouraged to ensure that they have a sufficient omega-3 intake in a way that suits their lifestyle. The optimal level of omega-3s can be reached by eating fatty fish, such as salmon, tuna, herring, sardine and anchovy, several times a week. However, this may not be compatible with modern eating habits for many people around the world for a variety of reasons. For many, supplements and/or fortified foods may offer the most convenient and cost-effective ways to ensure that the target level of EPA and DHA in the bloodstream is achieved regularly to optimize health.

### Key take-away messages

- **EPA and DHA are essential for overall human health.** However, a high proportion of the global adult population has inadequate omega-3 status.
- **Maintaining a healthy omega-6:omega-3 ratio is important for health,** but typical Western diets contain higher levels of omega-6 compared to omega-3. The imbalance needs to be addressed.
- **There is substantiated scientific evidence to show the vital function of omega-3s in cardiovascular health and risk reduction.**
- **Emerging research also shows the benefits that optimal omega-3 intake and status may have for brain health, eye health and liver health.**
- **Low intake and low status of EPA and DHA can have serious consequences on human health.** Low levels of omega-3s in the bloodstream are associated with an increased risk of a number of chronic diseases, such as heart disease, cancer, autoimmune disease, depression and diabetes.
- **There are also economic implications for low omega-3 intake.** Regular consumption of omega-3 supplements could save billions each year in healthcare costs in the EU alone.
- **Several consumer barriers can be attributed to insufficient omega-3 intake:** lack of education, inconsistent or unclear language on labels and packaging, conflicting communication about omega-3 benefits, capsule size, fishy burp and taste, and need for multiple dosage to achieve required intake.
- **Continued research and innovation in the field of nutritional lipids allows food, beverage and dietary supplements manufacturers to create appealing products that address consumer health concerns.**
- **Omega-3s are the most researched micronutrient in the world,** but there is still an ongoing need to raise awareness among healthcare practitioners, consumers and the food industry about the omega-3 deficiency among a high proportion of healthy adults worldwide. This can be done through education, continuous research and innovation.

For more information visit: [www.dsm.com/nutritional-lipids](http://www.dsm.com/nutritional-lipids)
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