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CORRECTION

Correction: Are we what we eat? Changes to the feed fatty acid composition of farmed salmon and its effects through the food chain (doi: 10.1242/jeb.161521)

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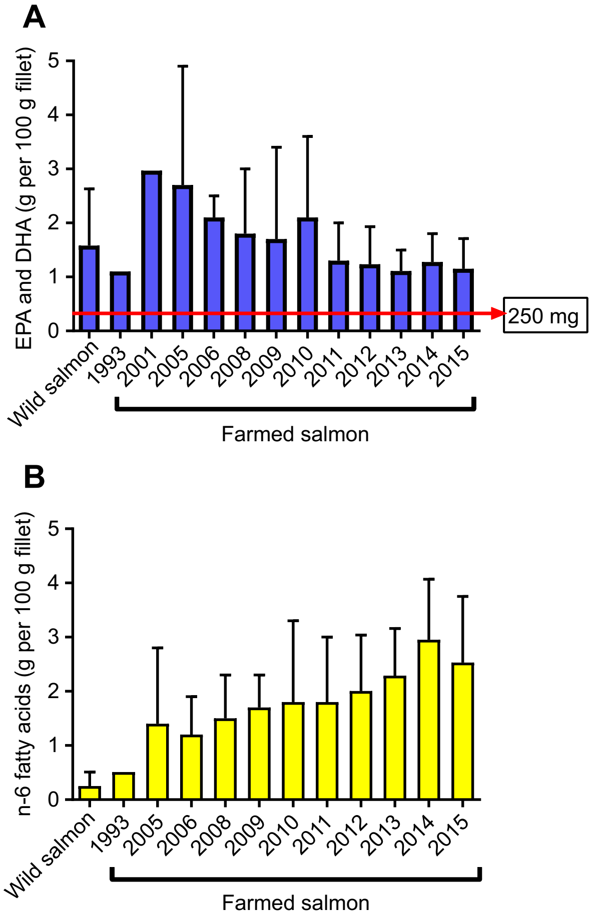
The *y*-axis labels in Fig. 3 should have the units ‘g per 100 g fillet’. The corrected figure appears below.



The author apologises to the readers for any inconvenience this may have caused.

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REVIEW

Are we what we eat? Changes to the feed fatty acid composition of farmed salmon and its effects through the food chain

Nini H. Sissener*

ABSTRACT

'Are we what we eat?' Yes and no. Although dietary fat affects body fat, there are many modifying mechanisms. In Atlantic salmon, there is a high level of retention of the n-3 fatty acid (FA) docosahexaenoic acid (DHA, 22:6n-3) relative to the dietary content, whereas saturated FAs never seem to increase above a specified level, which is probably an adaptation to low and fluctuating body temperature. Net production of eicosapentaenoic acid (EPA, 20:5n-3) and especially DHA occurs in salmon when dietary levels are low; however, this synthesis is not sufficient to maintain EPA and DHA at similar tissue levels to those of a traditional fish oil-fed farmed salmon. The commercial diets of farmed salmon have changed over the past 15 years towards a more plant-based diet owing to the limited availability of the marine ingredients fish meal and fish oil, resulting in decreased EPA and DHA and increased n-6 FAs. Salmon is part of the human diet, leading to the question 'Are we what the salmon eats?' Dietary intervention studies using salmon have shown positive effects on FA profiles and health biomarkers in humans; however, most of these studies used salmon that were fed high levels of marine ingredients. Only a few human intervention studies and mouse trials have explored the effects of the changing feed composition of farmed salmon. In conclusion, when evaluating feed ingredients for farmed fish, effects throughout the food chain on fish health, fillet composition and human health need to be considered.

KEY WORDS: Atlantic salmon, Farmed fish, Lipid, EPA, DHA, Fish feed

Introduction

What determines the body composition of an animal? Is it simply a reflection of their diet, as the popular saying 'we are what we eat' suggests? This is clearly not the case for all nutrients. The amino acid composition of an organism remains fairly constant regardless of the composition of their diet because amino acids are incorporated into proteins, and the amino acid sequence of proteins is determined in the genome. A deficiency of an essential amino acid will, thus, not result in a lower level of this amino acid in proteins, but simply lead to a reduced rate of protein synthesis. The level of free amino acids in animal tissues is limited: these free amino acids are used for energy or lipid synthesis if levels are increasing or appear imbalanced. As most energy reserves are stored in the body as lipids, and the dietary lipids are generally reflected in the body fatty acid (FA) composition. However, this is a gross oversimplification; although dietary FAs do influence overall body composition, there are also many modifying mechanisms.

Firstly, this is reflected in the great variation in FA composition between different tissues, and the even greater variation between different lipid classes within those tissues, all serving different biological functions. Secondly, the fate of individual FAs can vary greatly with regard to the extent to which they are oxidized for energy production, incorporated in triacylglycerols (TAGs) for storage or incorporated in different structural phospholipids (polar lipids). Docosahexaenoic acid (DHA, 22:6n-3), eicosapentaenoic acid (EPA, 20:5n-3) and arachidonic acid (ARA, 20:4n-6) constitute the major phospholipid component of cell membranes, and perform a variety of important physiological functions. In fish, they play key roles in ontogenesis, the development and functionality of the brain, vision and nervous system, growth, survival, pigmentation, and resistance to stress and disease (for a review see Sargent et al., 2002). Hence, an altered membrane content of and the balance between these FAs can have a large impact on fish health and development.

Over the past 15 years, the composition of the diet of farmed Atlantic salmon (*Salmo salar* Linnaeus 1758) has undergone major changes. Owing to the limited availability of marine ingredients such as fish meal and fish oil, high levels of vegetable oils are used, leading to drastic changes in the feed FA composition. This Review focusses on how this affects the FA composition of salmon tissues, and how these changes in turn affect humans that eat the salmon, following the FAs through the food chain. The health benefits for humans of eating seafood, and especially oily fish, are widely recognized. However, these may change as the dietary FA composition of salmon and, hence, the composition of salmon changes, which is an important point to consider when selecting feed ingredients for salmon. Given that Norway is the leading producer of farmed Atlantic salmon globally and that data on the changing FA composition of commercial feeds discussed in this Review were provided by national Norwegian surveillance programmes, the main focus of this Review will be on Norwegian salmon farming.

Feed composition for farmed Atlantic salmon

Global stagnation, or even decline, in reduction fisheries (Tacon et al., 2011), combined with a rapidly increasing aquaculture production, means that raw materials other than fish meal and fish oil are needed in the feed for farmed Atlantic salmon. In 1990, 90% of the ingredients in feed used for Norwegian salmon production were of marine origin (fish meal and fish oil); however, by 2013, this had decreased to 30% (Ytrestøyl et al., 2015). Reducing the amount of fish oil in the feed has a number of consequences, including a reduced content of the long chain n-3 FAs EPA and DHA. The fish oil needs to be replaced by other lipid sources such as vegetable oils, resulting in large changes in the FA composition of the feed. Large changes have also occurred in the macronutrient composition of the feed: 24.0% of the feed ingredients were oil in 1990 (100% fish oil); however, by 2013, this had increased to

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30.1% (two-thirds rapeseed oil and one-third fish oil) at the expense of decreased protein ingredients (Ytrestøyl et al., 2015). However, the lipid content of the feed is slightly higher than this because in addition to the oils, which are 100% lipid, there is also some lipid present in the protein ingredients used. In terms of energy% (E%), a typical composition of commercial salmon feeds in the grow-out phase in seawater would be ∼61 E% lipid and ∼32 E% protein, whereas for juvenile fish the protein/lipid ratio would be higher. As a carnivorous fish, Atlantic salmon does not utilize carbohydrates very well, and glucose plays a subordinate role to lipids and proteins in energy metabolism (Hemre et al., 2002).

Rapeseed oil (also known as canola oil) is currently the only vegetable oil used in Norwegian salmon feeds (Ytrestøyl et al., 2015). Rapeseed oil is produced in considerable quantities, is relatively low in n-6 FAs, very low in saturated FAs (SFA) and high in phytosterols compared with most other vegetable oils. Rapeseed oil has been tested extensively in diets for salmon (Bell et al., 2001; Jordal et al., 2005; Turchini et al., 2009). Although not used commercially at present, extensive research has also been carried out on the use of other vegetable oils, especially palm, soybean and linseed (flaxseed) oils, as well as oil blends (Turchini et al., 2009). Palm oil and soybean oil are the leading vegetable oils in terms of global production volume, and linseed oil has attracted interest owing to its high content of α-linolenic acid (ALA, 18:3n-3), constituting up to 57% of the total FAs (Table 1). Although used in experimental feeding trials, linseed oil oxidizes rapidly and, therefore, is not attractive for use in commercial feeds (Grethe Rosenlund, personal communication). Despite some species and seasonal variations, the FA composition of fish oils includes considerable amounts of both SFA (mainly 16:0), monounsaturated FAs (MUFA, 18:1n-9, 20:1n-9 and 22:1n-11, with the two latter being particularly high in oily fish species from the Northern Hemisphere) and n-3 FAs [primarily long-chain n-3 FAs such as EPA, docosapentaenoic acid (DPA, 22:5n-3) and DHA] (Table 1); however, the content of n-6 FAs is very low. By contrast, vegetable oils are often dominated by one or a few FAs (e.g. high 18:1n-9 in rapeseed and olive oil, high 18:2n-6 in sunflower, maize and soybean oil, high 16:0 and 18:1n-9 in palm oil and high 18:3n-3 in linseed oil). Despite the large variability in FA composition in vegetable oils, they all lack long-chain n-3 PUFA EPA and DHA, and have a higher n-6 FA content compared with fish oils.

Many studies involving Atlantic salmon have been conducted to elucidate the effects of vegetable oil-based diets on fish health and growth performance (reviewed in Turchini et al., 2009; Waagbø, 2006). In this Review, I will mainly focus on how changing dietary FA composition affects tissue FAs.

The effect of dietary fat on body fat

Tissue and lipid class composition

The common notion that the FA composition of fish reflects that of their diet is a simplification because some FAs are found in higher proportions in the fish than in their diets; the opposite is true for other FAs, and this may vary with the dietary inclusion level of the FA in question (Rosenlund et al., 2001; Bell et al., 2001). The possible metabolic fates of FAs within cells are diverse, including β-oxidation, elongation and desaturation, incorporation in cellular lipids or secretion of lipids through lipoprotein production. In an *in vitro* study involving Atlantic salmon hepatocytes, specificity regarding individual FAs was found both in the uptake across cell membranes, incorporation into different phospholipids and β-oxidation (Stubhaug et al., 2005). Different FAs may differ in their priority as an energy substrate, or be selectively retained owing to their functional properties.

The FA composition of neutral lipids (NLs; mainly TAGs) is affected by diet to a greater extent than that of polar lipids (PLs; mainly phospholipids) (Brodtkorb et al., 1997; Olsen and Henderson, 1997; Henderson, 1996). Thus, some tissue differences in the responsiveness to the dietary FA profile could be attributed to the distribution of NL versus PL in the tissues. However, Atlantic salmon is an oily fish species that stores high levels of NLs (TAGs) in muscle

Table 1. Fatty acid composition (weight %) of a range of oils relevant for use in the diets of farmed Atlantic salmon

	Capelin oil	Sardine oil	Anchovy oil	Krill oil	Soybean oil	Olive oil	Sunflower oil	Linseed oil	Palm oil	Coconut oil	Maize oil	Rapeseed oil
12:0	–	–	–	–	–	–	–	–	–	48	–	–
14:0	6.3	7.2	7.8	16.3	–	–	0.1	0.1	1.1	24	–	0.1
16:0	11.0	16.2	18.2	19.0	10.9	11.8	6.3	5.3	40.0	9	10.3	4.7
18:0	0.9	2.9	4.2	1.4	3.9	2.5	4.9	3.2	4.1	3	1.8	1.6
Sum SFA	18.9	27.3	30.2	38.6	15.6	14.7	12.3	8.6	45.2	89	12.5	7.5
18:1n-7	1.9	3.1	–	7.8	1.3	2.2	0.7	0.7	–	–	0.6	3.0
18:1n-9 (OA)	6.7	9.3	16.0	15.8	21.9	71.4	23.0	17.1	41.1	9	31.1	56.7
20:1n-9	15.9	1.5	1.0	1.4	–	0.3	0.2	–	–	–	0.2	1.7
22:1n-9	2.3	0.2	0.3	0.6	–	–	–	–	–	–	–	0.8
22:1n-11	20.2	0.9	1.6	0.3	–	–	–	–	–	–	–	–
Sum MUFA	56.5	25.4	29.6	38.1	23.3	75.0	23.9	17.8	41.1	–	32.0	62.2
18:2n-6 (LA)	1.3	1.1	2.8	1.6	54.3	9.5	62.5	14.3	10.8	2	54.1	19.5
20:4n-6 (ARA)	–	0.8	0.1	0.1	–	–	–	–	–	–	–	–
Sum n-6	1.3	1.9	2.9	2.1	54.3	9.5	62.5	14.3	10.8	–	54.1	19.6
18:3n-3 (ALA)	0.7	0.6	1.8	0.8	6.5	0.7	0.5	57.0	0.3	–	1.3	9.4
18:4n-3	4.8	3.2	2.3	3.6	–	–	–	–	–	–	–	–
20:5n-3 (EPA)	7.5	18.4	14.8	6.4	–	–	–	–	–	–	–	–
22:5n-3 (DPA)	0.6	2.2	1.8	0.2	–	–	–	–	–	–	–	–
22:6n-3 (DHA)	5.7	12.3	10.9	2.3	–	–	–	–	–	–	–	–
Sum n-3	19.8	37.7	29.3	14.6	6.5	0.7	0.5	57.0	0.3	–	1.3	9.4
n-6/n-3	0.07	0.05	0.10	0.14	8.35	13.6	125	0.25	36	–	41.6	2.1

Three examples of marine oils are shown in the first three columns of the table, followed by krill oil and different vegetable oils. The most important individual fatty acids are included, as well as the sum of saturated (SFA), monounsaturated (MUFA), n-6 and n-3 fatty acids, and finally the n-6/n-3 ratio. Adapted from Sissener et al. (2016a). ARA, arachidonic acid; ALA, α-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; OA, oleic acid.

tissue; the effect of diet on muscle tissue would be quite different for a lean fish species such as cod, where muscle lipids are mainly polar (Lie et al., 1986). Muscle lipid content and also the amount of NLs relative to PLs increases as the salmon grows. Torstensen and coworkers (2004b) reported a muscle lipid class composition of 69% NLs in ∼140 g Atlantic salmon, increasing to 76–82% NLs in ∼1500 g fish. This NL level appears to be maintained given that 78–83% NL was found in the white muscle tissue of harvest size fish of ∼4500 g (Nanton et al., 2007).

Fig. 1 shows how the total n-6 FAs, MUFA and SFA in muscle, liver PL, heart PL and red blood cells are influenced by diet. The PL and NL content of the liver and heart were analysed separately, unlike the red blood cells, which contain primarily PLs. The total lipid content (PL+NL) of muscle tissue was analysed because this is the part of the fish that is eaten and, hence, the full FA profile has implications for human nutrition. For total n-6 FAs (Fig. 1A), dietary content is reflected in all the tissues, but to the greatest extent in muscle, followed by liver PLs, heart PLs and finally red blood cells. For total MUFAs (Fig. 1B), there is a larger difference between the tissues, with the MUFA content of muscle reflecting the diet, whereas in other tissues the MUFA content appears to be more regulated and lower than the dietary content. The total SFA content (Fig. 1C) in the tissues other than muscle are quite stable, although in this instance are at a higher level than that provided in most of the experimental diets. In Atlantic salmon-fed diets with low and deficient levels of n-3 long-chain PUFA, the FA composition of muscle and skin most resembled that of the dietary composition, followed by the intestine and then the heart and liver, whereas the FA composition of the brain appeared very conserved and was the least affected by diet (Bou et al., 2017a). Curiously, despite the high tissue abundance of EPA in fish, ARA still appears to be the preferred precursor for eicosanoids, which are signalling molecules with diverse roles in fish reproduction, the stress response and the immune response (Bell and Sargent, 2003). Among the phospholipid classes, phosphatidylinositol has high levels of ARA and more ARA than EPA in a range of Atlantic salmon tissues, including liver, heart, gills, spleen, leucocytes and red blood cells (Waagbø et al., 1993; Bell et al., 1991a,b), leading to the unconfirmed theory that this particular lipid class is the main ARA source for eicosanoid production in fish (Bell and Sargent, 2003). Furthermore, among the phospholipid classes, phosphatidylinositol had the lowest levels of DHA and phosphatidylethanolamine had the highest (Waagbø et al., 1993). This was also the only lipid class in muscle in which DHA was not significantly reduced in salmon that were fed diets deficient in all n-3 FAs (Thomassen et al., 2017). These studies clearly show that the influence of dietary lipids on fish lipids depends on tissue-, lipid class- and FA-specific modifications.

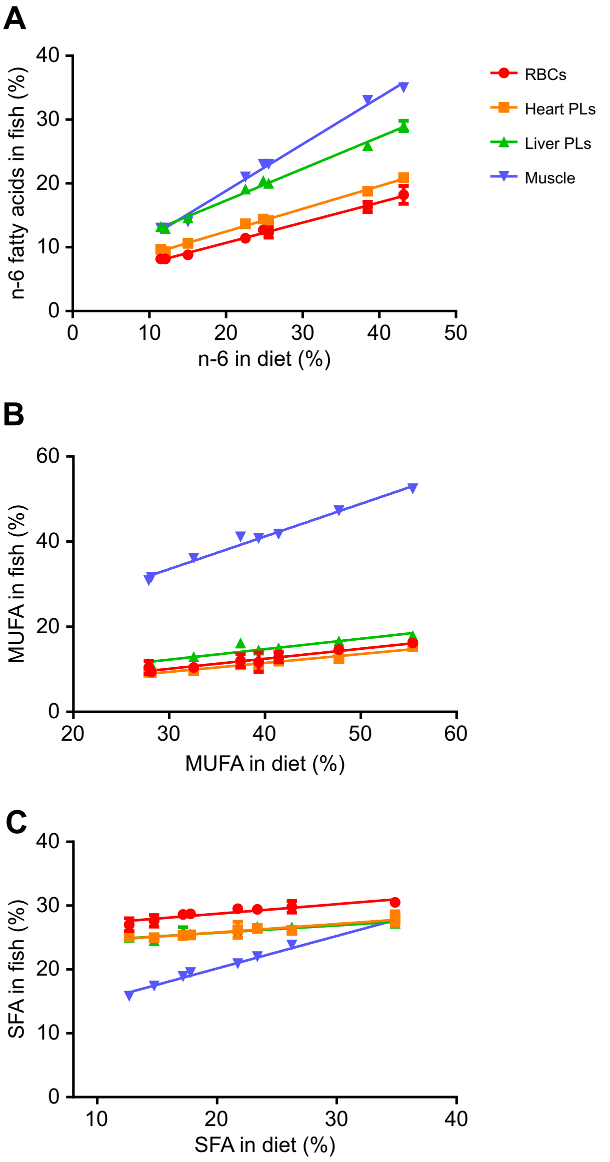

Fig. 1. Influence of salmon diet on the fatty acid composition in tissues. The amount of (A) total n-6 fatty acids, (B) monounsaturated fatty acids (MUFAs) and (C) saturated fatty acids (SFAs) in feeds versus different tissues of Atlantic salmon. All values are given as a percentage of the total fatty acids in red blood cells (RBCs), heart polar lipids (PLs), liver PLs and muscle (total muscle fatty acids). The values shown are means±s.d. of different diet groups (based on analysis of pooled samples of six individual fish from each of three fish tanks per diet group=18 fish per diet group; however, most of the error bars are smaller than the size of the symbols and, thus, cannot always be clearly seen). The lines in the figure represent significant linear regressions: (A) R^2=0.995, P<0.0001 for RBCs, R^2=0.996, P<0.0001 for heart PLs, R^2=0.994, P<0.0001 for liver PLs and R^2=0.994, P<0.0001 for muscle; (B) R^2=0.965, P<0.0001 for RBCs, R^2=0.960, P<0.0001 for heart PLs, R^2=0.872, P=0.0007 for liver PLs and R^2=0.985, P<0.0001 for muscle; (C) R^2=0.872, P=0.0007 for RBCs, R^2=0.930, P=0.0001 for heart PLs, R^2=0.822, P=0.0019 for liver PLs and R^2=0.989, P<0.0001 for muscle. See Sissener et al. (2017) for detailed information on the different diet groups and fish rearing conditions.

n-3 long-chain PUFA: EPA and DHA

As in all vertebrates, the n-3 and n-6 FAs are essential in fish because they lack the ability to introduce double bonds in the n-3 and n-6 positions of FAs. Although the requirements vary greatly between species, in general, marine fish have a barely functional enzymatic pathway for converting ALA (18:3n-3) and linoleic acid (LA, 18:2n-6) into EPA, DHA and ARA, meaning that they require preformed EPA, DHA and ARA, whereas freshwater fish only require the precursors (Vagner and Santigosa, 2011). Salmon is an anadromous fish species: salmon begin their life in freshwater and then migrate to the sea for most of their growth period before returning to freshwater to breed. However, their desaturase profile appears to be that of a freshwater fish (Owen et al., 1975; Bell et al., 1997), although desaturase activity is decreased at the seawater stage (Bell et al., 1997; Zheng et al., 2005).

There is increased relative retention of EPA and DHA in fish when the fish oil in feed is replaced with vegetable oil; however, this is not sufficient to maintain the fillet levels of EPA and DHA found in fish oil-fed fish (Bell et al., 2001, 2002; Tocher et al., 1997, 2002). Replacing 100% of the fish oil in feed with vegetable oil, while maintaining fish meal as the protein source, reduces fillet EPA+DHA by ~65% (Bell and Waagbø, 2008). Several studies have shown the selective deposition of much higher levels of DHA than of EPA (Rosenlund et al., 2001; Bell et al., 2001; Sanden et al., 2011). DHA in all tissues and EPA in the liver appear to be relatively spared from β-oxidation compared with other FAs (Torstensen et al., 2004a). This difference between EPA and DHA could reflect their respective biological roles, and the extent to which salmon has a specific requirement for EPA has been questioned (Emery et al., 2016; Bou et al., 2017a). Dietary DHA seems to be selectively retained regardless of the feed concentration, whereas EPA is only retained if the dietary concentration is low (Bell and Waagbø, 2008).

When dietary concentrations of EPA+DHA are low, synthesis of EPA and particularly DHA from shorter chain precursors also occurs (Fig. 2), which results in FA production values of >100% [i.e. the increase in the FA content of the whole fish during the trial (final content–initial content) as a % of the amount of FA fed to the fish during the trial] (Sissener et al., 2017; Rosenlund et al., 2016; Glencross et al., 2014; Bou et al., 2017a). FA production values of DHA of up to 200% have been reported in salmon receiving low dietary levels, meaning that twice as much DHA accumulated in the fish as that provided in the feed, clearly showing net *in vivo* production of this FA (Rosenlund et al., 2016). Increased production of DHA from 18:3n-3 was also confirmed in hepatocytes from salmon fed low dietary levels of EPA+DHA: when radiolabelled 18:3n-3 was added to the hepatocytes, three times more radioactivity was recovered as DHA in salmon fed 0.5% EPA+DHA (of the feed) compared with salmon fed 2.3% EPA+DHA (Sanden et al., 2016). Both product inhibition and substrate availability seem to affect the rate of elongation and desaturation of ALA to the longer chain n-3 FAs in Atlantic salmon (Tocher et al., 2003; Tocher et al., 1997). Despite this *in vivo* production, preformed long-chain n-3 PUFA are required for optimal growth, fish health and tissue integrity during long-term feeding in salmon (Rosenlund et al., 2016; Sissener et al., 2016b; Bou et al., 2017a). Although survival was high (>99%) when low EPA+DHA (≤1% of the feed) were used in land-based tanks with controlled and optimal conditions (Rosenlund et al., 2016), high levels of fish mortality occurred when the same levels were fed to fish in open net pens with fluctuating environmental conditions and stressful handling of the fish (Bou et al., 2017b). Such a reduction in fish robustness and survival means that it is highly unlikely that these low levels would be implemented in commercial culture; hence it is likely that feed with a minimum level of >1% EPA+DHA will be maintained.

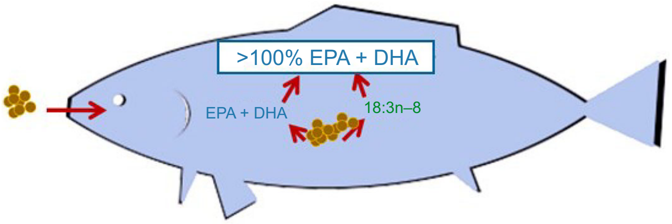

Fig. 2. Consequences in Atlantic salmon of reduced dietary levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Schematic drawing to show how the combination of selective retention of dietary EPA and DHA as well as *in vivo* production of these fatty acids from dietary 18:3n-3 can lead to fatty acid production values (often referred to as 'retention' within fish nutrition despite constituting a mix of retention and production) of EPA+DHA of more than 100%.

Salmon feed comprising 1% EPA+DHA is equivalent to ~2.4 E%; the European Food Safety Authority (EFSA) recommendation of 250 mg of EPA+DHA per day for healthy adult humans (EFSA, 2009) is equivalent to ~0.11 E% if we assume a daily energy intake of 2000 kcal. The International Society for the Study of Fatty Acids and Lipids (ISSFAL) recommends a higher daily intake than the EFSA of 500 mg of EPA+DHA for humans (www.issfal.org/statement-3); nevertheless, the EPA+DHA requirement of salmon is at least 10-fold higher than that of humans. This difference is also reflected in the content of these FAs in red blood cells of salmon and humans. Omega-3 index [EPA+DHA as a percentage of the total FA in red blood cells (Harris, 2007)] values of healthy human populations with highly varying dietary habits have been reported in the range of 4–12 (Harris, 2010; von Schacky, 2014), whereas the omega-3 index of salmon fed sufficient EPA+DHA was 43–47 (Sissener et al., 2016b). The omega-3 index appeared to level off as the requirement level was met, and the range of values from 43 to 47 reflected different rearing temperatures, with a higher omega-3 index recorded among fish kept at 6°C compared with those at 12°C (Sissener et al., 2016b), reflecting the need to maintain membrane fluidity at low temperatures (Cossins and Macdonald, 1989).

The tissue is the issue; interaction with n-6 fatty acids

It is well known that n-3 and n-6 FAs share the same series of enzymes for elongation and desaturation, and that an excess of one causes decreased conversion of the other (Schmitz and Ecker, 2008). In the freshwater fish species Eurasian perch (*Perca fluviatilis* Linnaeus 1758), an overabundance of LA (18:2n-6) in safflower oil-fed fish caused apparent deficiency of ALA (18:3n-3) (Blanchard et al., 2008). However, although conversion of LA is strongly suppressed by dietary ALA, 10-fold higher levels are needed for a similar suppression of ALA conversion by LA in rats (reviewed by Holman, 1998) owing to the affinity of enzymes for different FA families. This appears to be similar in Atlantic salmon given that an LA/ALA ratio of 8.6 (overall n-6/n-3 ratio of 4.1) did not negatively affect the retention of DHA when compared with an LA/ALA ratio of 1.1 (Sissener et al., 2017). This was a rather 'extreme' experimental diet; current commercial salmon diets in Norway have an overall n-6/n-3 ratio of ~0.9 (Sanden et al., 2015). For comparison, the overall n-6/n-3 ratio in a human 'Western' diet can be as high as 15–20 (Simopoulos, 2002).

However, although increasing dietary LA does not appear to have a negative effect on DHA retention, interactions between n-3 and n-6 FA families occur on several levels in the organism. High dietary n-6 FAs in the form of LA leads to arachidonic acid (ARA, 20:4n-6), displacing DHA and particularly EPA from cell membranes, both in humans (Hibbeln et al., 2006) and in salmon, even when the dietary supply of ARA, EPA and DHA remains constant (N.H.S., P. Ajuro, R. Waagbø, G. Rosenlund, I. Stubhaug and M. Sanden, unpublished data). Hence, tissue levels of long-chain FAs not only depend on the dietary content of these FAs themselves, or of their precursors, but also on the overall dietary balance between the different n-3 and n-6 FAs.

Saturated fatty acids

When looking at how dietary FAs affect the fillet composition of Atlantic salmon, SFAs are in a special position. It appears that the content of SFA in salmon muscle can never increase above a specified physiological level. This phenomenon is shown in Fig. 1C, where a dietary SFA content of 35% of the FAs only results in a muscle content of 27%. Similar findings have also been reported in Atlantic salmon fed high inclusion levels of palm oil

(Bell et al., 2002; Torstensen et al., 2000). Reduced levels of dietary SFA, compared with the 22–28% generally provided by a fish oil-based diet, will lead to reduced levels of SFA in muscles (Torstensen et al., 2000; Bell et al., 2002; Sissener et al., 2017). However, Fig. 1C also shows the highly selective retention of SFA in PLs, reflecting the structural role of 16:0 in membrane phospholipids where they are often located in the sn-1 position (Sargent et al., 2002). Compared with salmon, humans accumulate much higher levels of SFA in muscle (Andersson et al., 2002). One species difference here is probably the contribution of *de novo* lipogenesis to adipose tissue fat stores, which in humans operates significantly when carbohydrate intake exceeds energy requirements (Tamura and Shimomura, 2005). By contrast, in salmon fed >60 E% as fat, *de novo* lipogenesis is probably limited. However, the main explanation for the higher level of SFA in humans compared with salmon is more likely to be related to their different body temperatures: human muscle tissues remain at a fairly constant 37°C, compared with the ectothermic salmon, which can experience body temperatures close to 0°C, as well as rapid temperature fluctuations (Koskela et al., 1997; Bendiksen et al., 2003). Hence, the lipid stores cannot be of such a nature that they would solidify at low temperatures: salmon seemingly has mechanisms to keep the level of SFA below a physiologically specified level. Although there are exceptions and species variations, proportionally lower levels of SFA in colder water fish compared with warm water fish have been reported (Huynh and Kitts, 2009).

Changes in commercially farmed Norwegian salmon

Changes in feed lipid level and FA composition are not the only aspects that have changed as salmon has been domesticated. In addition to unlimited supplies of energy-dense feed that requires little effort to 'catch', there has also been genetic selection of these fish, starting in the 1970s with brood stock from many different Norwegian salmon rivers. Together with improvements in diets and production regimes, genetic selection has contributed to halving the production time for farmed salmon (now 8 months in freshwater and 12 months in seawater to reach a harvest weight of approximately 5 kg). Thodesen and coworkers (1999) found that after five generations of selection primarily for growth in Atlantic salmon, the growth rate had improved by 113%, partially owing to a 20% increase in the nutrient retention rate (FCR), and partially owing to a 40% increase in feed intake. Even though salmon have high fecundity and a generation time of only 4 years, with respect to selective breeding programmes, aquaculture generally lags far behind those of plant and terrestrial farm animals (Gjedrem et al., 2012). Recently, attempts have been made to select families that express high levels of the gene encoding Δ6-desaturase in the liver (Berge et al., 2015). Despite no differences in fillet EPA and DHA levels in harvest-size fish (~4000 g), EPA and DHA (as a % of total FAs) were higher in the liver of salmon from a high versus a low desaturase family when fed a high vegetable oil diet, and positive effects on fish health were also observed (Berge et al., 2015). This finding indicates the potential of using genetic selection as a strategy to improve synthesis of EPA and DHA in salmon.

Lipid stores in commercially farmed fish gradually increase as the fish grow, from 9% lipid (wet weight) in the whole fish just after seawater transfer (150 g fish), to 22% lipid (15–16% in the fillet) in harvest-size fish of 5 kg (Sissener et al., 2016c). The average muscle lipid content of wild Atlantic salmon is 8% compared with 14% in farmed fish (Lundebye et al., 2017). This is probably partially attributable to the lipid content of the feed used for the farmed fish given that muscle lipid levels are affected by dietary lipid level, but are generally not affected by changing dietary FA composition (Nanton et al., 2007; Bendiksen et al., 2003; Torstensen et al., 2005). Another factor here is probably genetic selection because a selected strain showed both increased growth, condition factor (increased weight relative to length) and body lipid level compared with that of a wild strain reared under the same conditions and fed the same diet (Thodesen et al., 1999). Furthermore, differences in flesh adiposity have been shown between different strains/families of farmed fish when reared under the same conditions and fed the same diets (Bell et al., 2010). Unlike in humans, where excessive TAG accumulation in skeletal muscle is considered unhealthy and is associated with insulin resistance (Kelley et al., 1999), this is not the case in Atlantic salmon because lipid is naturally stored in the muscle to a large extent. In white muscle (which constitutes the majority of muscle tissue in salmon), lipid stores are located in the myosepta (the white stripes in the pink tissue of a salmon fillet) (Zhol et al., 1995), which is a muscle connective tissue that is rich in adipocytes (Nanton et al., 2007). Although the salmon fillet has a pink colour, which arises from the pigment astaxanthin, physiologically this tissue is considered 'white' muscle. Within the muscle cells of white muscle tissue, only very small lipid droplets are located in close association with mitochondria, whereas the red muscle tissue (which is found in small amounts just below the skin) contains intracellular lipid droplets (Nanton et al., 2007), reflecting the important role of aerobic metabolism in red muscle versus anaerobic metabolism in white muscle.

In 2001, the EPA+DHA levels in the tissues of farmed salmon were almost twice as high as those of wild salmon (Fig. 3A, data from NIFES' seafood database: https://sjomatdata.nifes.no/#search/), partly because fish oil was being used as the main lipid source in the feed, providing high levels of dietary EPA+DHA for the farmed salmon, and because of a higher muscle fat content in the farmed fish than in the wild fish. However, from 2001 onwards, fish oils were increasingly replaced by vegetable oils in feeds, and fish meal, which contains some residual lipid with a high EPA and DHA content, was also reduced. Today, the amount of EPA+DHA is slightly lower in farmed salmon than in wild Atlantic salmon. However, farmed salmon still remains a good source of EPA+DHA for human consumption, with a 150-g dinner portion meeting the EFSA recommended intake of 250 mg per day (EFSA, 2009) for 7 days. Over the past 10 years, the levels of n-6 FAs in farmed salmon fillets (Fig. 3B, data from NIFES' seafood database: https://sjomatdata.nifes.no/#search/) have also increased. Current levels are much higher than those in wild salmon, reflecting both the increasing muscle lipid level and the increasing use of rapeseed oil rather than fish oil in commercial feeds.

Although not a major topic of this Review, the changing diet ingredients have also led to changes in the levels of contaminants: in particular, levels of lipid-soluble persistent organic pollutants have decreased in feeds and in salmon fillets over the past 10–15 years (Sissener et al., 2013; Nøstbakken et al., 2015) and are presently lower in farmed salmon than they are in wild Atlantic salmon (Lundebye et al., 2017).

Farmed salmon as human food

There is a large body of evidence supporting dietary n-3 long-chain-PUFA as beneficial to human health (Ruxton et al., 2004; Sinclair et al., 2007; von Schacky, 2014), including a balanced dietary n-6/n-3 ratio (Simopoulos, 2002; Hibbeln et al., 2006). Consequently, fish and seafood consumption, particularly oily fish, is recommended by most governmental food agencies. However, the changing FA composition of farmed fish will affect the health benefits of eating

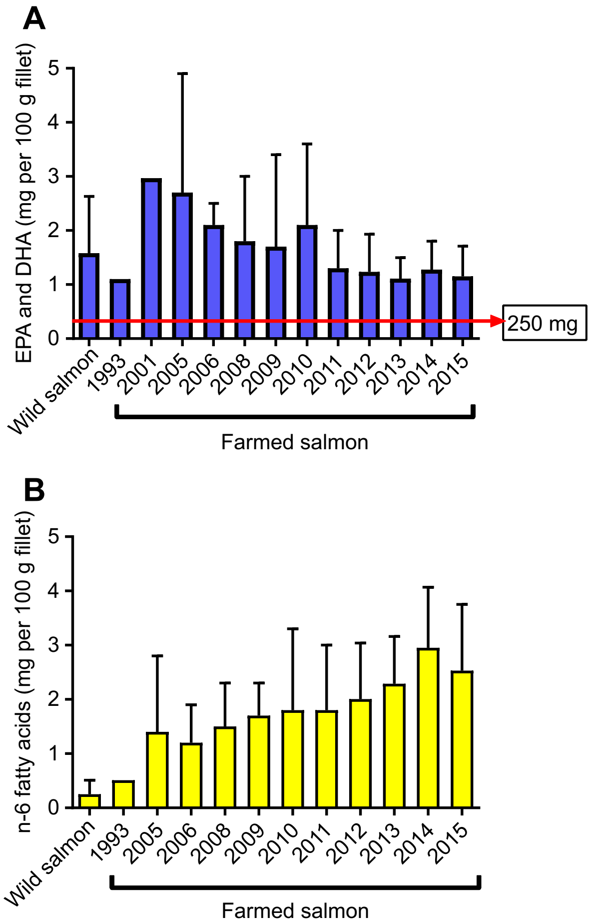

Fig. 3. Amount of eicosapentaenoic acid and docosahexaenoic acid (EPA+DHA) and total n-6 fatty acids in Norwegian Atlantic salmon. The amount of (A) EPA+DHA and (B) total n-6 fatty acids per 100 g fillet in wild and commercially farmed Norwegian Atlantic salmon, including the development over time for the farmed salmon. Values shown are means with error bars showing minimum and maximum values (the absence of an error bar indicates that these values were not available). Data are from the Norwegian surveillance programme, analysed by the Institute of Marine Research (IMR) for the Norwegian Food Safety Authority, and are available in the IMR seafood database https://sjomatdata.nifes.no/#search/, which provides analytical results on nutrients and contaminants in a large range of seafood products.

these foods, which needs to be considered when salmon diets are formulated. Much of the literature supporting the positive health effects of EPA and DHA is based on either observational studies or intervention studies (randomized controlled trials) using fish oil supplements. The number of intervention studies that have been performed with fish are limited, and if we focus specifically on studies using Atlantic salmon, the number is even lower. These studies, which are summarized in Table 2, generally show that positive effects on health biomarkers are achieved by including salmon as part of the diet, and that the FA composition of tissues such as plasma/serum, red blood cells, rectal biopsies, umbilical cord blood and breast milk are affected by the consumption of salmon. However, these intervention studies were generally of short duration and focussed on biomarkers as endpoints. Only two studies (Seierstad et al., 2005; Graff et al., 2016) have focused on the changing feed composition of farmed salmon and how this in turn may affect the health benefits for consumers.

Seierstad and coworkers (2005) performed a study involving farmed Atlantic salmon that were either fed a diet in which 100% of the added oil was fish oil, a diet with 50% fish oil and 50% rapeseed oil (fish oil/rapeseed oil) or a diet with 100% rapeseed oil. In all these diets, fish meal was used as the protein source, therefore, all the feeds contained some EPA and DHA, but with clear differences in EPA and DHA content in the different feeds. Even though the retention of these FAs in the fish increased with decreasing dietary content, the feed differences were largely reflected in the fillet FA composition. These fillets were eaten by heart patients (700 g week^{-1}) participating in a 6-week intervention study, at the end of which, changes were also evident in the serum FA profile of the patients. Arachidonic acid and total n-6 FAs were equally reduced in patients from all groups, serum EPA and total n-3 FAs were significantly increased in the fish oil-group only, whereas the n-6/n-3 ratio was decreased in both the fish oil and the fish oil/rapeseed oil groups. The positive effects on cardiovascular risk markers after the intervention period also depended on which diet the farmed fish were fed. Even though all groups experienced favourable changes in serum cholesterol when compared with the baseline level, serum TAG was only reduced in the fish oil group. Inflammatory markers were most changed in the fish oil group, followed by some changes in the fish oil/rapeseed oil group and no significant changes compared with baseline in the rapeseed oil group (Seierstad et al., 2005). The health improvements that were only seen in the fish oil group were most likely because of the high dietary intake of EPA+DHA, whereas the changes observed in all diet groups may also have been related to displacement of other food items from the diet, and/or other components in the fish such as selenium, vitamin D, anti-oxidants and fish proteins.

Vitamin D is another lipid soluble component affected by the changing dietary lipid sources of farmed salmon; the level of vitamin D in Norwegian commercial salmon feeds decreased significantly between 2003 and 2015 (Sissener et al., 2013; Sanden et al., 2015). Fish, including salmon, do not synthesize vitamin D and are dependent on dietary sources (Lock et al., 2010). Salmonids are resistant to excess dietary vitamin D3 and, hence, will respond to increased dietary levels by accumulating the vitamin in a dose-dependent manner (Horvli et al., 1998; Graff et al., 2002). In a human intervention study (Graff et al., 2016), salmon fillets with a vitamin D3 content of 0.09 mg kg^{-1}, which is slightly higher than the current commercially farmed salmon (IMR database; https://sjomatdata.nifes.no/#/seafood/105), were used in addition to salmon fillets enriched with vitamin D3 (0.35–0.38 mg kg^{-1}) by adding vitamin D3 to the salmon feed. When fed to healthy postmenopausal women during a 6-week intervention (two dinner portions, ∼300 g week^{-1}), in addition to calcium supplements, the high vitamin D salmon had a positive impact on bone biomarkers when compared with baseline levels; however, this was not the case for the low vitamin D salmon. Given that oily fish is an important dietary source of vitamin D, the reduced levels of vitamin D in the farmed fish is cause for concern. Unlike EPA and DHA, vitamin D3 could easily be added to commercial salmon feeds to achieve the same level of vitamin D as that in a fish oil-based feed; however, there are legal constraints that prevent this (EC directive 1970).

Animal models have also been used in an attempt to evaluate the effects of changing the dietary composition for farmed fish. As seen from Table 1, increased dietary LA is an issue regardless of which vegetable oil is used to replace marine oils in salmon feed; however, some oils, including soybean, maize and sunflower oils, stand out in terms of having a particularly high content of LA. Alvheim and coworkers (2013) investigated the use of fillets from salmon fed either 100% soybean oil or 100% decontaminated fish oil as a lipid source in feed for male C57BL/6J mice. The soybean oil salmon

Table 2. Human intervention studies involving Atlantic salmon

Reference	Aim of the study	Target group	Duration	Amount eaten	Main results reported
Seierstad et al., 2005; Bethune et al., 2006	Comparison of differentially fed salmon: 100% of lipid as FO, 50/50 FO and rapeseed oil or 100% rapeseed oil	Patients with coronary heart disease	6 weeks	700 g week^{-1}	Serum FA profile of patients mirrored that of the salmon fillet they were given (reduced n-3 LC-PUFA when salmon were fed rapeseed oil). FO-fed salmon had reduced plasma TAG and inflammatory markers compared with other salmon groups. Plasma cholesterol was improved in all salmon groups. There was a gradient in persistent organic pollutants both in the salmon fillet and in the plasma of the participants, with the highest levels in FO-fed salmon.
Moore et al., 2006	Comparison of oily (salmon and mackerel) and lean fish and impact of different cooking oils	Overweight subjects	24 weeks	300–350 g week^{-1}	Lower plasma TAG with oily compared with lean fish; the effect was maximized using rapeseed rather than sunflower oil for cooking. Also increased plasma EPA+DHA with oily fish.
Lara et al., 2007	Investigation of the effects of salmon eating on cardiovascular risk factors	Young, healthy subjects	8 weeks	875 g week^{-1} for 4 weeks +4 weeks 'washout'	Eating salmon decreased blood pressure, TAG, LDL-cholesterol and increased HDL-cholesterol
Thorsdottir et al., 2007; Ramel et al., 2008, 2010a,b; Parra et al., 2008; Gunnarsdottir et al., 2008	Comparison of oily fish (salmon), lean fish, FO supplements and control in an energy-restricted diet for weight loss	Overweight and obese young adults	8 weeks	450 g week^{-1}	Salmon and lean fish diets, and FO supplements resulted in increased weight loss. Greater plasma TAG reduction with the salmon diet than with the control diet. FO supplements improved fasting insulin and insulin resistance, whereas the change in the salmon group (in the same direction) was not significant. Both salmon and FO reduced diastolic blood pressure. The salmon diet was the most effective diet for reducing inflammation parameters. Participants eating salmon or taking FO supplements reported less hunger when given an energy-restricted diet.
Zhang et al., 2010	Evaluation of the effect of oily fish (salmon) in an Asian diet on CVD risk	Dyslipidemic Chinese adult men	8 weeks	500 g week^{-1}	Salmon diet increased serum levels of EPA and DHA, and decreased CVD risk markers, including reduced plasma TAG, reduced IL-6 and increased HDL-cholesterol
Zhang et al., 2012	Evaluation of the effect of each of three different oily fish (one of them being salmon) in an Asian diet on CVD risk	Chinese women with hypertriacylglycerolaemia	8 weeks	400 g week^{-1}	Dietary salmon reduced plasma TAG, lowered the inflammation-related markers TNF-α and IL-6 and raised adiponectin levels
Grimstad et al., 2011	Evaluation of the effects of a salmon diet in ulcerative colitis patients	Patients with ulcerative colitis	8 weeks	600 g week^{-1}	Eating salmon may have a positive effect on disease activity in patients with mild ulcerative colitis, including improved anti-inflammatory FA index
Telle-Hansen et al., 2012	Investigation of the mechanisms behind the TAG lowering effects of fish/n-3 FAs Comparison of oily (salmon) and lean fish with control (potato)	Healthy subjects	15 days	1050 g week^{-1} (150 g day^{-1})	Both lean and oily fish decreased plasma TAG
Miles et al., 2011; Urwin et al., 2012, 2014; Noakes et al., 2012	Investigation of the impact of salmon in pregnancy; diet ingredients for the farmed salmon were specifically selected to be low in contaminants (added oil in the salmon feed 60% VO/40% FO)	Pregnant women with a low habitual consumption of oily fish	20 weeks	300 g week^{-1}	The salmon diet increased EPA and DHA in plasma PC in maternal blood, umbilical cord blood and breast milk, and decreased secretory IgA in breast milk (immunological factor provided in the milk). Maternal salmon consumption did not affect maternal or infant fecal microbiota or infant fecal IgA. The diet had no effect on allergic outcomes in the children.

Continued

Table 2. Continued

Reference	Aim of the study	Target group	Duration	Amount eaten	Main results reported
Libuda et al., 2016	Enrichment of baby meals with either ALA or EPA+DHA (by adding salmon) from the age of 4–6 months to 10 months	Infants	4–6 months	Baby food with salmon twice per week	Only preformed DHA from salmon (not ALA from rapeseed oil) was effective in maintaining DHA levels in RBCs during the study period
Graff et al., 2016	Comparison of vitamin D3-enriched salmon with commercial farmed salmon (low vitamin D)	Postmenopausal women	12 weeks	~300 g week^{-1}	Vitamin D3-enriched fish has a positive effect on bone health, measured as bone biomarkers; however, this was not the case for the commercial salmon

When several publications are based on samples from the same intervention study, these are grouped together in the table. ALA, α-linolenic acid (18:3n-3); CVD, cardiovascular disease; DHA, docosahexaenoic acid, 22:6n-3); EPA, eicosapentaenoic acid (20:5n-3); FA, fatty acid; FO, fish oil; HDL, high-density lipoprotein; IL-6, interleukin 6; IgA, immunoglobulin A; LC-PUFA, long-chain polyunsaturated fatty acid; LDL, low-density lipoprotein; PC, phosphatidylcholine; RBC, red blood cell; TAG, triacylglycerol; TNF, tumour necrosis factor; VO, vegetable oil.

diet increased LA and ARA and decreased EPA and DHA in the liver and red blood cells of the mice, elevated endocannabinoids, increased liver TAG, and led to weight gain (despite no differences in feed intake) and adipose tissue inflammation compared with mice fed the fish oil salmon diet. The authors concluded that excessive dietary LA increases weight gain and counteracts the anti-inflammatory properties of EPA and DHA in mice (Alvheim et al., 2013). A similar study was conducted by Midtbø and coworkers (2013) using salmon that had been fed one of four different diets, with the main lipid source being fish-, rapeseed-, olive- or soybean oil. Once again, male C57BL/6J mice were used, a strain which is prone to developing obesity and metabolic complications when fed a high-fat diet. In this trial, there was no effect on body weight development, but the soybean oil-salmon diet exaggerated insulin resistance and increased the accumulation of TAG in the liver of the mice. The omega-3 index (EPA+DHA percentage of total FAs in red blood cells) was highest in mice fed the fish oil-diet because this was the diet with the highest dietary levels of EPA+DHA. Interestingly, the three other groups had similar dietary levels of EPA+DHA compared with each other; however, the omega-3 index was significantly lower in mice fed the soybean oil-salmon diet than in those fed the rapeseed oil and olive oil-salmon diets. (In the study, only significant differences in the fish oil group were tested; however, using the mean values and the standard error of the mean reported in the study, 95% confidence intervals can be calculated, which show no overlap of the soybean oil group with the rapeseed oil and olive oil groups.) This is likely owing to high levels of ARA produced from the dietary LA, displacing EPA from tissue membranes (DHA in red blood cells did not differ and, hence, the difference in the omega-3 index was driven by a difference in EPA). Indeed, both LA and ARA were significantly higher in the red blood cells of mice fed the soybean oil-salmon diet than they were when fed any of the other diets. The authors concluded that different vegetable oils used to replace fish oil in salmon feed have markedly different spillover effects on mouse metabolism, and that the content of LA may be a cause of concern warranting further investigation (Midtbø et al., 2013). A follow-up study using only the fish oil, rapeseed oil and soybean oil-fed salmon in diets for mice, confirmed the findings of hepatic steatosis and increased insulin resistance in the soybean oil-group (Midtbø et al., 2015).

Clearly, these studies show that care needs to be taken when feed ingredients for farmed salmon are changed, to maintain as far as possible the nutrients that have been associated with health benefits for consumers.

Future perspectives

As Atlantic salmon appears to have a minimum requirement of dietary EPA+DHA (>1% of the feed) that, together with elongation and desaturation processes in the fish, will ensure that a minimum fillet level of 87.5 mg 100 g^{-1} is found in harvest size fish (Rosenlund et al., 2016), farmed salmon will remain a useful dietary source of these FAs for humans in the future. Farmed salmon still contributes positively to the overall n-6/n-3 ratio of a Western diet, but to a much lesser extent than before. Combined with similar changes in much of our food supply (Simopoulos, 2002), this is a cause for concern, and efforts should be made to limit the amount of n-6 FAs in salmon fillets.

However, if global salmon production is to increase, an important question is where the EPA and DHA for the feed will come from in the future, and whether it is possible to further increase the EPA and DHA levels in the fillets of farmed salmon. There are alternative marine resources to the traditional fish meal and fish oil from reduction fisheries, including harvesting from lower trophic levels (e.g. copepods, krill or mussels), mesopelagic fish, by-catch and seafood industry processing by-products where utilization will depend on logistics, knowledge and technology (Olsen et al., 2010). Of these, some krill meal is currently used in commercial fish feeds, and there is a relatively large production of fish meal and oil from seafood industry by-products, currently constituting 20–30% of fish meal and oil used in Norwegian aquafeeds (Skretting, 2015). Although there might be some untapped potential in these resources, the amounts will necessarily be limited and subject to natural variations, and the impact on the ecosystem of harvesting new species needs to be carefully assessed. Algae oils have been recognised as a potential source of oil rich in EPA and DHA and tested in diets for Atlantic salmon (Kousoulaki et al., 2016; Miller et al., 2007). Despite the currently high costs of these products they are starting to be incorporated in commercial salmon feeds in limited amounts (http://news.algaeworld.org/2016/06/biomar-promotes-algae-omega-3-use-for-aquaculture-feed/). Another possible approach is to use oilseed crops genetically engineered to produce EPA and/or DHA. Although not yet commercially available, the use of a modified high EPA *Camelina* oil has already been tested in a trial with Atlantic salmon (Betancor et al., 2015), and testing of a high DHA rapeseed oil is ongoing in Norway, led by Prof. Bente Ruyter. Algae oils and genetically modified vegetable oils have the advantage that production can potentially be expanded to meet the demands of a growing aquaculture industry. As we attempt to move from a linear to a circular bioeconomy, finding feed resources that take advantage of 'waste' from other production systems will also be important, such as the use of by-products from seafood processing to make fish meal and oils used in salmon feeds. In this regard, insects are also a potential feed source for salmon because they can be grown on carbohydrate-rich organic waste, which they convert into protein and lipids for salmon feeds (Lock et al., 2015). Attempts have also been made to enrich insect larvae with marine nutrients by including macro algae in their feed (Lock et al., 2016). Other potential sources of feed are by-products from terrestrial farm animals, such as blood, intestine and feathers from poultry, which are used in other salmon-producing countries but are not currently used in Europe.

In conclusion, there are many possibilities and many potential pitfalls. Changing the feed ingredients of farmed salmon requires extensive research and knowledge of effects throughout the food chain, from feed composition to fish health and fillet composition, and ultimately the health effects in humans consuming the salmon.

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Competing interests
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