Journal of Nutrition & Intermediary Metabolism 5 (2016) 3–10

Contents lists available at ScienceDirect

Journal of Nutrition & Intermediary Metabolism

journal homepage: http://www.jnimonline.com/

Marine oils: Complex, confusing, confounded?

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ARTICLE INFO

Article history:
Received 14 December 2015
Received in revised form
24 March 2016
Accepted 25 March 2016
Available online 29 March 2016

ABSTRACT

Marine oils gained prominence following the report that Greenland Inuits who consumed a high-fat diet rich in long-chain n-3 polyunsaturated fatty acids (PUFAs) also had low rates of cardiovascular disease. Marine n-3 PUFAs have since become a billion dollar industry, which will continue to grow based on current trends. However, recent systematic reviews question the health benefits of marine oil supplements, particularly in the prevention of cardiovascular disease. Marine oils constitute an extremely complex dietary intervention for a number of reasons: i) the many chemical compounds they contain; ii) the many biological processes affected by n-3 PUFAs; iii) their tendency to deteriorate and form potentially toxic primary and secondary oxidation products; and iv) inaccuracy in the labelling of consumer products. These complexities may confound the clinical literature, limiting the ability to make substantive conclusions for some key health outcomes. Thus, there is a pressing need for clinical trials using marine oils whose composition has been independently verified and demonstrated to be minimally oxidised. Without such data, it is premature to conclude that n-3 PUFA rich supplements are ineffective.

1. Introduction

In 1971, Bang and Dyerberg reported low rates of cardiovascular disease in Greenland Inuits who consumed a fatty diet made up almost exclusively of oily fish and seal meat, a paradox given the contemporary understanding of the association between dietary fat and cardiovascular disease [1]. While this observation has recently been questioned [2], it sparked considerable scientific interest. Since then, a vast scientific literature has emerged exploring the health effects of marine oils rich in n-3 polyunsaturated fatty acids (PUFAs), in particular the long chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Alongside, a billion dollar industry has arisen [3], marketing fish oil and other marine oils to consumers, such that marine oils are now one of the most popular supplements worldwide [4]. In the USA, they are used by 6.5% of the population (37% of supplement users) [4] and 8% of college students [5]. In a study in New Zealand, 15% of women undergoing fertility treatment were taking marine oil supplements [6].

In many ways, scientists and physicians have approached marine oils as they would a medication, investigating their health effects using randomised controlled trials, with controlled doses, for specific indications. Marine oils have a long list of apparent indications, including prevention of cardiovascular disease [7] and cognitive decline [8], improvement of infant neurodevelopment [8], and treatment of inflammatory diseases such as rheumatoid arthritis and asthma [9]. Recommended doses differ depending on indication [9,10], and products are labelled so that consumers can determine a target dose of n-3 PUFAs.

However, there is increasing evidence to suggest that marine oils are actually ineffective for secondary prevention of cardiovascular disease, which is their highest profile indication [11,12]. In reality, marine oil supplements are quite unlike medications in many respects, including the complexity of their biological effects, their impurity (containing many chemical compounds), the inaccuracy of labelled content, their potential to degrade to toxic compounds, and limited regulation of sales and marketing. Consideration of the complexity of marine oils and the ways they differ from typical drugs may help explain why they appear not to have delivered on the promising tale of the Greenland Inuits.

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http://dx.doi.org/10.1016/j.jnim.2016.03.003

2. n-3 PUFA actions

There is a very large range of physiological effects associated with n-3 PUFAs, which is quite unlike most medications.

2.1. Anti-inflammatory

They inhibit inflammatory processes at 5 distinct levels:

1) Increasing cell membrane fluidity, which interferes with activation of immune cells such as T-lymphocytes [13].
2) Activating the transcription factors PPAR-α [14] and PPAR-γ [15], and the transmembrane receptor GPR-120 [16], which inhibit the proinflammatory NF-κB pathway [17–19]. This reduces the production of inflammatory cytokines such as TNF-α and IL-6 and cell adhesion molecules such as ICAM and VCAM [9].
3) Competing with n-6 PUFAs as a substrate for the COX-2 enzyme, shifting the balance of eicosanoids from the proinflammatory n-6 series to the anti-inflammatory or less inflammatory n-3 series [9].
4) Competing with n-6 PUFAs as a substrate for endocannabinoid synthesis, which leads to the production of anti-inflammatory endocannabinoids [9].
5) Forming protectins and resolvins which have a role in ending the inflammatory response [9].

2.2. Lipid metabolism

n-3 PUFAs also have important effects on lipid metabolism through interaction with key transcription factors. They activate PPAR-α [14] and inhibit SREB1-c [20] and HNF-4α [21] in the liver. The combined effect is to increase fatty acid β-oxidation for energy production and reduce lipid synthesis [20,22], reduce hepatic fat storage [14,23], and limit the release of triglycerides into the circulation [14,23]. PPAR-γ is a key regulator of adipose tissue function that is also activated by n-3 PUFAs [23]. Activation of PPAR-γ increases adipogenesis [24], up regulates enzymatic pathways involved in uptake and storage of lipid [25] and insulin signalling [26], inhibits free fatty acid release, and normalises adipokine production [27]. It is noteworthy that the activation of PPAR-γ is the primary mechanism for the insulin-sensitising effects of thiazolidinediones, which are used in the management of diabetes mellitus [26].

2.3. Redox status

While n-3 PUFAs function as antioxidants [28], their impacts on biological systems are complex. Their participation in redox reactions leads to the production of a lipid peroxide radical, which itself is highly reactive [29]. In one study, lower doses of n-3 PUFAs had an antioxidant effect, but higher doses (≥1600 mg/day) were associated with increased markers of oxidative damage [30]. Aside from dose, many other factors are likely to influence the redox effect of n-3 PUFAs, including the degree to which the oil was oxidised prior to consumption, the concentration of antioxidants in the oil, and the endogenous antioxidant status of the consumer. Further, as obesity, inflammation, infection, and hyperglycaemia all influence oxidative stress [31,32], many aspects of health may modulate the redox effects of marine oils.

2.4. Central nervous system

DHA is a major structural component of the central nervous system and the retina, making up 35% of fatty acids within synaptic membranes [33]. There is rapid uptake of DHA in late gestation [34] and infancy [35], and deficiency is associated with cognitive defects in animal models [36]. Supplementation with n-3 PUFAs has been investigated as a treatment for a wide range of neurological and psychiatric disorders, and they are frequently taken during pregnancy or infancy with the aim of improving neurodevelopment [6,8].

n-3 PUFAs also have anti-arrhythmic properties [37], and like any fatty acid can be stored in adipose tissue or undergo β-oxidation for energy production.

2.5. Diversity of effects

As outlined above, n-3 PUFAs have a wide diversity of effects through many different mechanisms. Whilst it could be assumed that these are synergistic, some of these effects may be conflicting.

Ferrannini observed that medications that have a very specific action (affecting a single metabolic pathway) are usually preferable, because unintended/unpredicted adverse effects are less likely [38]. The statins (a class of drugs that reduce synthesis of cholesterol by inhibiting the enzyme HMG–CoA reductase) are a good example [38]. In contrast, the thiazolidinediones act through PPAR-γ, which is expressed in many tissues, and has many transcriptionally-regulating actions [26]. While these drugs do have important insulin sensitising effects, reports have shown an increased risk of congestive heart failure [39] and fractures [40]. From this perspective, marine oils, which affect many pathways in addition to PPAR-γ, have greater potential for unpredictable and potentially adverse effects.

Importantly, the multiple mechanisms by which n-3 PUFAs modulate inflammation and metabolism may also make it harder to translate the results of animal studies to humans. To standardise between species, doses are often considered adjusted for weight or body surface area [41]. This is reasonable if there is only one mechanism of action, as if there are differences in the affinity of enzymes or receptors for a drug or compound of interest, these are likely to differ by a constant factor, which may simply change the required dose to achieve a biological effect. However, when there are multiple distinct biological effects, such as for n-3 PUFAs, it is possible that the activity through each mechanism could vary by a different factor. In that case, the overall effect in different species would be very difficult to predict. Notably, the insulin-sensitising effects of marine oils have not clearly translated from rodents [16] to humans [42].

3. Marine oils contain more than n-3 PUFAs

The n-3 PUFAs EPA and DHA are considered to be the active compounds in marine oils, and the typical labelled content is between 300 and 600 mg/g of oil. However, marine oils also contain significant quantities of monounsaturated and saturated fatty acids, as well as small amounts of n-6 PUFAs. Further, in addition to fatty acids, there are other chemical species, including fat-soluble vitamins, carotenoids, phospholipids, cholesterol, and glycerol. In fact, two recent clinical trials that presented an independently measured fatty acid profile of the trial oil showed that the fatty acid content was only 42% of the oil mass in a krill-salmon blended oil [43] and 75% in a fish oil [44].

Oils made from krill are becoming an increasingly popular source of n-3 PUFAs. These oils may contain an even wider range of chemical components as the fatty acids are in the form of phospholipids [45,46], which have water-soluble and lipid-soluble poles. Thus, krill oils may also contain water-soluble molecules. In a randomised controlled trial of krill-salmon blended oil, supplementation lead to reduced insulin sensitivity, which was unlikely to

be mediated by the n-3 PUFA components of the oil [43].

4. Current understanding of the health effects of marine oils

4.1. Early trials

Initial evidence from clinical trials suggested cardiovascular, anti-inflammatory, and cognitive benefits of n-3 PUFA supplementation. It was shown to reduce plasma triglyceride levels [47], lower blood pressure [48], reduce platelet aggregation [49], and stabilise atherosclerotic plaque [50]. Together these effects would be expected to slow atherosclerosis and reduce the tendency of atherosclerotic plaques to rupture, thrombose, and occlude (i.e. the processes leading to myocardial infarction). Further, the reported anti-arrhythmic effects [51] might prevent sudden death after myocardial infarction. Some trials are consistent with this, including the open-label GISSI-Prevenzione [52] and JELIS [53] trials. Similarly, the anti-inflammatory effects of n-3 PUFAs would suggest a useful role in the treatment of inflammatory diseases [9], and benefit has been demonstrated in the treatment of rheumatoid arthritis [54,55].

4.2. Systematic reviews

With the growing number of trials of n-3 PUFAs, there has been progression to detailed systematic reviews that have cast doubt on the benefits suggested by early trials. Recent systematic reviews of randomized placebo-controlled trials on the use of n-3 PUFAs for secondary prevention of cardiovascular disease showed no effect on the risk of myocardial infarction or sudden death [11,12]. Further, there was no overall effect in the treatment of asthma or inflammatory bowel disease, with individual trials showing conflicting results [56,57]. Recent systematic reviews have also found no overall effect of n-3 PUFA supplementation on a variety of pregnancy outcomes, including gestational diabetes, preterm birth, pre-eclampsia, intrauterine growth restriction, and measures of infant neurodevelopment [58–60], but yet again the individual trial data are mixed [58–60].

4.3. Conflicting results

Together, these data suggest that n-3 PUFAs have little overall effect on cardiovascular risk, pregnancy outcomes, and some inflammatory diseases. However, other potential explanations for a mixed and overall negative literature have been raised. These include heterogeneity of the study populations and their background fish consumption, the trial dose of n-3 PUFAs, the appropriateness of the chosen placebos and study outcomes, as well as concomitant medications [57,61,62]. A possible explanation that has received little attention [63,64], is that there is substantial variability in the composition of marine oils sold at retail, which may often contain potentially toxic oxidation products in excess of industry standards [65–67], lower than labelled concentrations of n-3 PUFAs, and variation in the ratio of EPA and DHA [67–70].

5. Oxidation of n-3 PUFAs

n-3 PUFAs are highly prone to oxidative degradation, owing to their many double bonds that have a low activation energy for free radical formation [29]. Oxidation is a highly complex process, and the degree and rate of oxidation of a marine oil is influenced by many factors, including the fatty acid composition, antioxidant content, temperature, exposure to oxygen and light, and the presence of water and heavy metals [29]. Importantly, added antioxidants reduce, but do not prevent oxidation during storage [71].

The initial step of oxidation leads to increased levels of hydroperoxides, which decompose into a variety of radicals. These react with unoxidised PUFAs to form additional hydroperoxides, while also breaking down to form a wide range of secondary oxidation products, such as volatile ketones and alcohols that contribute to the smell of rancid oil [29].

While measurement of specific chemical species is difficult, simple industry standard tests provide a proxy measure of oxidative products. The peroxide value (PV) provides a quantitative measure of hydroperoxide concentration. However, the most common method to estimate secondary oxidation is the p-anisidine value (AV), which measures aldehydic compounds. Note that the AV can be increased by some flavourings (such as citrus oils) [72], but it remains the recommended test for estimating secondary oxidation [73,74]. By measuring both PV and AV, primary and secondary oxidation products are characterised, enabling an overall assessment of the degree of oxidation, which is reflected in the Totox value (2PV + AV). A number of authorities have published maximum limits of oxidation in fish oils, most commonly set as PV < 5, AV < 20, Totox < 26 [73–75]. Notably, there are insufficient data to indicate safe levels of oxidation for human consumption, and these limits based on palatability provide the only available reference point.

There are now multiple studies from around the world indicating that retail n-3 PUFA supplements are frequently oxidised above these limits. These include 31% [76] and 50% [66] of products tested in independent Canadian studies, 44% in Brazil [77], 84% in South Africa [65], and 92% in New Zealand [67]. Of note, one of the Canadian studies [66] included plant-based oils, which are less prone to oxidation and therefore underestimated the problem. In addition, Labdoor, a for-profit company from the United States that tests and sells supplements, reported that 28% of products tested had greater than twice the recommended level of lipid peroxides [78]. Together this indicates that consumers purchasing marine oil products are likely to be exposed to excess lipid oxidation products. Importantly, it appears that there are no reliable indicators that a consumer could use to select an unoxidised product, since cost, best before date, and country of manufacture country were not associated with differences in oxidation levels [67].

6. Safety of oxidised marine oils

The safety of lipid oxidation products present in marine oils is poorly understood. Studies in a variety of animal models have shown toxic effects including growth retardation and organ toxicity [79]. In a rabbit model, supplementation with fish oil led to a marked increase of lipid peroxidation products in serum and accelerated atherosclerosis [80]. A plausible mechanism is through oxidation of LDL particles, as lipid oxidation products are transported within LDL particles [81], which must be oxidised before they can be incorporated into the foam cells of atherosclerotic plaques [82–84]. Further, lipid oxidation products are mutagenic [85,86], and could increase the risk of malignancy. However, the comparatively high doses and unusual methods of administration used in many animal toxicity models make translation to humans difficult. In one human study, short-term supplementation with oxidised fish oil, did not affect markers of oxidative stress [87], but long-term effects on organ function, atherosclerotic cardiovascular disease or the risk of cancer have not been assessed.

It is important to consider that many fish oil consumers may be especially vulnerable to toxic effects. For example, marine oils are used in both primary and secondary prevention of cardiovascular disease. Many of these consumers are at increased cardiovascular risk, for example due to obesity, diabetes, increasing age, or a history of ischaemic heart disease. Thus, if oxidised marine oils

increase the rate of atherosclerosis, they may be of greater harm in such populations. Pregnant women are another particularly vulnerable population, who consume marine oils primarily because of purported benefits to neurodevelopment of the fetus. Pregnancy is a time associated with reduced endogenous antioxidants, and the early embryo has very little antioxidant defence. A recent study has suggested potential adverse effects of fish oil on neurodevelopment of the offspring, although the oxidative state of the trial oil was not reported [88].

Given the high frequency of oxidised supplements on the retail market, it is likely that in many clinical trials of n-3 PUFAs the oil has been oxidised. Current evidence is insufficient to determine whether oxidised supplements have poorer efficacy or have adverse effects on health. Thus, oxidation remains a potential explanation for the mixed literature investigating the effects of n-3 PUFA supplementation.

7. Marine oils and labelled n-3 PUFA content

Unlike medications where consumers and physicians can rely on accurate and consistent dosing, the accuracy of supplement labels is often poor. Studies of marine oil products from Africa [65,70], Australasia [67,89,90], North America [68,69,76], South America [77] and Europe [68,91] have examined the accuracy of labelled n-3 PUFA content of fish oils. Opperman et al. arbitrarily but reasonably defined adequate accuracy as n-3 PUFA content between 90% and 110% of that labelled [70]. Using this threshold, in 6 of the 10 studies at least 30% of products under-delivered [65,67–70,89], while in 4 studies more than half of the products tested under-delivered [67–70].

Thus, many products sold at retail have less n-3 PUFA content than labelled. This is a potential problem both for clinical trial participants and consumers, as it limits their ability to take a target dose of n-3 PUFAs. This may also hinder interpretation of the trial literature, as an independent analysis of trial oils is usually not reported, so that trials failing to demonstrate effects may have inadvertently under-dosed participants. As a result, the failure of marine oil supplements to alter hard cardiovascular outcomes in the current literature might be explained by excess oxidation products and inaccurate dosing.

8. Benefits of fish consumption: beyond n-3 PUFAs

In contrast to the evidence for marine oil supplements, there is substantial epidemiological evidence that fish consumption is associated with reduced cardiovascular [92–96] and cerebrovascular risk [97]. Further, greater circulating n-3 PUFA levels are also associated with greater insulin sensitivity [98,99] and a reduction in sudden cardiovascular death [100,101]. However, it is important to recognise that in cross-sectional and epidemiological studies n-3 PUFA levels are markers of fish consumption (not fish oil). Thus, it may not be the circulating n-3 PUFAs *per se* that account for the reduced risk.

Fish consumption differs from supplementation with marine oil by three major factors. Firstly, eating a meal of fish displaces other foods from the diet, such as red meat that is rich in saturated fat. Secondly, fish meat has substantial protein content [102]. Consumption of fish protein has important biological effects in humans, including antihypertensive [103] and insulin-sensitising effects [104]. Salmon calcitonin, which inhibits bone resorption in humans [105], has been detected in plasma after salmon feeding in rats [106], suggesting it might convey some of the biological effects of salmon consumption. Interestingly, fish protein also reduces urinary 8-OH deoxyguanosine [103] (a marker of oxidative DNA damage), so that when fish meat is consumed, the protein component might help to counter potential oxidative stress associated with the n-3 PUFAs. Thus, some of the beneficial effects of fish consumption are likely to be due to its protein content. Lastly, while consumers of fish oil are frequently exposed to excess oxidation products, this is unlikely to occur with fish consumption, as rancid fish is malodourous and unpalatable.

9. Alternative approaches to getting the benefit of n-3 PUFAs

Many problems with the use of marine oils as an intervention have been discussed, including the complex chemical composition, many biological effects, presence of oxidation products, and problems with the accuracy of dosing. In this light, two diametrically opposite directions should be considered.

Firstly, rather than using fish oil, oily fish as a whole food may be a better intervention to improve cardiovascular risk. Current evidence clearly indicates that it is beneficial, which is not true of marine oils [96]. The Heart Foundation of Australia recommends that 2–3 servings of fish are consumed each week [107]. This is reasonable but may not be achievable at a population level, since fish is costly, many people do not like it, and there are concerns about the sustainability of fisheries. It appears that the greatest incremental benefit is observed between those who eat fish very rarely and those eating fish once per week [95], suggesting that one fish meal per week may be an appropriate minimum intake.

Secondly, a precise pharmacological approach might be more efficacious than supplementation with marine oils. Many drugs already modulate the pathways affected by n-3 PUFAs, including the thiazolidinediones (PPAR-γ), fibrates (PPAR-α), and salicylates (COX-2 and NF-κB). Recent evidence showed that the cell surface receptor GPR-120 mediates the insulin-sensitising effect of n-3 PUFAs in rodents, through reduced inflammation of adipose tissue [16]. In obesity, adipose tissue inflammation leads to abnormal release of free fatty acids and adipokine production [108], which in turn lead to insulin resistance [109], the major factor that connects obesity to hypertension, dyslipidemia, type 2 diabetes, and cardiovascular disease [110]. Thus, GPR-120 may be an especially promising target for drug development, which may improve cardiometabolic risk. Importantly, a synthetic GPR-120 agonist confers the same insulin-sensitizing effect as n-3 PUFAs in rodents [111]. Further, GPR-120 also has effects on the regulation of appetite [112] and insulin secretion [113,114]. While there are currently no data on the effects of a GPR-120 agonist in humans, a report indicating that patients with GPR-120 mutations develop obesity and insulin resistance [115] suggests that the effect could translate to humans. Because of the central importance of insulin sensitivity to cardiometabolic risk [110], if GPR-120 agonists do improve insulin sensitivity, they could potentially ameliorate much of the disease risk associated with obesity. Notably, their action through a single receptor may increase the likelihood that effects can be successfully translated from rodent models to humans without unexpected adverse effects. Lastly, it is likely that a synthetic agonist would be chemically stable, with reliably reported active ingredient, and require a smaller mass of medication than the many marine oil capsules needed to reach a high n-3 PUFA dose.

10. Market success in the face of weakening scientific evidence

The great promise for n-3 PUFAs emerging out of the 1970s has not been confirmed by contemporary trials and systematic reviews. Yet, while the evidence base has eroded, the market for marine oil supplements has grown substantially [116], and is expected to reach US$ 1.7 billion by 2018 [3]. This implies that the marketing is disconnected from the current scientific evidence.

In part, this can be ascribed to the way that health supplements are regulated and marketed in many countries. For example, in the United States [117], Australia [118], and New Zealand [119], it is not necessary to prove the efficacy or safety of supplements prior to marketing, and there is no formal post-marketing safety surveillance to detect potential uncommon adverse events. In these countries, while specific claims such as treating or curing a disease cannot be made without strong supporting evidence, 'structure/function claims' (i.e. that a supplement can promote, maintain or enhance health or well-being, or affect the structure or function of an organ or the body) can be made with minimal support [117,120–122]. In Europe, the bar is set higher as "general health claims" for supplements must be submitted to the European Food Safety Authority for review, who consider the scientific evidence and publish lists of allowable and non-allowable claims [123]. Allowable claims for n-3 PUFA rich supplements in Europe include that they contribute to the normal function of the heart, and to the maintenance of normal blood pressure and triglycerides [124]. In contrast, n-3 PUFA rich supplements cannot be claimed to help maintain normal blood glucose or LDL-cholesterol [124]. This type of regulation, while more costly, reduces the range of general claims to those that are probably true to some extent.

Nevertheless, structure/function claims and even the approved general claims in Europe are likely to confuse many consumers. For example, across all of the discussed regions, fish oil products could not be claimed to "prevent myocardial infarction", but they could be claimed to "support cardiovascular health". These two claims are technically very different, but it is likely that many (if not most) consumers would interpret them in the same way. This would hamper the ability of consumers to make an informed decision about supplements, and may in part explain the continued success of marine oils in the face of weakening evidence for benefit [3,116,125]. Importantly, outside of Europe, because structure/function claims are vague and not based on scientific evidence, they do not need to be changed in light of new evidence to the contrary.

11. Regulation and the unknown risk to consumers of oxidised marine oils

Weak regulation of health supplements around the world enables them to be sold without first determining their safety [117–119], and this has the potential to allow harmful substances to be sold as supplements. Marine oils that have become oxidised may be such a product. Reports from around the world including Australasia, Africa, North America, and South America have shown a high frequency of oxidation above recommended limits [65–67,76–78]. Further, not only have some of these studies included products imported from other regions [66,67], but most fish oils are actually sourced from the West coast of South America, where they undergo the same initial steps in manufacture [64]. Thus, oxidation of marine oil supplements is likely to be a global problem, and the risk to consumers remains unknown.

In this light, it is important to consider whether current regulation is sufficient to keep consumers safe. European regulation of supplements is stronger than in other regions, and the European Food Safety Authority (EFSA) has given some consideration to the oxidation of fish oil supplements [73]. In their report, they indicated that there were insufficient data to set a safe limit of oxidation products, and recommended that the effects of individual oxidation products on human health be investigated [73]. However, despite this lack of evidence, as has occurred outside of Europe, marketing has been allowed without any requirement to determine safety prior to sale or afterwards. As a result, this issue has been barely investigated and all oxidation limits are arbitrary and based on palatability, whether published by the EFSA (Europe) [73], Food and Drug Administration (USA) [126], Therapeutic Goods Administration (Australia) [127], Health Canada [74], the Codex Alimentarius Commission (draft) representing the World Health Organisation and Food and Agriculture Organisation of the United Nations [128], or industry groups such as the Global Organisation for EPA and DHA [129] or Council for Responsible Nutrition [75].

While the appropriateness of these limits is unknown, they are frequently exceeded in retail products [65–67,76–78]. This suggests that oxidation of marine supplements is rarely audited, testing is unreliable, or the oil tested is not representative of that available for purchase at retail. Nonetheless, despite this fact, we believe that the most pressing issue in the regulation of marine oil supplements is not enforcement of oxidation limits, but establishment of what those limits should be. Regulation should have compelled studies investigating safe limits of oxidation to be performed and funded, but it is clear that this has not been the case. In the absence of such regulation, this has been left to independent members of the scientific community.

12. Conclusions

Supplementation with marine oils constitutes a complex intervention. In addition to having a broad range of chemical compounds, the n-3 PUFAs that are considered to be the active ingredients affect a wide range of biological processes in many different tissues. Further, oxidation products may also have important adverse biological effects. The current scientific literature, which has increasingly shown no overall benefit of marine oils, may have been confounded by other oil components (including unrecognised oxidation products), as well as inadvertent underdosing of participants. Thus, there is a pressing need for trials to be conducted with supplements where content is independently verified and the oxidative state is determined. Until these data emerge, we cannot be sure that marine oils are as ineffective as current evidence suggests. It is important that a potentially effective treatment such as marine oils is not discarded out of hand. However, there is also a need for studies investigating the potential toxicity of specific marine oil oxidation products. In the meantime, consumption of oily fish can be recommended to reduce cardiovascular risk, and the development of drugs targeting specific pathways that are affected by n-3 PUFAs may provide greater benefit still. Lastly, the poor regulation of supplements and their label claims serves to confuse consumers, such that the market success of marine oils far exceeds the scientific evidence. As it stands, current evidence suggests that consuming marine oil supplements is not money well spent.

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