The n-3 docosapentaenoic acid (DPA): A new player in the n-3 long chain polyunsaturated fatty acid family

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Abbreviations: ALA: α-linolenic acid, COX: cyclooxygenase, DHA: docosahexaenoic acid, EFOX: oxo derivatives, EPA: eicosapentaenoic acid, LCPUFA, long-chain polyunsaturated fatty acid(s), LOX, lipoxygenase, n-3 DPA: n-3 docosapentaenoic acid, RBC: red blood cells.

Keywords: docosahexaenoic acid DHA, eicosapentaenoic acid EPA, polyunsaturated fatty acid (PUFA) metabolism, specialized pro-resolving mediator SPM,

Abstract

The n-3 docosapentaenoic acid (n-3 DPA) is less studied n-3 long-chain polyunsaturated fatty acid (LCPUFA), compared to its counterparts eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Present in food sources in non-negligible quantities, as well as in human milk, dietary n-3 DPA is of current interest both for its ability to increase EPA and DHA tissue status and for its specific or shared biological effects. Indeed, some evidence showed that dietary n-3 DPA is a source of EPA and slightly DHA in the major metabolic organs. n-3 DPA is also the precursor of a large panel of lipid mediators (protectins, resolvins, maresins, isoprostanes) principally implicated in the pro-resolution of the inflammation with specific effects compared to the other n-3 LCPUFA. Recent results showed that n-3 DPA is implied in the improvement of cardiovascular and metabolic disease risk markers, especially plasma lipid parameters, platelet aggregation, insulin sensitivity and cellular plasticity. Moreover, n-3 DPA is the most abundant n-3 LCPUFA in the brain after DHA and it could be specifically beneficial for elderly neuroprotection, and early-life development. These results led to the development of two drugs specifically containing n-3 DPA. This review summarizes the different knowledge about n-3 DPA direct and indirect sources, availability and purification methods, focusing thereafter on the recent findings showing n-3 DPA relationship with fatty acid metabolism, lipid mediators, Finally, the n-3 DPA biological and pharmacological effects are described.

Highlights

- n-3 DPA could be considered like a dietary source of EPA tissue content
- No evidence showed that dietary n-3 DPA increased brain DHA
- Hydroxy-metabolites from n-3 DPA are involved in the pro-resolution of inflammation
- More and more evidences about the n-3 DPA specific effects to decrease lipid parameters
- n-3 DPA purification methods will allow its accessibility for further *in vivo* studies

Contents

1. Introduction

The n-3 long-chain polyunsaturated fatty acids (LCPUFA) have been widely studied and contribute to numerous beneficial effects, mainly associated with cardiovascular prevention [1], neurodevelopment, but also with the reduction of the risk of neurodegenerative diseases. [2]. Indeed, these n-3 LCPUFA are involved in many processes such as the increase of membrane plasticity, the synthesis of oxygenated metabolites and the resolution of inflammation or the regulation of genes [3].

The majority of the n-3 LCPUFA studies were conducted using fish oils, composed of a mixture of three major n-3 LCPUFA: docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and n-3 docosapentaenoic acid (n-3 DPA). Most of the beneficial effects of fish oils have been attributed to DHA and then to EPA, for which there is growing interest in the independent and shared functions. On the other hand, the literature concerning the potential protective effects of n-3 DPA is brief because n-3 DPA represents less than one-third of each EPA and DHA in fish oils. In addition, n-3 DPA is not commercially available in sufficient quantity, with high purity (> 98%) and at an affordable price to set up *in vivo* nutritional supplementation studies [4].

Studies about n-3 DPA have however begun to grow in recent years. n-3 DPA is indeed the second n-3 LCPUFA found in the brain (w/w), although its cerebral concentration is about 70 times lower than DHA. Moreover, the level of n-3 DPA in human milk is higher than that of EPA, similar to that of DHA and its level is more stable [5], implying a potential impact of n-3 DPA during pregnancy and development, which is the subject of a recent review [6]. While obtaining optimal tissue status in n-3 LCPUFA is one of the current public health challenges, n-3 DPA is also the only intermediate between EPA and DHA in the n-3 LCPUFA conversion pathway from α-linolenic acid (ALA) present in significant quantities in the diet. Therefore, could n-3 DPA serve as a dietary source or biological reservoir of DHA and EPA?

This paper reviews and summarizes the different knowledge about n-3 DPA and focus on the most recent findings synthesized in Table 1. To more thorough review concerning specific knowledges, the reader is encouraged to read another reviews specific about n-3 DPA or including it, as mentioned in adequate sections below [2,4,6–12].

2. Dietary sources and availability of n-3 DPA

2.1. Commercial availability

Suppliers who offer n-3 DPA> 98-99% purity cannot provide on demand enough quantities of n-3 DPA for *in vivo* studies at prices that are affordable for most research laboratories (supplier communications, 2017). Thus, studies focusing on n-3 DPA are often association studies in humans or *in vitro* studies. Most *in vivo* studies thus used n-3 DPA with a purity level <98% which therefore also contains mainly DHA, EPA and n-6 DPA, limiting the interpretation of these findings [8,9,13]. In addition, only one supplier offers radiolabelled ^{14}C- n-3 DPA (ARC, 10μCi), which is also very expensive and inaccessible for n-3 DPA metabolism monitoring studies, although two studies have reported its use *in vivo* [14,15]. A n-3 DPA-based dietary supplement has also recently appeared on the market and contains 15% n-3 DPA in proportion to n-3 LCPUFAs (Super n-3 DPA Fish Oil®, Swanson, USA, 2018).

2.2. Purification and synthesis

To alleviate this problem of commercial availability as well as to study n-3 DPA in various dietary lipid forms, some teams have been interested in the synthesis or in the purification of n-3 DPA from natural sources. Foremost, a five-step synthesis of n-3 DPA from EPA has been described in 30% overall yield for making multi-milligram quantities of n-3 DPA [16]. Concerning n-3 DPA purification, historically, a Japanese study first focused on the industrial scale purification of n-3 DPA in ethyl ester form from *Schizochytrium sp.* algae oil by industrial high-performance liquid chromatography (HPLC) using two reverse phase columns. They obtained n-3 DPA (and DHA) > 99% purities with a production of 70 g/hour of n-3 DPA [17]. A Chinese team then focused on purifying n-3 DPA in the laboratory from tuna oil, firstly by crystallization of the fatty acids complexed with urea, then by purification by liquid chromatography (LC) on a silver nitrate silica column. [18]. They obtained n-3 DPA at 22.3% purity with a purification efficiency of 70.7%. Very recently, the same team managed to purify n-3 DPA from 16.4% to 28.1% of the total fatty acids in the form of diacylglycerol by crystallization (6h, -80 ° C) from the *Schizochytrium sp* oil [19]. Various patents have also been filed to produce, extract and purify n-3 DPA (and DHA) as fatty acid methyl esters from *ulkenia* [20–22]. In addition, n-3 DPA monoglycerides have been synthetized through esterification at the *sn*-1 position of the glycerol backbone by using n-3 DPA ethyl esters as starting materials [23]. The self-assembly of this compound has been structurally characterized [24], which could give it a better bioavailability than n-3 DPA ethyl ester and triglyceride forms, as shown previously for EPA monoglycerides [25]. More recently, we have purified tens of grams of n-3 DPA> 99% by flash and preparative LC from commercial fish oils enriched with n-3 LCPUFA [26,27]. The purification involved seven successive purification cycles with a purification efficiency > 70% and allowed to purify 8g of n-3 DPA/week [26] as well as EPA and DHA> 99% [27].

The advance of these methods could quickly allow access to the amounts of n-3 DPA needed for clinical studies in humans, requiring several hundred grams of pure n-3 DPA. n-3 DPA-enriched dietary supplements could be a good source for the purification of n-3 DPA by LC compared to fish or algae oils, as well as the combination of LC purification methods, crystallization and distillation [28] or the use of drug under development enriched with n-3 DPA [25,29].

2.3. Dietary sources and consumption

The major source of n-3 DPA is obviously seafood, including fish from the *Clupeidae* family that gave the n-3 DPA its common name: clupanodonic acid (USDA, 2014). Seal meat and fats appear to be the richest in n-3 DPA, containing 5.6% of n-3 DPA [30], which would amount to a daily consumption between 1.7 and 4.0 g of n-3 DPA per day for the Inuit population [31]. Among the most common consumer products in Western society, salmon contains 393 mg of n-3 DPA per 100g serving, Atlantic mackerel 200 mg, and other oily fish between 100 and 200mg (USDA, 2014). Beef liver and lamb are the richest land-based sources of n-3 DPA but are also highly variable in terms of provenances [4]. Thus, they contain about 140 mg of n-3 DPA/100 g in New Zealand, but only 20-30mg in the United Kingdom, while American beef does not contain any, surely associated with differences in

pasture production and quality [32–34]. Indeed, the quantities of n-3 DPA in organic meat are around 50% greater than in conventional meat [35]. While the dominant sources of EPA and DHA are seafood products that contain less n-3 DPA, n-3 DPA is the most prevalent n-3 LCPUFA in meat [36], thus varying the sources and amounts consumed of n-3 DPA according to eating habits. In another hand, the ruminal biohydrogenation of n-3 DPA was similar to that of EPA and appears complete without the formation of intermediate derivatives expected after biohydrogenation of DHA [37]. Food supplements made from fish oils enriched with n-3 LCPUFA may also provide a n-3 DPA intake, with mackerel oils containing about 4.9% n-3 DPA, compared with 3.0% for salmon or 2% for sardine.

The main dietary sources of n-3 DPA in pregnant and lactating women are seafood (59%), poultry (14%), meat products (11%) and dairy products (9%) [4]. About two-thirds of seafood-derived n-3 DPA intake in these women was attributed to salmon consumption [38]. In Australian children, intake of EPA and DHA is strongly correlated with consumption of fish and seafood, while intake of n-3 DPA is moderately correlated with meat consumption [39]. The main contributor to n-3 DPA consumption among these children was meat, poultry and wildfowl (56%), fish and seafood (23%), cereal products and dishes (5.7%), dairy products (5.6%) and finally egg products (3.6%) [39,40]. In Europe, the average daily intake of n-3 DPA in adults is between 25 mg/day (Belgium, women aged 18-39) and 75 mg/day (France, male> 45 years), with quartile intakes of 12 to 80 mg/day. In France, the maximum intake, estimated by the five highest percentiles of the population, is 129 mg / day of n-3 DPA [38]. There is no database of young children for n-3 DPA (0-3 years old) and adolescents (13-19 years old). Swedish, Norwegian and German consumption data indicate that the average daily intake of n-3 DPA in 4-year-old children is 30 mg/day, 40 mg/day for 8-12 years and 120 mg/day for 8-12 years old [38,40]. Thus, n-3 DPA could contribute up to 30% of the intake of n-3 LCPUFA in the diet of these populations [41] but there are important disparity of consumption beyond populations and ethnicity [42].

Dietary sources of n-3 DPA can also be indirect, either by providing the precursors of the n-3 LCPUFA conversion pathway, or by providing lipid mixture to increase the conversion from ALA to n-3 DPA. Several studies have shown that n-3 DPA can be increased in the blood compartment in human as well as in tissues in animals after a diet rich in ALA or EPA [43]. More recently, the addition of *echium* oil rich in stearidonic acid in the diet of rats increased the tissue n-3 DPA status, showing that stearidonic acid could also be a source of n-3 DPA, in addition to a source of EPA for which it is mainly described [44,45]. While human milk contains n-3 DPA and cerebral accumulation of n-3 LCPUFA occurs mainly during the first years of life [5], some studies have shown that the addition of milk lipids in the diet of young people, whose fatty acid composition are closer to breast milk than a mixture of vegetable oils, also increased tissue n-3 DPA status. First, in a monocentric, double-blind controlled and randomized trial, healthy newborns fed formula containing a mixture of dairy lipids and plant oils from birth to 4 month-old increased their n-3 DPA content in red blood cells (RBC) compared to newborns fed with a formula composed with plant oils only [46]. Moreover, this increase in RBC n-3 DPA was more important than in breastfed newborns. In healthy post-weaning Sprague Dawley rats, a partial incorporation of dairy lipids in the diet with vegetable oils (50% w/w) during 6 weeks increased the n-3 DPA status in the RBC, brain, liver and principally in the heart, compared to 100% vegetable oil diets [47]. Thus, dairy lipids could be a potential indirect help to increase the n-3 DPA status in early life. Surprisingly, it has been shown that n-3 DPA supplementation (0.5% of total fatty acids, 10% lipid w/w) and the partial incorporation of dairy lipids in the diet (50% w/w) had a

complementary effect to increase the n-3 LCPUFA status in tissues of Sprague Dawley rats fed from weaning for 6 weeks, especially EPA and n-3 DPA tissue contents [26].

2.4. Markers of food consumption

The n-3 DPA composition of the RBC membranes and the different lipid classes of plasma in humans are positively correlated with dietary intake of n-3 LCPUFA, as for EPA and DHA. This increase, however, tends to be relatively limited compared to that of EPA and DHA [48]. In addition, n-3 DPA is present in whole blood in lower amounts than EPA and DHA and the proportion of n-3 DPA decreases less than EPA or DHA as the proportion of n-6 PUFA increases in the blood [49].This suggests that n-3 DPA present in other blood compartments than RBC (plasma, platelets, peripheral blood mononuclear cells) may have a different metabolism than EPA and DHA and that the n-3 DPA blood level would be preserved [50].

n-3 DPA is for now not considered in the calculation of the Omega-3 index (EPA + DHA of the RBC membranes), which is used as a marker of consumption but also as a risk marker for total mortality, sudden cardiac death or other cardiovascular risks in epidemiological studies [51]. Although the inclusion of n-3 DPA in the Omega-3 index was more precise to estimate n-3 LCPUFA contents in whole blood [50], it did not improve the prediction of the risks associated with the existing Omega-3 index [11].

2.5. Nutritional recommendations

The different health national agencies agreed that the data about n-3 DPA were insufficient to produce specific recommendations for this n-3 LCPUFA. Nevertheless, England [52], Australia and New Zealand [53] as well as the Netherlands [54] included the n-3 DPA in the sum of the recommended n-3 LCPUFA (EPA + n-3 DPA + DHA).

3. Products derived from n-3 DPA

3.1. A reservoir of EPA and DHA

n-3 DPA is the direct intermediate between EPA and DHA, in the conversion pathway from ALA, to be present in significant amounts in the human diet compared to the C24:5 n-3 and C24:6 n-3 derivatives [39]. This conversion pathway is well known and involves a sequence of desaturase enzymes adding one double bond to the carbon chain and elongase enzymes extending the carbon-chain of two carbons (Figure 1). The n-3 LCPUFA conversion pathway is parallel to that of n-6 LCPUFA using the same sequence and enzymes. Thus, the two pathways are in competition for substrates with each other. In the n-3 LCPUFA conversion pathway, the n-3 DPA is elongated to the C24:5 n-3 derivative by the elongase-5 and weaker elongase-2 enzymes, then desaturated to the C24:6 n-3 by the action of the Δ6-desaturase, and finally converted to DHA by a peroxisomal β-oxidation step [55]. The Δ6-desaturase and more recently elongase-2 are considered as the limiting enzymes in this conversion pathway to DHA [56]. Thus, it has been hypothesized that dietary n-3 DPA could be a better precursor of DHA than dietary

EPA, bypassing the conversion of EPA to n-3 DPA using elongase-2 and elongase-5 as well [26,27]. One Δ4-desaturase activity has also been described *in vitro* in humans to convert n-3 DPA directly to DHA but these results need to be confirmed [57]. Some authors have also hypothesized that n-3 DPA could not only serve as a reservoir of DHA but also of EPA in humans, in farm animals and potentially in other mammals [58].

The ability of dietary n-3 DPA to increase tissue status in DHA remains however controversial and seems tissue-dependent. In humans, a 7-day supplementation with a single daily dose of pure n-3 DPA resulted in an increase in plasma DHA in triglycerides only [58]. Gavage of rats for 7 days with 50 mg of n-3 DPA/day in the form of free fatty acid led to an increase in DHA in the liver only compared to ALA control [59]. In the miniature poodle, intravitreal injection of 1-^{14}C-n-3 DPA showed an increase in radiolabeled DHA in the retina [15]. Conversely, in the C57BL/KsJ-db/db obese mouse supplemented for 4 weeks with tri-n-3 DPA, no increase in DHA was found in studied tissues [60], as in the C57BL/6J mouse fed a high-fat diet and force-fed with 50mg of n-3 DPA daily for 6 weeks [13]. In these mice, n-3 DPA supplementation tended to impact tissue fatty acid composition more like DHA than EPA supplementations [13]. While brain tissue composition is known to remain highly stable, oral administration of n-3 DPA to rats resulted in the increase of cerebral n-3 DPA and DHA, regardless of animal age [61]. However, these both studies used n-3 DPA nearby 70% purity containing DHA and is not easy to interpret. The addition of n-3 DPA in endothelial cell cultures of aorta [62,63], rat hepatocyte line (FaO) [64], primary rat hepatocytes [65] or human hepatocyte line (HepG2) [66] caused an increase in EPA in cells and media, as well as DHA in media, but DHA was conversely not increased in human intestine (Caco-2) or monocyte (THP-1) cell lines [66].

Dietary n-3 DPA could also be used as a source of EPA. The EPA produced from n-3 DPA certainly comes from the retroconversion of n-3 DPA, implicating, as for DHA, the acyl-CoA oxidase and one peroxisomal β-oxidation step. This pathway was demonstrated in acyl-CoA oxidase deficient fibroblasts which do not led to n-3 LCPUFA [67]. In Sprague Dawley rats, we showed that the overall tissue fatty acid change following a dietary n-3 DPA supplementation was more similar to EPA supplementation than DHA supplementation [27]. In this study, the apparent retroconversion of n-3 DPA into EPA was particularly important in the kidney (68%), the liver (38%) and the spleen (20%). These results are confirmed by another study showing a higher apparent retroconversion of n-3 DPA in the kidney than in the liver in rats (50 mg/day by oral gavage) [68] (Figure 1). Finally, the apparent retroconversion of n-3 DPA to EPA was shown in humans [58], Sprague-Dawley rat [59], C57BL/6J-db/db mouse [60], C57BL/6J mouse (high-fat diet) [13] and miniature poodle [15]. However, this retroconversion is still estimated relative to control without dietary n-3 DPA and there is a lack of labeled n-3 DPA monitoring studies to really quantify the importance of this pathway.

We recently investigated for the first time the tissue distribution of n-3 LCPUFA in 18 tissues, following a 3 week nutritional pure n-3 DPA supplementation (0.5% of the total fatty acids included in the diet) of healthy Sprague Dawley rats in post weaning [26]. The n-3 DPA content increased in half of the studied tissues and mostly in the spleen, lung, heart, liver and bone marrow from +50% to +110% compared to the control group. n-3 DPA was mostly retroconverted into EPA, especially in the liver (35%) and the kidney (46%) and slightly converted into DHA, showing an increased content of these two LCPUFA in affected tissues. Moreover, the n-3 DPA supplementation decreased total n-6 PUFA in affected tissues and especially n-6 DPA and adrenic acid (C22:4 n-6)

[26]. In organs most affected by its supplementation, another study showed that dietary n-3 DPA was mainly incorporated into the phospholipid fractions, (phosphatidylethanolamines and phosphatidylcholines) [68].

To conclude, dietary n-3 DPA is mainly incorporated in major metabolic organs and esterified into the same lipid species than EPA and DHA. It is mainly retroconverted into EPA and slightly converted to DHA. It could therefore be considered as a source of EPA but also DHA to a lesser extent, implying potential physiological effects associated within these tissues.

3.2. Bioavailability

Only one study investigated the bioavailability (efficiency with which dietary n-3 DPA is used systematically through normal metabolic pathways) of dietary n-3 DPA. After oral administration of 2.5 µCi of 1-^{14}C-n-3 DPA, 1-^{14}C-EPA or 1-^{14}C-DHA in the rat housed in metabolic cage for 6h, 1-^{14}C-n-3 DPA was catabolized to $^{14}CO_2$ in the same proportion as the 1-^{14}C-DHA (about 7% of the ingested dose) and less than the 1-^{14}C-EPA (about 18%). In addition, the percentage of the ingested radioactivity measured in the heart and muscle was similar from 1-^{14}C-n-3 DPA and 1-^{14}C-DHA and higher from 1-^{14}C-EPA. Conversely, the radioactivity found in liver, brain and kidney was similar from 1-^{14}C-n-3 DPA and 1-^{14}C-EPA but less than from 1-^{14}C-DHA [14].

The digestibility (difference between intake and excretion) of dietary n-3 DPA in ethyl ester form (96.6%) was similar than DHA (96.9%) and lower than EPA (98.3%) in post weaning Sprague Dawley healthy rats [27]. In another study, the excretion of n-3 DPA was 4.6 times greater than that of EPA after ingestion of 250 mg/day of n-3 DPA or EPA as free fatty acids for 3 days in rats [69]. n-3 DPA was also preferentially hydrolyzed by porcine pancreatic lipase *in vitro* compared to EPA and DHA, suggesting a faster absorption [70].

Thus, the n-3 DPA seems slightly less absorbed than the other n-3 LCPUFA. Nevertheless, its digestibility remains greater than 95% regardless of its form of intake. More studies are needed to better address the n-3 DPA bioavailability compared to other n-3 LCPUFA.

3.3. Precursor of lipid mediators

Like DHA, n-3 DPA is a precursor of docosanoids whose physiological effects are however poorly known. Several metabolites of n-3 DPA are indeed discovered each year in different tissues, [10,71–75]. The multiple lipid mediators identified from n-3 DPA and their deduced biosynthesis pathways are summarized in Figure 2.

The 17S-hydroperoxy-n-3 DPA is first synthesized by the action of the 15-lipoxygenase (15-LOX). It can thereafter be converted either into 16S,17S-epoxy-7Z, 10Z, 12E, 14E, 19Z-n-3 DPA which will be converted by enzymatic hydrolysis into the family of Protectins $_{\text{n-3 DPA}}$: Protectin 1$_{\text{n-3 DPA}}$ (10R,17S-dihydroxy-7Z,11E,13E,15Z,19Z-n-3 DPA) and Protectin 2 $_{\text{n-3 DPA}}$ (16,17R-dihydroxy-7Z,10,13,14,19Z-n-3 DPA)[76,77]; or into 7,17S-dihydroperoxy-n-3 DPA by the 5-LOX to give the family of Resolvins $_{\text{n-3 DPA}}$: Resolvin D1 $_{\text{n-3 DPA}}$ (7,8,17S-trihydroxy-9,11,13,15*E*,19Z-n-3 DPA), Resolvin D2 $_{\text{n-3 DPA}}$ (7,16,17-trihydroxy-8,10,12,14E,19Z-n-3 DPA) and Resolvin D5 $_{\text{n-3 DPA}}$ (7S,17S-dihydroxydocosa–8E,10Z,13Z,15E,19Z-n-3 DPA) [75]. The maresins derived from n-3 DPA come

from the action of the 12-LOX followed by the reduction of 14S-hydroperoxy-7Z,10Z,12E,16Z,19Z-n-3 DPA to 13,14S-epoxy n-3 DPA, itself enzymatically hydrolyzed to give the family of Maresins $_{\text{n-3 DPA}}$: Maresin 1 $_{\text{n-3 DPA}}$ (7S,14S-dihydroxy-8E,10E,12Z,16Z,19Z-n-3 DPA), Maresin 2 $_{\text{n-3 DPA}}$ (13,14-dihydroxy-7Z,9,11, 16Z,19Z-n-3 DPA) and Maresin 3 $_{\text{n-3 DPA}}$ (14, 21-dihydroxy-7Z,10Z,12E,16Z,19Z-n-3 DPA). The 5-LOX can also produce mono- and di-hydroxylated derivatives from n-3 DPA. The 15-LOX pathway is the most efficient, converting 85% of the n-3 DPA to its 17S-hydro(peroxy) n-3 DPA derivative *in tubo*, compared to only 10% for 12-LOX and 5-LOX [78]. Some of these mono-hydroxylated metabolites as well as Resolvin D5 $_{\text{n-3 DPA}}$ and Maresin 1 $_{\text{n-3 DPA}}$ were detected in human serum after n-3 DPA supplementation for 7 days [79].

n-3 DPA can additionally undergo the induced action of cyclooxygenase-2 (COX-2), to form the 13R-hydroxy-7Z,10Z,13R,14E,16Z,19Z-n-3 DPA which will be able, as for derivatives from DHA, to be reduced to 13-oxo derivatives (EFOX). The 17-EFOX-D5 was for instance produced when aspirin was added to the culture medium of macrophages, as for EFOX derivatives from DHA [80]. The 13-serie resolvins from 13R-hydroxy-7Z,10Z,13R,14E,16Z,19Z-n-3 DPA (RvT1: 7,13R,20-tri hydroxy-n-3 DPA, RvT2: 7,12,13R-tri hydroxy- n-3 DPA, RvT3: 7,8,13R-trihydroxy-n-3 DPA, RvT4: 7,13R-dihydroxy-n-3 DPA) have been identified in co-incubations of neutrophils and endothelial cells [81]. These derivatives are formed by COX-2 then by S-nitrosylation. The cytochrome P450 can also metabolize n-3 DPA, but to a lesser extent than other n-3 LCPUFAs, although this result must be confirmed [82,83]. Isoprostanes resulting from the peroxidation of n-3 DPA are not yet known. Nevertheless, a series of isoprostanes derived from n-3 DPA have recently been described from the n-6 isomer of n-3 DPA [84]. Very few studies report on the overall distribution and action of oxygenated metabolites from n-3 DPA because of their very recent discovery and the lack of synthetic standards [85]. More information on the chemical synthesis, availability and biological effects of n-3 DPA-derived metabolites can be found in these reviews [10].

4. Biological and pharmacological effects of n-3 DPA

4.1. Inflammation and cancer

The decrease in inflammation associated with n-3 DPA seems to come mainly from these lipid mediators, and mainly the specialized pro-resolving mediator (SPM) (maresins, protectins, resolvins). Indeed, incubation of human macrophages with Protectin D1$_{\text{n-3 DPA}}$ increased the monocyte differentiation, the phagocytic activity of macrophages and the apoptosis of neutrophils, which are key factors in the resolution of inflammation [71,76]. Moreover, the incubation of n-3 DPA-derived Maresin1$_{\text{n-3 DPA}}$ also stimulated macrophage phagocytosis and clearance of human apoptotic neutrophils in a similar manner to DHA-derived Maresin1 [72]. In human inflammatory bowel disease colon biopsies, the Protectin D1$_{\text{n-3 DPA}}$ and Resolvin D5$_{\text{n-3 DPA}}$ increased [86]. These lipid mediators protected against colitis and intestinal inflammation in mice and decreased the extent of leukocyte adhesion and emigration post-stimulation. Contrary, the inhibition to their metabolic pathway (15-LOX) led to increased intestinal inflammation [86]. In a series of other studies, 13-series resolvins from n-3 DPA accelerated the resolution of inflammation and increased survival by 60% in *Escherichia coli*-infected mice [72,81,87]. The independent effects of each 13-series resolvins from n-3 DPA were well described previously (supp. data) [87]. In

LPS-activated murine macrophage like RAW264.7 cells incubated with n-3 DPA, EPA or DHA, n-3 DPA increased EPA and DHA cell contents, down-regulated mRNA expression of pro-inflammatory factors (IL-6, IL-1β, iNOS, COX-2), and especially decreased IL-6 mRNA expression dose-dependently more than EPA and similarly than DHA [88]. Interestingly, the down-regulation of IL-6 and IL-1β mRNAs were similar when cells were incubated with an inhibitor of the delta-6 desaturase, demonstrating that n-3 DPA exhibited anti-inflammatory effects independent of DHA conversion [88].

Several studies from the same research team have shown that n-3 DPA-monoacylglyceride had greater anti-inflammatory, anti-proliferative and pro-apoptotic effects than EPA- or DHA- monoacylglycerides [25], in a model of colorectal cancer [89], in a model of rheumatoid arthritis [34], and in pulmonary hypertension where n-3 DPA reduced the markers of inflammation and remodeled vascular pattern [90]. As a consequence, a prescription drug containing monoglyceride n-3 DPA is in the final stages of development by SCF Pharma for its anti-inflammatory and anti-proliferative properties and has been patented [91]. In healthy adult men, a high level of n-3 DPA was correlated with a lower inflammation score, mainly associated with decrease in C-reactive protein (CRP) and TNF-α scores [92]. In another study, n-3 DPA reduced the expression of genes involved in the inflammation of blood vessel membranes [93]. Treatment of aortic endothelial cells with n-3 DPA strongly inhibited angiogenesis, implicated in tumor growth, inflammation, and microangiopathies [94]. A prospective study associated dietary n-3 DPA with a reduction of breast cancer risk (like EPA and DHA intake) [95].

On the other hand, n-3 DPA anti-inflammatory properties could benefit adults with comprised pulmonary health. n-3 DPA was positively associated with forced expiratory volume in the first second (FIV_1), forced vital capacity (FEV) and FEV_1/FVC, modified by smoking and sex, in meta-analyses across seven cohorts (n=16,134) [96]. A recent epidemiological study has shown that the consumed n-3 DPA was the most fatty acid associated with a better average FEV_1 and slower FEV_1 decline in the smoking patient [42]. Interestingly, the FEV_1 decline from the adverse effect of continuous current smoking was completely negated with high n-3 DPA intake in the Lovelace Smokers cohort [42]. In human bronchus and guinea pig trachea preparations treated with n-3 DPA-monoacylglyceride, the higher concentration of n-3 DPA reduced the TNF-α/NF κB pathway, suppressed COX-2 expression, decreased the Ca^{2+} sensitivity of bronchial explants and reversed the induced contractile reactivity [97].

4.2. Cardiovascular and metabolic diseases

The effect of n-3 DPA on the lipid parameters associated with the prevention of cardiovascular diseases is the most documented topic (anti-inflammatory properties, inhibition of cytokine synthesis, decrease in thrombosis, decrease in plasma lipids, inhibition of atherosclerosis...). Studies on the potential effect of n-3 DPA in the prevention of cardiovascular diseases in humans are usually association studies and concern the blood compartment. It has been shown that a high level of n-3 DPA in the red blood cell membranes in men and in women is associated with a lower risk of developing metabolic syndrome in Chinese adults [98]. In addition, a high plasma n-3 DPA (and DHA) level would also be the most correlated with a reduction of the risk of cardiovascular disease with plasma DHA level [51,99–102]. Moreover, in a pool of 19 cohort studies, n-3 DPA (in plasma and adipose tissue) was the only n-3 LCPUFA associated with a lower risk of total coronary heart disease, while all n-3 LCPUFA were associated with a lower risk of fatal coronary heart disease [103]. In addition, a cross-sectional study found that

decrease in RBC n-3 DPA concentrations (3.0% vs. 3.9%) was associated with an increased incidence in cardiovascular diseases [104]. Plasma n-3 DPA was also inversely correlated with arterial obstruction and stroke. n-3 DPA was the only fatty acid whose plasma level is inversely correlated with arterial obstruction in smokers [42,105]. In addition, a cross-sectional study of carotid ultrasonography showed an association between n-3 DPA consumption and carotid wall thickness reduction [106]. Serum n-3 DPA (1^{st} vs 3^{rd} tertile) was the only n-3 LCPUFA inversely associated with the risk of orthostatic hypotension [107]. However, the association of n-3 DPA with the reduction of cardiovascular risk was moderate (but significant) [108] and these results remain controversial because some studies didn't show any impact of n-3 DPA intake on these factors [11].

In another hand, in children, the highest RBC levels of n-3 DPA have also been associated with a decreased risk of pancreatic islet autoimmunity in children with type I diabetes [109]. Moreover, plasma n-3 DPA and DHA were strongly and positively associated with insulin sensitivity using a global lipidomic approach in rats fed high-fat or high-fructose diets [110]. Serum n-3 DPA was influenced by lifestyle: in obese adolescent with cardiometabolic syndrome following a 1-year interdisciplinary therapy, changes in n-3 DPA were negatively associated with leptin and leptin/adiponectin ratio and positively with adiponectin [111]. Moreover, high-fat diets supplemented with n-3 DPA decreased serum adiponectin level in mice [13].

Some *in vitro* and *in vivo* studies, mainly in the rodent model, tried to decrypt the mechanisms by which n-3 DPA could help improving cardiovascular diseases risk markers. Compared with ALA, EPA or DHA contents, the rate of n-3 DPA in RBC was inversely and dose-dependently the most correlated with fasting plasma triglycerides in humans, after a 5 month supplementation with EPA + DHA [112]. Thus, several studies in animals have shown that n-3 DPA improved the lipid profile of plasma like EPA and DHA. In healthy rats fed 0.1% n-3 DPA (in energy) for 6 weeks, plasma total cholesterol, non-HDL cholesterol and cholesterol esters decreased compared to control group [26]. Compared to EPA and DHA supplementations in ethyl ester forms, n-3 DPA-fed rats (7.6 mg/day/kg.bw) were the only one with lower plasma triglycerides, total cholesterol, non-HDL cholesterol, total cholesterol/ HDL cholesterol ratio and cholesterol esters concentrations [27]. The n-3 DPA-supplemented group also increased its plasma total antioxidant status and superoxide dismutase activity like EPA and DHA fed-rats, with no change in complete blood count, white blood cell and splenocytes subpopulations [27]. In hamster fed high-cholesterol diets, supplementation with n-3 DPA (50 mg/day) reduced plasma total cholesterol and non-HDL cholesterol, associated with inhibition of SREBP2 mRNA, resulting in a decrease in the transcription of the HMG-CoA Reductase involved in cholesterol synthesis [113]. Mice supplemented with dietary n-3 DPA showed a decrease in the activity of Fatty Acid Synthase (FAS), plasma total cholesterol and triglyceride concentrations [114]. A very interesting recent study in C57BL/6J mice fed high-fat diets (23% w/w) and supplemented with n-3 DPA (72% purity), pure EPA or pure DHA for 6 weeks showed that only n-3 DPA improved insulin resistance (HOMA) [13]. In this study, both n-3 DPA and DHA prevented the increase in serum alanine aminotransferase (ALT) levels, probably associated with inhibition of the TLR-4/NFκB signaling pathway and decreased liver lipogenesis. Another study showed that C57BL/KsJ-db/db mice receiving purified tri-n-3 DPA or DHA decreased their hepatic triglyceride levels significantly more than mice treated with EPA [60]. In a human liver cell culture model (HepG2), the decrease in triglyceride synthesis after supplementation with n-3 LCPUFA in the medium was associated with a decrease in FAS mRNA expression and was classified as depending on the supplementations as follow: C24:6 n-3> DHA> n-3 DPA> EPA [114]. In a rat hepatocyte cell line model (FAO) treated with 50 μM EPA, n-3 DPA or

DHA, n-3 DPA decreased most strongly the expression of HMG-CoA reductase, FAS, acetyl-CoA carboxylase 1 (ACC-1), SREBP1-c and ChREBP [64]. On the other hand, the concentration of postprandial plasma chylomicrons decreased in healthy women after a breakfast supplemented with n-3 DPA, compared to supplementation with EPA or olive oil [58]. Finally, it appears that the n-3 DPA is transported mainly in the triglyceride part of the chylomicrons and not in the PL after the evaluation period of 5 hours in humans [115].

Based on these studies, Matinas BioPharma has patented and placed on the market a prescription-only drug containing a mixture of n-3 DPA and EPA in the form of ethyl ester and containing only traces of DHA for the treatment of severe hypertriglyceridemia [29]. Compared to the ingestion of EPA ethyl esters in humans with severe hypertriglyceridemia (200-400 mg of triglycerides/dL plasma), this drug (MAT9001) helped reducing the plasma triglycerides, total cholesterol, non-HDL cholesterol and VLDL concentrations more significantly [29]. The lack of comparison with the ethyl ester of DHA nevertheless reduces the scope of these findings.

n-3 DPA can also decrease platelet aggregation more significantly than EPA and DHA. n-3 DPA indeed inhibited collagen or ARA-stimulated platelet aggregation in a dose-dependent manner using rabbit platelets [116] or human platelets, but this regulation appears sex-dependent in humans because only platelet aggregation in women were inhibited [117,118]. n-3 DPA also increased the LOX pathway and may act as a strong inhibitor of COX-1 and COX-2 activities leading to decreased platelet aggregation and active aortic tension [113,116]. n-3 DPA also stimulated the migration of endothelial cells, whose migration and proliferation are processes involved in the control of the healing response of blood vessels [63]. In addition, the treatment of aortic endothelial cells with n-3 DPA inhibited their migratory activity due to the stimulation of vascular endothelial growth factor (VEGF) [63]. The supplementation of Sprague Dawley rats with *echium* oil, rich in stearidonic acid and potential source of n-3 DPA, showed an anti-arrhythmic action comparable to that obtained by supplementation with fish oils rich in DHA and was associated with tissue augmentation. of the n-3 DPA [119].

The association between n-3 DPA blood status and prevention of cardiovascular and metabolic risks remains uncertain. Nevertheless, an even greater level of evidence is accumulating in favor of a specific effect of n-3 DPA on the improvement of risk factors associated with metabolic diseases, including improvements in blood lipid parameters, in platelet aggregation, in pro-resolution of inflammation, improvement of insulin sensitivity or modulation of adiponectin. On the other hand, these effects and their mechanisms remain to be elucidated in humans.

4.3.Neuroprotection and development

n-3 DPA is the most abundant n-3 LCPUFA in the brain after DHA and it could be specifically beneficial for neuroprotection and for depression prevention [2]. In a mouse model of epilepsy, Frigerio *et al.* interestingly showed that in the hippocampus of 72 post-status epilepticus mice, IL1β and TNFα transcripts (neuroinflammation markers) as well as 5-LOX and 15-LOX transcripts (key enzymes in pro-resolving mediator biosynthesis) were upregulated supporting the hypothesis that neuroinflammation in epileptogenesis could result from a failure to engage pro-resolving mechanisms. The authors then showed that some lipid mediator production derived from n-3 DPA were downregulated in the hippocampi of epileptogenic mice (Resolvin D2 $_{\text{n-3 DPA}}$, Resolvin D5 $_{\text{n-3 DPA}}$), while Protectin D1 $_{\text{n-3 DPA}}$ was upregulated [120]. Moreover, the intracerebroventricular administration of Protectin D1 $_{\text{n-3 DPA}}$ in methylester form (20-200ng) during epileptogenesis dose-dependently controlled the onset and the

propagation of neuroinflammation during epiletpgenesis in the hippocampus. Providing new leads for treatment, the authors also showed that the injection of Protectin D1 $_{n\text{-}3\ DPA}$ improved weight recovery, decreased cognitive deficit, the frequency (- 2-fold) and the average duration (- 40%) of spontaneous seizures [120].

Elderly rats (20-22 months) supplemented with n-3 DPA, EPA, or purified monounsaturated fatty acids for 56 days had neuro-restorative benefits associated with decrease in microglial activation and oxidative stress in the hippocampus, two mechanisms involved in the loss of synaptic functions and therefore related to cognitive decline [61]. Moreover, n-3 DPA (and n-6 DPA) inhibited sphingosylphosphorylcholine-induced Ca^{2+}-sensitization of vascular smooth muscle contraction by inhibiting Rho-kinase activation and translocation to the cell membrane, a major cause of cerebrovascular vasospasm [121]. Some authors also hypothesized that RBC n-3 DPA content could be one of the diagnostic marker of Alzheimer's disease and one therapeutic target because RBC n-3 DPA decreased in cognitively normal elderly participants with high neocortical β-amyloid load [122]. Conversely, no association was found between serum n-3 DPA and performance on neuropsychological tests in an older population [123]. While n-3 LCPUFA are well-known to decrease the risk of age-related macular degeneration, plasma level of n-3 DPA was the only n-3 LCPUFA associated with higher macular pigment optical density in subjects with family history of age-related macular degeneration [124].

Concerning depression, purified n-3 DPA supplementation at 150 mg/kg/day for 6 days in rats resulted in a reduction of symptoms associated with depression and increased levels of cerebral n-3 DPA [125]. In a prospective cohort study in aged subjects, the third quartile of n-3 DPA intake was also correlated with a reduced risk of major depressive disorder as well as EPA and fish intake. However, only n-3 DPA and fish intake remained significant when odd ratios were adjusted for cancer, myocardial infarction, stroke and diabetes [126]. RBC n-3 DPA (and both ALA and DHA) levels were also negatively associated with depression of postmenopausal women only if they used hormone therapy, suggesting an interaction between n-3 DPA and hormones on depression [127].

n-3 DPA is also present in non-negligible quantities in human and mammalian milk, so it could be involved in fertility [128], pregnancy [129]and early-life development. Indeed, high n-3 DPA intake by lactating mothers was linked to better neuro-development and bone health of children [6]. Moreover, n-3 DPA blood levels in mothers were associated with lower allergic diseases in children and mothers. These findings were recently well reviewed [6] and are not detailed here.

5. Conclusion and prospects

An increasing number of association studies support the hypothesis that n-3 DPA is a bioactive fatty acid beneficial to human health. The suggested mechanisms involve the importance of n-3 DPA-derived lipid metabolites in the pro-resolution of inflammation in various models and mainly the importance of protectin D1 and resolvin D5 found in humans. Many other n-3 DPA-derived metabolites have also recently been identified and their potential physiological effects are not yet known. Likewise, in vivo and in vitro studies suggest that n-3 DPA is implied in the improvement of cardiovascular and metabolic disease risk markers, especially plasma lipid parameters, platelet aggregation, insulin sensitivity and cellular plasticity. Moreover, n-3 DPA is the most abundant n-3 LCPUFA in the brain after DHA and it could be specifically beneficial for elderly neuroprotection, and early-life development. Nevertheless, there is still a lack of clinical intervention studies in humans to elucidate the specific biological effects of n-3 DPA and its underlying mechanisms and no studies are currently underway (search on

ClinicalTrials.gov, September 21, 2018). The increase in commercial n-3 DPA availability as well as the efficiency and diversity of n-3 DPA purification methods should facilitate the implementation of new studies in the coming years.

While the effects associated with n-3 LCPUFA are studied independently, it remains difficult to differentiate the effects specific to n-3 DPA itself compared to those of EPA and DHA as they are biologically interconverted. For this, labeled-n-3 DPA monitoring studies are necessary to better understand the independent effects of n-3 DPA compared to other n-3 LCPUFA. In contrast, dietary n-3 DPA appears to be a good source of EPA and a low source of DHA in major metabolic organs, in addition to being well assimilated. The n-3 DPA could thus contribute to increasing the omega-3 status. Indeed, n-3 DPA is more present in meat than EPA or DHA and while the sources of fatty fish are limited, its food consumption is not negligible and n-3 DPA should surely be considered as well as DHA and EPA within the next nutritional recommendations. While food sources most often contain a mix of different n-3 LCPUFAs, they are studied independently, and it would be interesting to see if the impact of dietary n-3 DPA alone on omega-3 status is of nutritional interest. compared to a mixture of n-3 LCPUFA representative of human consumption.

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Table 1 – Recent findings about n-3 docosapentaenoic acid (june 2016-sept. 2018)

Ref	Year	Model	Main findings
			Sources
[35]	2016	Meta-analysis (meat)	n-3 DPA content was 47% greater in organic meat than in conventional meat
[45]	2016	Humans	Echium oil diet increased n-3 DPA level in plasma, RBC and PBMC compared to linseed oil diet.
[47]	2018	Sprague Dawley rats	A partial incorporation of dairy lipids in the diet increased n-3 DPA status in tissues (RBC, liver, heart, brain)
[46]	2018	Newborns (0-4 month)	Infant fed with dairy lipids containing formula increased RBC n-3 DPA status compared to plant oils formula and breastfeeding
[24]	2018	*In tubo*	Structural characterization of self-assemblies of n-3 DPA monoglycerides
[19]	2018	Algae	n-3 DPA diglyceride production from *Schizochytrium sp.* (16.4% oil purity) and crystallization purification (28% purity)
[11]	2018	Review	Current scientific evidence does not support including n-3 DPA into the Omega-3 index
			Metabolism
[26]	2018	Sprague Dawley rats	Dietary n-3 DPA was assimilated in major tissues and mainly retroconverted in EPA (18 tissues). Dietary dairy lipids and n-3 DPA had complementary positive effect on n-3 LCPUFA status.
[66]	2016	Human cell lines	n-3 DPA was converted to DHA in HepG2 but not in Caco-2 and THP-1 cells. n-3 DPA was retroconverted into EPA in all cell lines and a greater increase of EPA was found in phospholipid than in neutral lipid fraction
[79]	2016	Humans	7-day n-3 DPA supplementation increased plasma specialized pro-resolving mediators derived from n-3 DPA
[77]	2017	Human neutrophils	Elucidation of stereocontrolled total synthesis of the intermediate 16(S),17(S)-epoxy-protectin n-3 DPA, its role in PD1 biosynthesis by human neutrophils and its regulation of the formation of the potent neutrophil chemoattractant LTB4
[37]	2017	Cannulated cows and ewes	n-3 DPA ruminal biohydrogenation was complete and like that of EPA, contrary to DHA forming intermediate derivatives
[128]	2017	Rabbit	n-3 DPA-enriched semen did not affect semen characteristics but had a negative impact on the lipid peroxidation and DNA integrity of the spermatozoa
			Inflammation and cancer
[96]	2018	Meta-analysis (human)	n-3 DPA is positively associated with spirometric measures of pulmonary function tests in meta-analyses
[97]	2016	Airway models	n-3 DPA monoglyceride mediated antiphlogistic effects in stimulated human bronchi or guinea pig trachea by increasing the resolution of inflammation, while resetting Ca2+ sensitivity and contractile reactivity
[42]	2017	Epidemiological	n-3 DPA intake is the most potent n-3 LCPUFA associated with slower forced expiratory volume decline in smokers
[88]	2017	Mouse macrophage cell line	n-3 DPA increased EPA, n-3 DPA and DHA contents in activated RAW264.7 cells, down-regulated mRNA expression of pro-inflammatory factors in a dose-dependent manner similarly than DHA supplementation and independently of DHA conversion from n-3 DPA.
[76]	2018	Human monocytes	Protectins n-3 DPA positively regulated monocyte differentiation and macrophage efferocytosis and phagocytosis
[86]	2017	Mice	ProtectinD1 and resolvin D5 n-3 DPA protected against colitis and intestinal inflammation and cell adhesion
[95]	2016	Cohort	Dietary n-3 DPA was inversly associated with breast cancer risk, as well as dietary EPA and DHA
[74]	2017	Review	An overview of recent knowledge about ProtectinD1 n-3 DPA
[10]	2017	Review	Update in biosynthesis and chemistry of specialized pro-resolving mediators from n-3 DPA
[25]	2016	Review	Anti-inflammatory and anti-proliferative effects of n-3 LCPUFA monoacyglycerides
			Metabolic diseases
[27]	2018	Sprague Dawley rats	n-3 DPA (>99% obtained by liquid chromatography) was the only n-3 LCPUFA improving lipid parameters. Fatty acid tissue changes were similar with dietary n-3 DPA and EPA but not with dietary DHA.
[12]	2018	Review	DPA and cardiometabolic health.
[13]	2017	C57BL/6J mice	Following High-fat diet, only n-3 DPA (not DHA and EPA) improved insulin resistance. n-3 DPA- and DHA-supplementations acted similarly on the decrease in serum adiponectin, ALT and liver lipogenesis.
[51]	2016	Cohort	Only n-3 DPA tissue contents were associated with a lower risk of total coronary heart diseases (CHD), and as well as the others n-3 LCPUFA with fatal CHD in a pool of 19 cohort studies.
[110]	2016	Sprague Dawley rats	Plasma n-3 DPA was strongly and positively associated with insulin sensitivity index in rats fed high-fat or high-fructose diets
[111]	2016	Association	In obese adolescent with cardiometabolic syndrome following a 1-year interdisciplinary therapy, changes in n-3 DPA were negatively associated with leptin and leptin/adiponectin ratio and positively with adiponectin.
[107]	2016	Association	Serum n-3 DPA was the only n-3 LCPUFA inversely associated with the risk of orthostatic hypotension
[102]	2016	Association	Plasma n-3 DPA was negatively associated (less than EPA) with all-cause mortality in men but not in women
			Neuro-visual protection
[120]	2018	Mice	Protectin $D1_{n\text{-}3\ DPA}$ promotes resolution of neuroinflammation and arrests epileptogenesis
[126]	2017	Cohort	n-3 DPA intake was the only n-3 LCPUFA independently associated with reduced risk of major depressive disorder in aged Japanese individuals
[127]	2016	Humans	Negative association between RBC n-3 DPA and depression in postmenopausal women using hormone therapy
[122]	2017	Humans	n-3 DPA decreased in RBC of cognitively normal elderly participants with high neocortical β-amyloid load and could be an early potential marker of Alzheimer's disease
[121]	2017	Human CASMC cells	n-3 DPA (and n-6 DPA) inhibited sphingosylphosphorylcholine-induced Ca2+-sensitization of coronary artery smooth muscle cell (CASMC) contraction by inhibiting Rho-kinase activation and translocation to the cell membrane
[123]	2016	Cohort	No association was found between serum n-3 DPA and with performance on neuropsychological tests in an older population
[124]	2017	Humans	n-3 DPA plasma level was the only one associated with higher macular pigment optical density
[6]	2016	Review	Links between n-3 DPA intake and blood level in pregnant and lactating mothers with better neural and bone

developments and fewer allergy diseases.

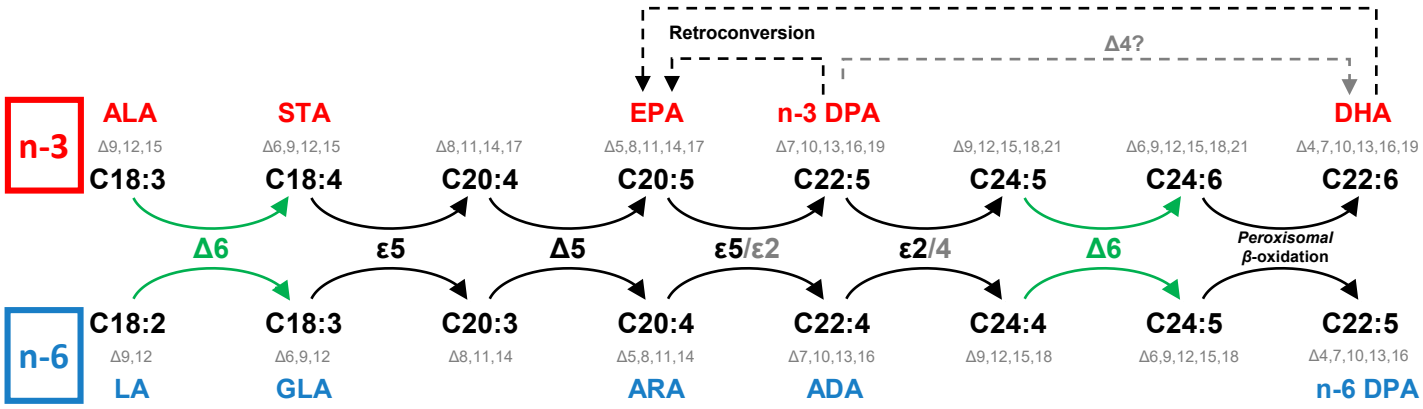
EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; n-3 DPA, docosapentaenoic acid; LCPUFA, long-chain polyunsaturated fatty acid(s); PBMC, peripheral blood mononuclear cells; RBC, red blood cells.

Figure 1 –Bioconversion pathways of n-3 and n-6 polyunsaturated fatty acid families

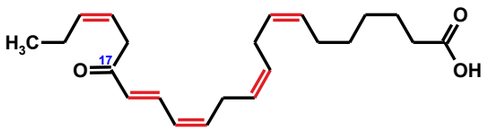
Δ: desaturase, ε: elongase, ALA: α-linolenic acid, ADA: adrenic acid, ARA: arachidonic acid, EPA: eicosapentaenoic acid, GLA: γ-linolenic acid, DHA: docosahexaenoic acid, n-3 DPA: n-3 docosapentaenoic acid, LA: linoleic acid, STA: stearidonic acid.

Figure 2 – Biosynthesis pathway of n-3 docosapentaenoic acid-derived metabolites

COX: cyclooxygenase, DPA: docosapentaenoic acid, EFOX: oxo derivative, isoP: isoprostane, LOX: lipoxygenase, HDPA: hydroxy-DPA, H(p)-DPA: hydro(peroxy)-DPA

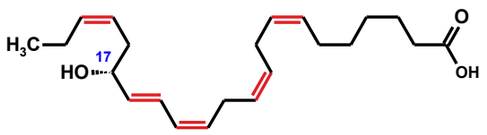

Retroconversion
Δ4?
n-3
ALA
Δ9,12,15
C18:3
STA
Δ6,9,12,15
C18:4
Δ8,11,14,17
C20:4
EPA
Δ5,8,11,14,17
C20:5
n-3 DPA
Δ7,10,13,16,19
C22:5
Δ9,12,15,18,21
C24:5
Δ6,9,12,15,18,21
C24:6
DHA
Δ4,7,10,13,16,19
C22:6
Δ6
ε5
Δ5
ε5/ε2
ε2/4
Δ6
Peroxisomal β-oxidation
n-6
C18:2
Δ9,12
LA
C18:3
Δ6,9,12
GLA
C20:3
Δ8,11,14
C20:4
Δ5,8,11,14
ARA
C22:4
Δ7,10,13,16
ADA
C24:4
Δ9,12,15,18
C24:5
Δ6,9,12,15,18
C22:5
Δ4,7,10,13,16,19
n-6 DPA

EFOX

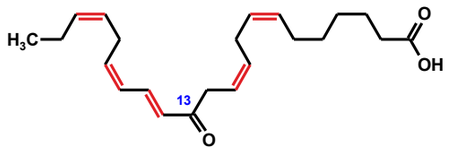


17-oxo-DPA (17-EFOX-D5)

Deshydrogenase

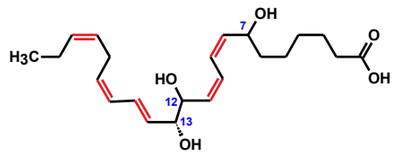


17S-HDPA

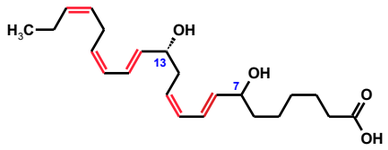


13-oxo-DPA (13-EFOX-D5)

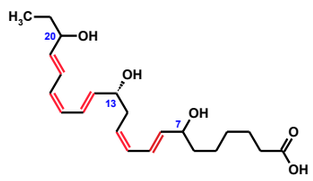
Resolvins (13-series)



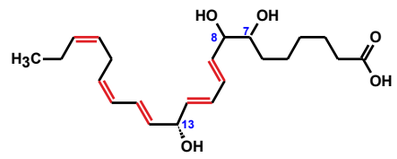
7,12,13R-triHDPA (RvT2)



7,13R-diHDPA (RvT4)



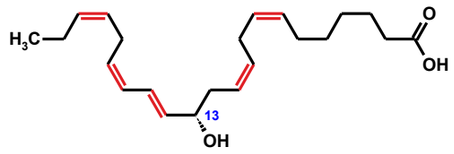
7,13R,20-triHDPA (RvT1)



7,8,13R-triHDPA (RvT3)

5-nitrosogluthathione

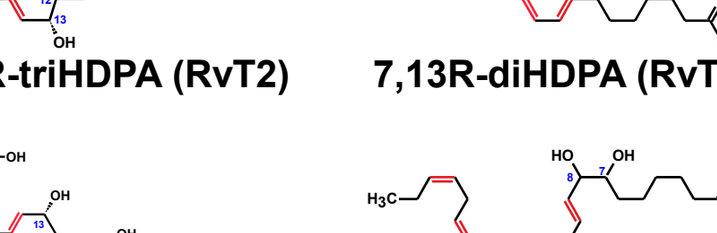
Deshydrogenase



13R-HDPA

COX-2

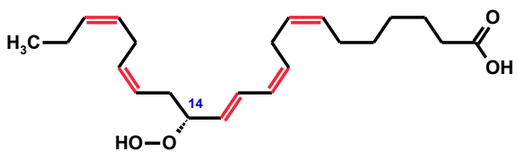
COX-2 + aspirine



All cis-7,10,13,16,19-docosapentaenoic acid (n-3 DPA)

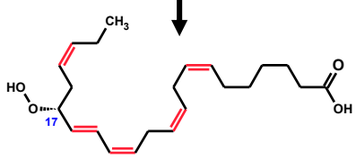
O_2

12-LOX



14S-H(p)-DPA

15-LOX

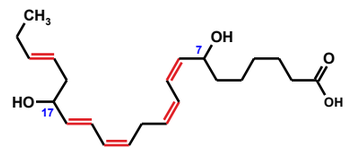


17S-H(p)-DPA

H_2O

5-LOX

12-LOX



7,17-diHDPA

10,17S-diHDPA

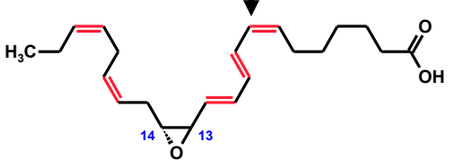
15-LOX

11-HDPA

17-HDPA

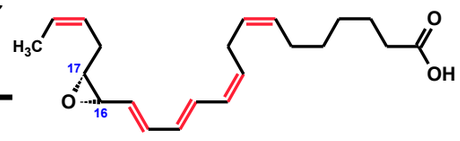
8,14-diHDPA

H_2O

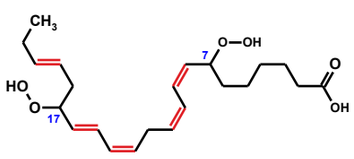


13,14S-epoxy-DPA

Non-enzymatic hydrolysis

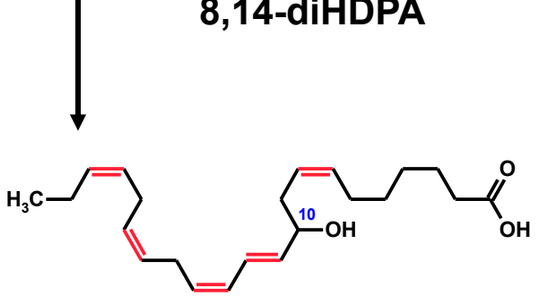


16S,17S-epoxy-DPA



7,17S-diH(p)-DPA

5-LOX



10-HDPA

11-HDPA

13-HDPA

14-HDPA

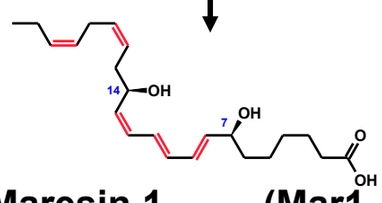
16-HDPA

17-HDPA

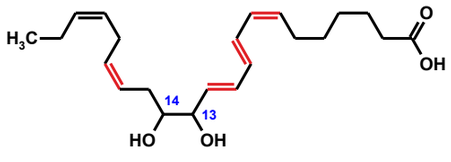
20-HDPA

16,20-diHDPA

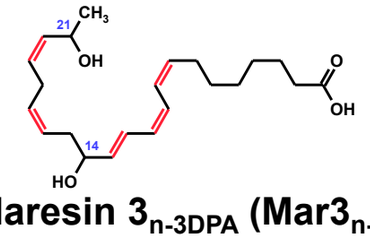
Epoxyde hydrolase



Maresin $1_{n\text{-}3DPA}$ ($Mar1_{n\text{-}3DPA}$)



Maresin $2_{n\text{-}3DPA}$ ($Mar2_{n\text{-}3DPA}$)

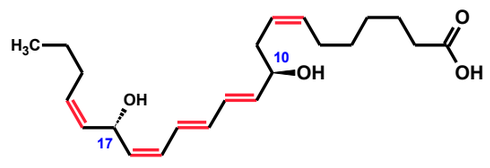


Maresin $3_{n\text{-}3DPA}$ ($Mar3_{n\text{-}3DPA}$)

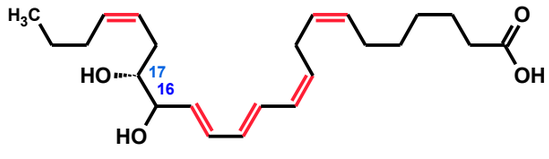
10,17S-diHDPA

16,17S-diH-DPA

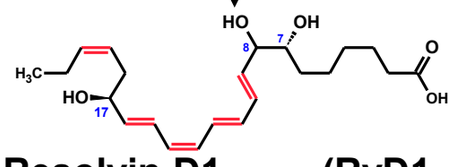
Epoxyde hydrolase



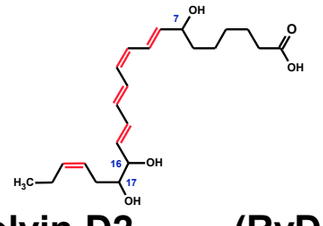
Protectin $1_{n\text{-}3DPA}$ ($PD1_{n\text{-}3DPA}$)



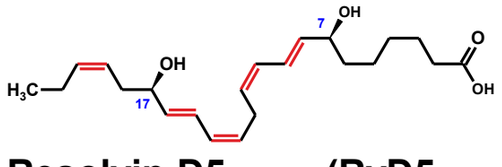
Protectin $2_{n\text{-}3DPA}$ ($PD2_{n\text{-}3DPA}$)



Resolvin $D1_{n\text{-}3DPA}$ ($RvD1_{n\text{-}3DPA}$)

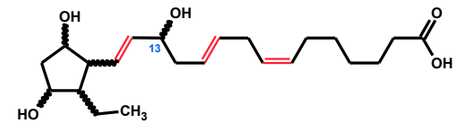


Resolvin $D2_{n\text{-}3DPA}$ ($RvD2_{n\text{-}3DPA}$)

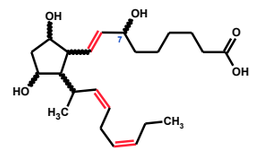


Resolvin $D5_{n\text{-}3DPA}$ ($RvD5_{n\text{-}3DPA}$)

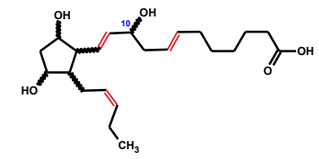
Isoprostanes



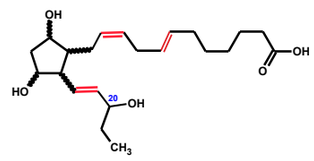
13-F3-IsoP-DPA



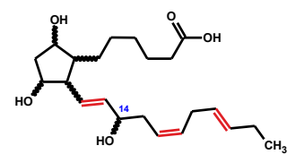
7-F3-IsoP-DPA



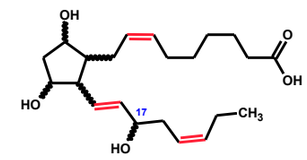
10-F3-IsoP-DPA



20-F3-IsoP-DPA



14-F3-IsoP-DPA



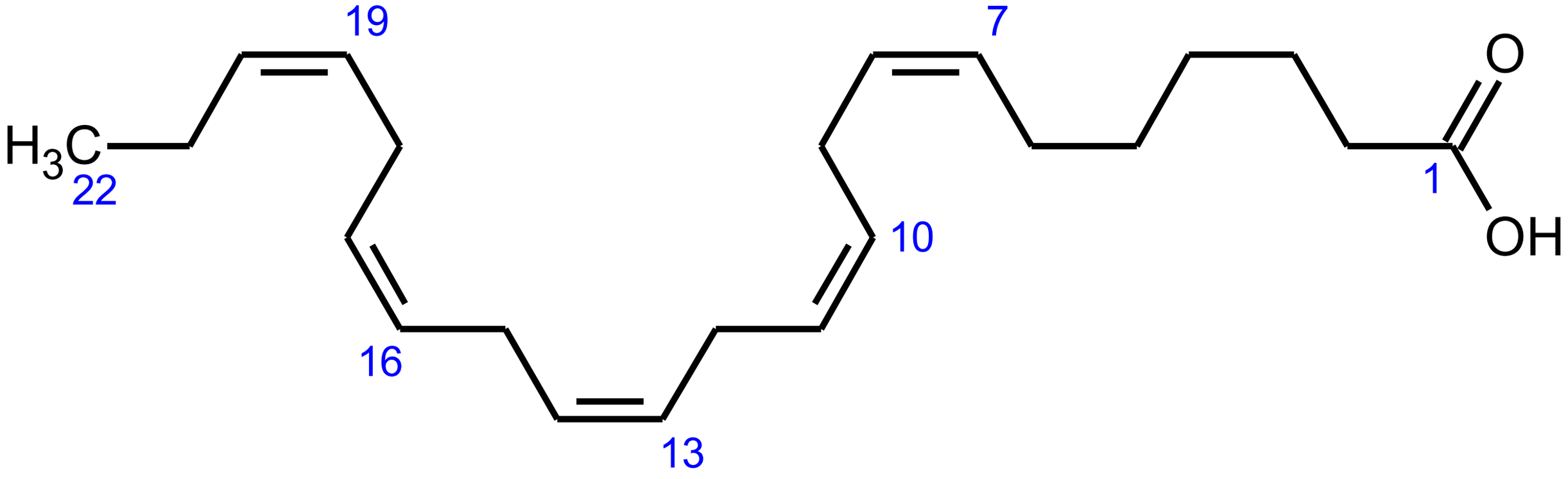
17-F3-IsoP-DPA

Maresins

Protectins

Resolvins

Hydroxy-DPA



n-3 docosapentaenoic acid