



REVIEW

REVISED A review of the biologic and pharmacologic role of docosapentaenoic acid n-3 [v2; ref status: indexed, <http://f1000r.es/41a>]

Previously titled: A review of the biologic and pharmacological role of docosapentaenoic acid

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Abstract

Fish oil contains a complex mixture of omega-3 fatty acids, of which eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) are the three predominant forms. There has been a plethora of previous research on the effects and associations of fish oil supplementation with various clinical manifestations. While the majority of this work was focused on EPA and DHA as the active compounds, emerging research has begun to elucidate the specific role that DPA plays in these physiological processes and its differences with the other omega-3 fatty acids. The purpose of this review is to focus on the new studies undertaken with DPA. This review summarizes the biochemical mechanisms involved in the biosynthesis and metabolism of DPA before focusing on its effects in cardiovascular disease, immune function, and psychiatric and cognitive health. The limited studies point toward a positive role that DPA supplementation can play in these processes and that is separate and distinct from traditional supplementation with DHA and EPA.

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Invited Referee Responses

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version 1 published 25 Nov 2013	 report	 report
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version 2 published 19 Aug 2014 REVISED	 report	 report

- 1 **Philip Calder**, University of Southampton UK
- 2 **Bruce Bistrrian**, Beth Israel Deaconess Medical Center USA

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REVISED Amendments from Version 1

I thank both reviewers for their wonderful suggestions. I have accepted all their suggestions and revised the paper accordingly. The paper has a changed title, fixed or added text as suggested by the reviewers, and has additional text making it clearer that many of these findings are associations and not causations.

See referee reports

Introduction

As a result of anecdotal reports of their low incidence of coronary heart disease, Bang and Dyerburg began to study the Greenland Eskimo (Inuits) population in the late 1960s. Their pioneering findings confirmed the anecdotal evidence; Inuits had lower incidences of myocardial infarction, better lipid profiles, reduced platelet activity, and lower incidence of immune and inflammatory diseases compared with western controls¹⁻³. These findings were attributed to the Inuit diet, and specifically to the large quantities of seal and whale meat consumed by the Inuits. Eventually it was deduced that marine n-3 fatty acids found in the seal and whale meat was the main protective agent against cardiovascular heart disease⁴. These findings, along with separate research that demonstrated mammalian brain grey matter was also rich in n-3 fatty acids, became an impetus for much scientific and clinical research into the potential health benefits of n-3 fatty acids^{5,6}. Over the ensuing years, n-3 fatty acids have been found to hold great therapeutic promise in a myriad of conditions including, but not limited to, neural function, diabetes mellitus, cardiovascular health, cancer, lipid regulation, and as a anti-inflammatory agents⁷⁻¹².

The majority of the studies conducted on n-3 fatty acids were conducted on fish oils that contain a mixture of the three n-3 fatty acids: eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid, (DHA). While much attention has been focused on DHA and EPA, the literature on DPA remains brief. In recent years, research on DPA has increased. Much of the increased interest in DPA came about from two observations. First, the seal meat so readily consumed by the Inuits contains high concentrations of DPA; and second, human mother's milk also contains high concentrations of DPA¹³. There already exists extensive literature and reviews on the beneficial effects of EPA and DHA which the reader is encouraged to read¹⁴⁻¹⁸. The following review will aim to address some basic biological insights behind DPA and some of its potential beneficial effects. Additionally, for a more thorough review of the biochemical and molecular pathways related to DPA, the reader is encouraged to read another recent DPA review, cited in the biosynthesis section below. This review will focus on the clinical associations involved with DPA and it will do this by focusing on DPA specific studies in addition to studies conducted on fish oils or mixtures of omega-3 n-fatty acids that contained DPA. Studies in which the role of DPA was studied specifically will be noted as well studies that were conducted on animal models or *in vitro*.

Biosynthesis and metabolism of essential polyunsaturated fatty acids

EPA, DHA, and DPA are the three major polyunsaturated fatty acids formed by a series of desaturation and elongation enzymes from

Alpha-linolenic acid (ALA)¹⁹. Fatty acid elongase is responsible for the direct conversion of EPA into DPA by direct chain elongation²⁰⁻²². The conversion of DPA into DHA is more circuitous involving chain elongation followed by desaturation in the cytoplasm before being moved to the peroxisome to be chain shortened by β -oxidation to form DHA^{23,24}. It is worth noting that in living cells this process can go in reverse yielding EPA, a process that most likely involves peroxisomal acyl-coA and β -oxidation²⁵. For a more thorough review of the biochemistry behind DPA the reader is encouraged to read the previously aforementioned DPA review²⁵. **Figure 1** summarizes the major pathways involved in n-3 fatty acid production.

Potential clinical effects of DPA

Cancer

Numerous studies have reported possible anti-cancer effects of n-3 fatty acids, particularly for breast, colon, and prostate cancer²⁶⁻²⁸. Omega-3 fatty acids reduced prostate tumor growth, slowed pathological progression, and increased survival in mice²⁹. Among n-3 fatty acids, high levels of DHA, which is the most abundant n-3 polyunsaturated fat in erythrocyte membranes, were associated with a reduced risk of breast cancer³⁰. Additionally, a 2007 systematic review of n-3 fatty acids and cachexia found evidence that oral n-3 fatty acid supplementation was beneficial as adjuvant cancer therapy by improving appetite, weight, quality of life, and retaining muscle mass^{31,32}. Additionally, a recent study looking at the anti-tumorigenic effects of n-3 fatty acids on colorectal cancer found anti-proliferative and pro-apoptotic effects for all 3 fatty acids, with DPA demonstrating the strongest effects in both *in vitro* and *in vivo* models of colorectal cancer³³.

Cardiovascular disease

Not surprisingly, some of the main initial work was done on the effects of n-3 fatty acid in heart disease and specifically myocardial infarction. As early as three months and onwards, treatment with 1gram per day of n-3 fatty acids resulted in a statistically significant reduction of the occurrence of death, sudden cardiac death, and cardiovascular death^{34,35}. It is worth noting that these trials were done on a commercial preparation of n-3 fatty acids that contained very low concentrations of DPA and hence additional work needs to be done to determine what role if any DPA can play in conferring this cardiovascular protection. Furthermore, it has also been demonstrated that n-3 fatty acids have a statistically significant antihypertensive effect by lowering systolic blood pressure by 3.5–5.5 mmHg³⁶. For a more thorough review of all the potential benefits of n-3 fatty acids in general on the cardiovascular system, the reader is advised to read a recent review¹⁸.

While much of this previous work has shown that omega-3 fatty acids can possibly play a protective role in maintaining a healthy cardiovascular system, recent studies have demonstrated a positive association between DPA itself and cardiovascular disease prevention in humans³⁷⁻³⁹. A prospective population study of 1871 subjects in Eastern Finland demonstrated that subjects with plasma blood concentrations of DPA plus DHA in the 20th percentile had a decreased relative risk of acute coronary events of 44%, compared to those subjects in bottom 20th percentile. The decreased relative risk rose to 67% so long as the top 20th percentile group

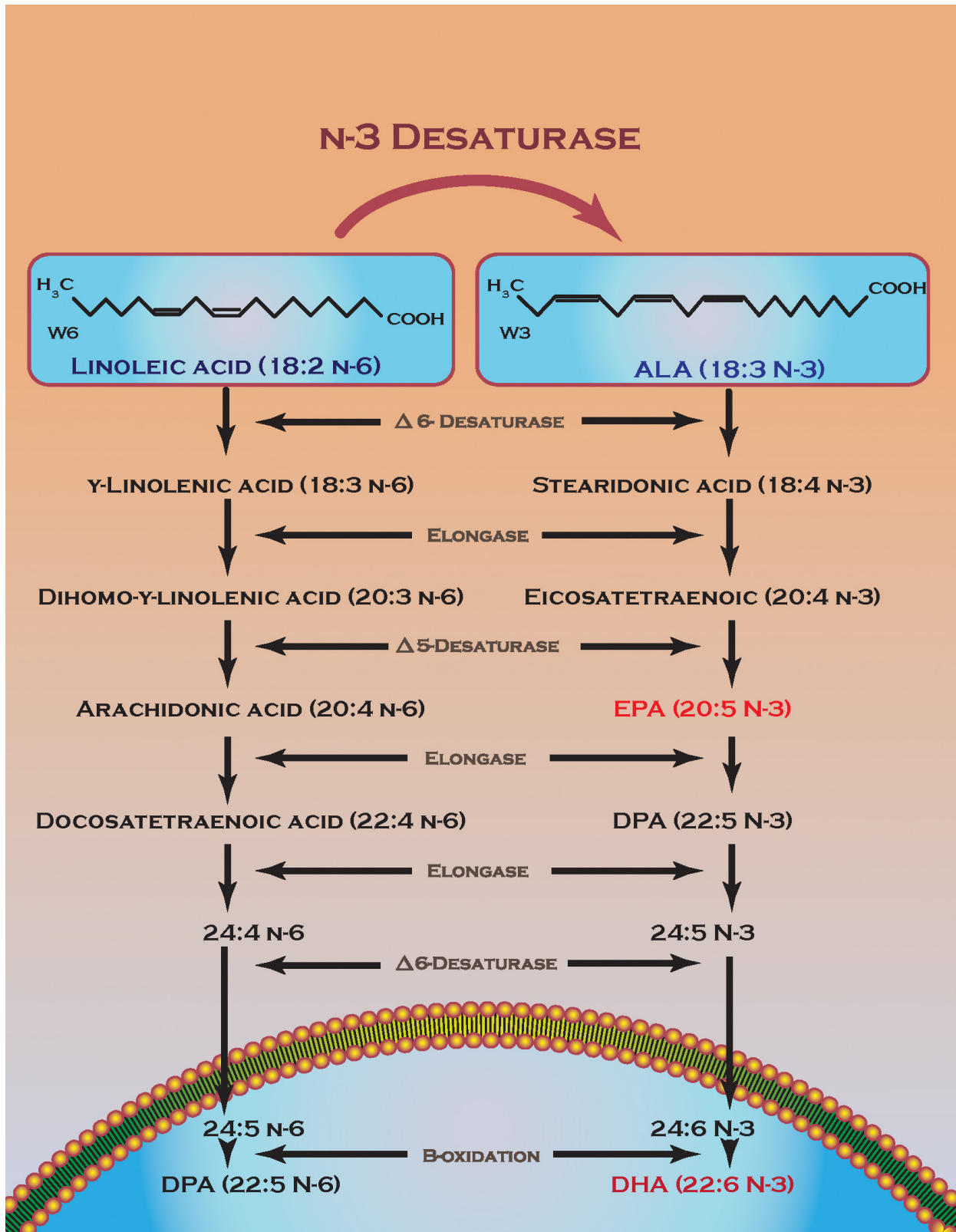


Figure 1. n-3 fatty acid production. Summary of the biochemical enzymes and intermediates involved in n-fatty acid production in cells. The blue underneath the lipid bilayer represents a peroxisome with steps occurring outside in the cytoplasm.

had mercury levels below or equal to 2 micrograms/g compared to those in the bottom 20th percentile who had mercury levels above 2 micrograms/g³⁸. This study was followed up by a Japanese study, published five years later that further corroborated these findings by showing a significant association between DPA supplementation and reduced cardiovascular disease³⁷. A nested-case control study of 6438 adults with seven years of follow up also showed that DPA was associated with a reduced the odds ratio of heart disease⁴⁰. More importantly, this same finding was further confirmed by another nested-case control study of 32,826 subjects with 6 years of follow up that also demonstrated that this association was independent of the other n-3 fatty acids⁴¹. Interestingly, a cross-sectional study of 26 subjects and 24 matched controls revealed that decreased DPA concentrations in the cell membrane of erythrocytes (3.0+/-0.19% for subjects vs. 3.9+/-0.12% for controls, P<0.001) were statistically significantly associated with increased heart disease⁴².

Recent studies have further developed our understanding of which pathophysiologic mechanisms DPA supplementation can potentially target in cardiovascular disease. First, a prospective cohort study which directly measured circulating levels of n-3 fatty acids in the blood of 2735 US adults without existing heart disease who were enrolled in the Cardiovascular Health Study from 1992 to 2006 found that total n-3 fatty concentration was associated with lower incidence of congestive heart failure with DPA, conferring as much as a 40% reduction⁴³. A second study looked at the impact of n-3 fatty acid on coronary plaque instability by use of conventional and integrated backscatter intravascular ultrasound approaches⁴⁴. Their results demonstrated that low serum concentrations of DPA were significantly associated with lipid-rich plaques, suggesting that decreased DPA levels can contribute to increased incidence of plaque formation leading to acute coronary syndrome and myocardial infarction⁴⁴. Besides heart disease, stroke prevention and arterial blockage also comprise a significant part of cardiovascular health. Plasma levels of DPA are inversely related to blocked arteries and DPA the only n-3 fatty acid that has been shown to significantly reduce blocked arteries regardless of lifetime smoking⁴⁵. A cross-sectional study with carotid ultrasonography revealed that carotid artery wall thickness was inversely associated with DPA intake⁴⁶.

Additionally, *in vitro* work has started to isolate the biochemical mechanisms by which DPA could help combat cardiovascular disease. For instance, platelet aggregation is an early event in the development of thrombosis and is initiated by thromboxane A₂⁴⁷. Recently, an *in vitro* study conducted in rabbit platelets showed that EPA, DPA and DHA inhibited collagen- or arachidonic acid stimulated platelet aggregation in a dose dependent manner, with DPA being the most potent inhibitor and possibly ten times more powerful than EPA in inhibiting platelet aggregation⁴⁸. A further study conducted on human whole blood corroborated these earlier findings⁴⁹. Endothelial cell (EC) migration and proliferation are important processes in the control of the wound-healing response of blood vessels⁵⁰. DPA has been shown to be a potent stimulator of EC migration⁵¹. Furthermore, DPA pretreatment of bovine aortic endothelial (BAE) cells inhibits their migrating activity due to vascular endothelial growth factor (VEGF) stimulation⁹. Additionally, that same pretreatment suppresses tube formation

demonstrating that DPA is a potent inhibitor of angiogenesis, a physiological mechanism that contributes to tumor growth, inflammation, and microangiopathy⁹.

Numerous studies have demonstrated that EPA and DHA can lower triglycerides (TG) and cholesterol levels in the plasma and liver, by increasing β -oxidation activity in the mitochondria and peroxisomes in hepatic cells, and suppressing TG synthesis in the liver⁵²⁻⁵⁴. Similar work is now showing that DPA also possesses lipid metabolism improving effects similar to EPA and DHA in improving cholesterol and TG levels. A recent *in vivo* study demonstrated that DPA can reduce non-HDL cholesterol by 50% in hamsters⁵⁵. Finally, DPA has been shown to have a positive role in reducing the expression of inflammatory genes (inflammation in the walls of blood vessels is thought to play a role in the development of atherosclerotic plaques leading to cardiovascular disease) thereby improving cardiovascular health⁵⁶.

Immune function

The role of n-3 fatty acid supplementation in immune function is just beginning to emerge as a new frontier in fatty acid research. In a study regarding fish oil supplementation in infants, the authors found that fish oil supplementation could lead to quicker immune maturation without a concomitant reduction in immune activation⁵⁷. Additionally, owing to the anti-inflammatory properties of n-3 fatty acids and the pro-inflammatory properties of n-6 fatty acids found in most western diets, many researchers currently believe that fish oil supplementation can aid many chronic inflammatory conditions by decreasing the n-6 to n-3 fatty acid ratio⁵⁸. As one example, patients suffering from rheumatoid arthritis report reduced pain symptoms when taking n-3 fatty acids in conjunction with NSAIDS compared to those only taking NSAIDS⁵⁹. Finally, enzymatically oxygenated derivatives (oxylipins) of DPA have been shown to be potent anti-inflammatory compounds in animal models⁶⁰. Significant work remains to be done to elucidate the possible role if any played by DPA in immune function.

Psychiatric and neurological function

There is now emerging evidence that n-3 fatty acids can play a role in psychiatric disorders due to the observation that schizophrenic patients demonstrate reduced levels of both n-3 and n-6 fatty acids⁶¹. Treating high-risk children with a dietary supplement of n-3 fatty acids demonstrated a statistically significant decrease in progression to schizophrenia⁶¹. Additionally, it has also been shown that patients with schizophrenia have decreased levels of DPA in erythrocytes⁶². Finally, a meta-analysis based on 10 clinical trials, found that n-3 fatty acids significantly improved depression in patients with both unipolar and bipolar disorder⁶³.

Neurological and cognitive decline as a result of aging or disease is now emerging as a new avenue of further research in n-3 fatty acid supplementation. First, in a rat model of Alzheimer's disease, EPA supplementation revealed a statistically significant efficacy in countering memory impairment⁶⁴. This study spurred interest in studying the possible benefit of DPA supplementation in cognitive decline due to aging. Specifically, during the aging process, there is a loss of synaptic function which leads to deficits in spatial learning tasks and reduced ability of rats to sustain long term potentiation⁶⁵.

By supplementing the normal diets of rats with DPA it was found that DPA possesses neuro-restorative effects in the hippocampus by decreasing microglial activation and oxidative stress, the two major biochemical mechanisms involved in cognitive decline due to synaptic function loss⁶⁶. These authors concluded that DPA supplementation might play a significant role in neuro-protection against age-related cognitive decline by attenuating the age-related decline in spatial learning and long-term potentiation.

Conclusions

While much work has been done on the potential therapeutic benefits of n-3 fatty acids, the majority of that work has been done on EPA and DHA. Initially, the Inuit population and their diet caught the attention of the medical community because of their much lower incidence of cardiovascular disease, which was attributed to their consumption of n-3 fatty acids. What has been forgotten in the ensuing years was that their seal meat also had high concentrations of DPA in addition to the more familiar EPA and DHA counterparts. Additionally, levels of DPA in human breast milk are high, and DPA levels in adult human blood are similar to EPA¹³. These findings are a part of a growing body of work on DPA with promising results. Additionally, this research has also begun to elucidate important differences between DPA and EPA and DHA. Specifically, DPA inhibits platelet aggregation more efficiently than EPA or DHA, DPA stimulates endothelial cell migration much more efficiently than EPA, and finally DPA is incorporated into human

plasma and red blood cell lipids faster than EPA and hence may act as a reservoir of the major n-3 fatty acids in humans^{9,51,67}. Studies looking into DPA and its clinical associations are beginning to demonstrate that lack of DPA in diets and blood circulation may serve as an independent predictor and marker for various health conditions. The existing evidence points to DPA as showing potential as a nutritional and therapeutic supplement. While much work still needs to be addressed on the possible benefits of DPA consumption in human health and disease, the limited data available seems to indicate that DPA can have additional health benefits in conjunction with the more common n-3 fatty acids.

Competing interests

PGY is a consultant for Cyvex Nutrition Inc, which is a distributor of nutritional supplements based on DPA and other n-3 fatty acids.

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Open Peer Review

Current Referee Status:



Referee Responses for Version 2



Philip Calder

Faculty of Medicine, University of Southampton, Southampton, UK

Approved: 08 September 2014

Referee Report: 08 September 2014

doi:[10.5256/f1000research.5230.r5855](https://doi.org/10.5256/f1000research.5230.r5855)

The revisions have greatly improved this manuscript which now adequately distinguishes DPA from the other important omega-3 fatty acids and which now provides an accurate, relevant and timely coverage of the possible important functional role of DPA.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.



Bruce Bistrrian

Nutrition/Infection Laboratory, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

Approved: 20 August 2014

Referee Report: 20 August 2014

doi:[10.5256/f1000research.5230.r4765](https://doi.org/10.5256/f1000research.5230.r4765)

The changes made meet my concerns. This is a useful article.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Responses for Version 1



Bruce Bistrrian

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Approved with reservations: 19 May 2014

Referee Report: 19 May 2014

doi:[10.5256/f1000research.2985.r4785](https://doi.org/10.5256/f1000research.2985.r4785)

In general this article does make a good point that DPA may well be an important omega 3 fatty acid and provides references from in vitro studies, animal studies, and some human epidemiologic studies that DPA may have some unique, beneficial properties. However many of the studies quoted for support in cardiovascular disease confuse association with causation, and this should be noted. Moreover there is still some controversy about the extent of the effectiveness of very long chain omega 3 fatty acids in the improvement of cardiovascular health according to different health authorities. That said the article does provide a useful review that should promote more research into this potentially important fatty acid. As an additional comment there are some misstatements which are presumably typographic on the first page. The retroconversion is DPA to EPA rather than the reverse. Also there is only one elongase necessary to convert EPA to DHA.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.



Philip Calder

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Approved with reservations: 17 February 2014

Referee Report: 17 February 2014

doi:[10.5256/f1000research.2985.r3468](https://doi.org/10.5256/f1000research.2985.r3468)

There remains significant interest in the health impact of omega-3 fatty acids from oily fish and fish oil type supplements on human health. The physiologic and health benefits are usually ascribed to EPA and DHA. However a third fatty acid, DPA, is present and this has been relatively little researched. Some new work on DPA has been performed which has suggested that it has some unique functional properties. These are reviewed elsewhere, but new updates, views and insights are always to be welcomed. This article aims to provide a current review of DPA and, I think, to distinguish it from EPA and DHA. To be frank, I do not think it achieves the latter aim as well as it might (see comments below).

Specific comments:

1. Title. If the "biologic" is used then this should be countered by "pharmacologic".
2. Title. Should clarify that this is about DPA n-3 not DPA n-6.
3. Abstract. We are told in line 1 that fish oil contains a complex mixture of EPA, DPA and DHA. Therefore it cannot be correct to state on line 5 that "It is not correct to state that work with fish oil was previously done on EPA and DHA". Perhaps the author means that the work has focussed on EPA and DHA as the active components?

4. The last sentence of the abstract makes the same error. We are told first (line 1) that fish oil contains EPA, DPA and DHA. Thus it cannot be correct to state that traditional supplementation is "*with DHA and EPA*" - it is with all three marine omega-3 fatty acids. Perhaps the author means that DPA has "separate and distinct properties compared with EPA and DHA"?
5. Page 2, column 1, 5 and 2 lines from the bottom. 'b' in b-oxidation should be shown as the Greek symbol beta.
6. Page 2, column 1, 3 lines from bottom. I think "*DPA from EPA*" should read "DPA from DHA" since the former is not "reverse" metabolism and would not involve beta-oxidation.
7. Page 2, column 2, line 3. What is meant by "*Clinical associations*"? Does the author mean "Clinical effects"?
8. The author is setting out to establish that DPA has independent functional features. However in many parts the evidence for this is based upon rehearsing the effects of fish oil supplements - these data cannot be used to say DPA has effects, since the effects may be due to any one of EPA, DPA and DHA or indeed to all three. Too often effects are due to "n-3 fatty acids" and it is then concluded that DPA is functional. I would much rather that the author is explicit in picking out and describing those studies where DPA is shown to have a function. A really poor example is in the first paragraph about cardiovascular disease where the effects seen in the GISSI trial are described. It is NOT acknowledged that these can have nothing to do with DPA since the preparation used in that study was a pharmaceutical preparation composed almost entirely of ethyl esters of EPA and DHA. To say otherwise is to mislead readers.
9. Page 4, column 1, line 31. Should "en" read "ten"?
10. Page 4, column 1, 4 lines from bottom. Please add "in hamsters" after "50%".

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.
