Chapter 20

Anthropogenic and Naturally Produced Contaminants in Fish Oil: Role in Ill Health

Adrian Covaci and Alin C. Dirtu

Key Points

- Fish oil dietary supplements are recommended to increase the intake of polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), renowned for their beneficial effects to human health.
- Fish oil dietary supplements contain anthropogenic contaminants, such as organochlorine pesticides, polychlorinated biphenyls, polychlorinated dioxins and furans, polybrominated diphenyl ethers and mercury. Recently, a number of organobrominated compounds, such as methoxylated-PBDEs and polybrominated hexahydroxanthenes derivatives, naturally produced by marine organisms (e.g., algae and sponges) have also been identified in commercial fish oil dietary supplements.
- Since fish oil dietary supplements are consumed on a daily basis, concerns are issued about the presence of various contaminants in these capsules with improvements in the preparation and purification of supplements have reduced dramatically the contaminant's concentrations.
- Fish oil dietary supplements might be a suitable alternative to fish consumption for certain groups of the population for which fish consumption advice has been issued such as pregnant women or children.
- There is also a stringent need to regularly monitor the presence of "classical" and "new" contaminants together with naturally occurring compounds, in marine products destined for human consumption.

Keywords Anthropogenic · Organohalogenated contaminants · Naturally produced · Beneficial health effect · Fish oil dietary supplements · Dietary intake

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A. Covaci (✉)
Department of Pharmaceutical Sciences, Toxicological Center, University of Antwerp, Universiteitsplein 1, 2610, Antwerp, Belgium
e-mail: adrian.covaci@ua.ac.be

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1 Beneficial Effects of Consumption of Fish Oils Rich in *n*–3 Unsaturated Fatty Acids

Both marine fish and fish-derived products, e.g., fish oils, contain essential long-chain polyunsaturated fatty acids (PUFAs), such as 5,8,11,14,17-eicosapentaenoic acid (EPA) and 4,7,10,13,16,19-docosahexaenoic acid (DHA), which are essential in the human diet [1]. They are needed for many metabolic functions including growth, structural maintenance, repairing of nervous tissue, cellular membrane phospholipid structure, or regulation of lipid metabolism [1–3]. Moreover, the intake of high amounts of PUFAs has been suggested to have several beneficial effects to human health, including decreasing the incidence and progression of vascular diseases, as well as reducing the symptoms of multiple sclerosis and/or osteoporosis [2, 3]. In recent years, fish oil dietary supplements (FODS) have been increasingly promoted as an alternative to fish consumption. Indeed, FODS may contain high and balanced custom-made amounts of DHA and EPA [1] and can sometimes be found in combinations with other nutritional supplements, such as vitamins, minerals, or even other PUFAs.

1.1 n – 3 Fatty Acids and Cardiovascular Diseases

The evidence from prospective studies and randomized trials [4–25] suggests that ingestion of $n-3$ fatty acids (especially EPA and DHA) through consumption of fish or fish oil might beneficially influence cardiovascular disease. The first studies that showed the importance of fish consumption demonstrated low rates of death from coronary heart disease (CHD) among Greenland Eskimos [26]. Therefore, many effects were reported in relation with EPA and DHA ingestion, namely preventing arrhythmias [27], lowering plasma triacylglycerols [28, 29], decreasing blood pressure [30], decreasing platelet aggregation [31, 32], improving vascular reactivity [33, 34], and decreasing inflammation [35].

Across different studies, compared with little or no intake, modest consumption of $n-3$ fatty acids (250–500 mg/d of EPA and DHA) lowers relative risk by more than 25%. Higher intakes do not substantially further lower CHD mortality, suggesting a threshold effect [36]. This threshold effect explains findings among Japanese populations [18, 24] in whom high background fish intake (e.g., median 900 mg/d of EPA and DHA) is associated with very low CHD death rates (87% lower than comparable Western populations) [10, 18], and additional $n-3$ PUFA intake predicts little further reduction in CHD death. When comparing different types of fish, lower risk appears more strongly related to intake of oily fish (e.g., salmon, herring, sardines), rather than lean fish (e.g., cod, catfish, halibut) [11, 16]. Fish intake may modestly affect other cardiovascular outcomes, but evidence is not as robust as for CHD death [24, 37–44].

$n-3$ PUFAs may influence several cardiovascular risk factors [23, 24, 27, 42–50]. Effects occur within weeks of intake and may result in altered membrane fluidity and receptor responses following incorporation of omega-3 PUFAs into cell membranes [51, 52] and direct binding of omega-3 PUFAs to intracellular receptors regulating gene transcription [53].

The heterogeneity of the effects of fish or fish oil intake on cardiovascular outcomes is likely related to varying dose and time responses of effects on the risk factors [3]. At typical dietary intakes, anti-arrhythmic effects predominate, reducing risk of sudden death and CHD death within weeks. At higher doses, maximum anti-arrhythmic effects have been achieved, but other physiologic effects may modestly impact other clinical outcomes (possibly requiring years to produce clinical benefits). Yet, the heterogeneity of clinical effects may also be related to differing pathophysiologies of the clinical outcomes. Biological differences in the development of atherosclerosis vs. acute plaque rupture/thrombosis vs. arrhythmia would account for heterogeneous effects of $n-3$ PUFAs on plaque progression vs. nonfatal myocardial infarction vs. CHD death.

Fish may replace other foods in the diet, such as meats or dairy products. However, the increase in fish consumption is unlikely to have important health benefits, since the replaced foods are highly variable among individuals and across cultures. n–3 PUFAs most strongly affect CHD death [10, 14, 15] and are unlikely to affect appreciably other causes of mortality.

Effects on total mortality in a population would therefore depend on the proportion of deaths due to CHD, ranging from one quarter of deaths in middle-age populations [54] to one half of deaths in populations with established CHD [10]. This is consistent with a meta-analysis of randomized trials through 2003 that found a nonsignificant 14% reduction in total mortality with $n-3$ PUFAs [5, 10, 25, 55, 56]. When additional placebo-controlled, double-blind, randomized trials performed since 2003 were added [41], marine $n-3$ PUFAs reduced total mortality by 17% (pooled relative risk, 0.83; 95% CI, 0.68–1.00; $P = 0.046$).

1.2 Neurologic Development

DHA is preferentially incorporated into the rapidly developing brain during gestation and the first 2 years of infancy, concentrating in gray matter and retinal membranes [57]. Infants can convert shorter chain $n-3$ PUFAs to DHA [58], but it is unknown whether such conversion is adequate for the developing brain in the absence of maternal intake of DHA [59].

Effects of maternal DHA consumption on neurodevelopment have been investigated in observational studies and randomized trials, with heterogeneity in assessed outcomes (visual acuity, global cognition, specific neurologic domains) and timing of DHA intake (gestational vs. nursing). In a meta-analysis of 14 trials, DHA supplementation improved visual acuity in a dose-dependent manner [60]. Results for cognitive testing are less consistent, possibly due to differences in neurologic domains evaluated [57, 59, 61]. A quantitative pooled analysis of eight trials estimated that increasing maternal intake of DHA by 100 mg/d leads to an increased child IQ by 0.13 points (95% CI, 0.08–0.18) [62].

Most trials evaluated effects of maternal DHA intake during nursing, rather than pregnancy. In a trial among 341 pregnant women, treatment with cod liver oil from week 18 until 3 months postpartum increased DHA levels in cord blood by 50% and raised mental processing scores, a measure of intelligence, at age 4 [63]. This is consistent with observational studies showing positive associations between maternal DHA levels or fish intake during pregnancy and behavioral attention scores, visual recognition memory, and language comprehension in infancy [64–66]. Thus, while dose responses and specific effects require further investigation, these studies together indicate that maternal intake of DHA is beneficial for early neurodevelopment.

2 Toxic Contaminants from Fish Oil Dietary Supplements

2.1 Anthropogenic Contaminants

Besides PUFAs, it was already shown in many studies that fish may contain a variety of persistent contaminants, such as polychlorinated dibenzo-*p*-dioxins and furans (PCDD/PCDFs), polychlorinated biphenyls (PCBs), or polybrominated diphenyl ethers (PBDEs). This may result in a potential increase of health risks that could counteract the beneficial effects of $n-3$ PUFAs [67, 68]. In general, the concentrations of such contaminants are proportional with the position of the fish in the food chain. Therefore, fish situated at the base of the food chain usually carries lower levels of contaminants compared to predatory fish situated high on the fish chain [69]. Another important parameter related to contaminant's concentrations in fish is the content of fat; fatty fishes (e.g., salmon, herring) contain significantly higher concentrations of persistent contaminants when compared to lean fish species [69].

The ingestion of persistent contaminants through fish consumption may lead to a wide range of toxicological and hormonal effects, including endocrine disruption, reproductive, neurobehavioral, and developmental disturbances [3, 70]. Such toxic effects on human health recorded for these contaminants made several environmental and health agencies to have already issued consumption recommendations, which range between 0.5 and 2 meals of fatty fish per month [67]. The general public is given seemingly conflicting reports about the risks and benefits of fish intake, resulting in controversy and confusion over fish and fish-derived products and their role in regard to a healthy diet [71].

Nevertheless, these contaminants persist for long periods in the environment, and thus, while levels are steadily declining, PCBs and dioxins continue to be present in low concentrations in many food items.

Considering these information, it become obvious that FODS may also be a potential source of toxic contaminants, especially when the fish oil produced originates from fish caught in contaminated waters or from farmed fish fed with contaminated feed. Fish oil produced from these sources may contain markedly higher amounts of contaminants than fish originating from less polluted sites [72–74]. Since FODS are recommended to be taken on a daily basis, it is therefore important to closely monitor the levels of contaminants that might be contained by these PUFA-enriched products. Hereby, the presence of above-mentioned contaminants in fish oils may counteract the highly claimed benefits of such capsules.

The following paragraphs will be focused on discussing the levels and profiles of each class of contaminants reported as present in FODS and also in relation with their acceptable norms.

2.1.1 Polychlorinated Biphenyls

PCBs are synthetic organochlorine compounds previously used in industrial and commercial processes, but their manufacture and processing was prohibited in 1977 [75]. Based on exposed animal experiments and also some evidence in humans, PCBs may cause adverse human health effects, such as cancer (possibly related to effects on the aryl hydrocarbon receptor), may interfere with transcription factors affecting gene expression, may affect the immune system, and may cause neurological effects [76, 77]. Also prenatal exposure to PCBs has been associated with childhood neurodevelopmental deficits in several studies [78–80]. Hereby, in order to counteract the negative effects on human health by the presence of PCBs in FODS, the additional health risks would have to exceed possible benefits by more than 100-fold to meaningfully alter the present estimates of risks vs. benefits [3].

From their chemical structure, theoretically PCBs may exist in a maximum number of 209 congeners (generically listed according to the number/position of the chlorine atoms in the molecule), although only about 130 are found in commercial PCB mixtures [75]. From all possible PCBs, 12 congeners do not present any chlorine atoms on *ortho*-positions (non-*ortho* PCBs) or have only one chlorine in *ortho*-position (mono-*ortho* PCBs). These congeners present a coplanar chemical structure, having a geometrical configuration like 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), being therefore called *dioxin-like PCBs* (DL-PCBs). The coplanar PCBs have demonstrated a close toxicological similarity to dioxins and are thought to operate by the same general mechanism [81].

However, depending on the mixture containing PCBs used, the number of possible congeners which may be measured in fish and fish oil samples differs. In general, the profile for these contaminants consists from a smaller number of congeners, mainly tri- (CB-28), tetra- (CB-52), penta- (CB-101, 118), hexa- (CB-138, 149, 153), and hepta- (CB-170, 180) chlorinated components [75]. From above-mentioned PCB congeners, the least important are CB-28 and CB-52, which usually are measured in such samples close to the limit of quantitation of different methods applied, while the most important are CB-153, CB-118, and CB-138. Considering only the number of chlorine atoms in molecule, the profile of PCBs measured in general in FODS consists from penta- and hexa-CBs which are usually present at highest concentrations, followed immediately by hepta-CBs and at the lowest levels being usually measured tetra-CB congeners. Regarding the concentration in which PCBs are usually measured in such samples, this parameter differs according to a multitude of factors, namely year/region of sample collection, type of purification process applied on the fish oil considered, type of fish, or fish organ used for oil manufacture. A non-exhaustive summary of the available literature related to the content of PCBs, including DL-PCBs, from fish oils is presented in Table 20.1.

Most of the samples included in presented studies from Table 20.1 shows that reported ΣPCB concentrations for are below of the Belgian regulatory limit (75 ng PCBs/g), with very low levels in some samples [73, 85, 86]. There are also cases where the concentrations seem to exceed the regulatory limits for PCBs, namely for unrefined oil [87] or for samples collected in the late 1990s [82], when most probably the control of such hazardous substances was not as rigorous as it is nowadays or the refining processes were not very developed. The type of fish or fish tissue used to produce fish oils can easily influence the concentrations of contaminants in the obtained products. Therefore, oils obtained from cod liver appear to be significantly more contaminated compared with the one obtained from whole fish [73].

2.1.2 Polychlorinated Dibenzo-p-dioxins and Polychlorinated Dibenzofurans

The chemical compounds included in the class of polychlorinated dibenzo-*p*-dioxins (PCDDs) (75 different components) and also in the class of polychlorinated dibenzofurans (PCDFs) (135 different components) are commonly referring to the term "*dioxins*." They are organochlorine by-products of waste incineration, paper bleaching, pesticide production, and production

Table 20.1 Median and concentration range (ng/g oil) of polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), and polychlorinated dibenzo-*p*-dioxins and furans (PCDD/PCDFs) in fish oil dietary supplements

	Median (range) concentrations (ng/g)				
	ΣPCBs (ng/g)	ΣOCPs (ng/g)	ΣDL-PCBs (pg WHO-TEQ/g)	ΣPCDD/Fs (pg WHO-TEQ/g)	
Legal limit (ng/g)	75	1,000	10	2	
Sample (origin of sample), N					Year (Reference)
FODS (mainly cod liver oil) (Australia), $N = 5$	9 (5–341)^{a}	9 (4–227)^{a,b}	–	–	1994–1995 [82]
FODS (fish oil) (Belgium), $N = 4$	124 (20–744)^{a}	19 (5–851)^{a,b}	–	–	1994–1995 [82]
FODS (mainly cod liver oil) (the United Kingdom), $N = 6$	655 (5–975)^{a}	84 (5–128)^{a,b}	–	–	1994–1995 [82]
Fish oil (Japan), $N = 41$	–	–	8.2 (0.91–19.3)	2.0 (0.2–4.9)	2000–2005 [83]
FODS (cod liver oil), $N = 7$	108 (87–202)	138 (100–224)	–	–	2001–2002 [73]
FODS (fish oil), $N = 6$	34 (0–49)	31 (5–47)	–	–	2001–2002 [73]
FODS (unspecified) (the USA), $N = 20$	50.4 (10.3–94.3)	–	–	–	2003 [84]
FODS (cod oil) (the USA), $N = 4$	153.3 (47.4–276.2)	–	–	–	2003 [84]
FODS (cod liver) (Italy), $N = 15$	86 (25–201)	71 (25–133)^{b}	–	–	2004 [74]
FODS (Belgium), $N = 27$	12 (<0.3–57)	3.9 (<0.3–150)	–	–	2004–2006 [85]
FODS (The Netherlands), $N = 17$	14 (<0.3–60)	2.9 (<0.3–230)	–	–	2004–2006 [85]
FODS (the United Kingdom), $N = 12$	7.6 (<0.3–22)	4.4 (<0.3–62)	–	–	2004–2006 [85]
FODS (other countries)^{c}, $N = 13$	6.0 (<0.3–95)	3.8 (<0.3–21)	–	–	2004–2006 [85]
FODS (mixed—no salmon), $N = 8$	24.2 (0.711–37.9)	10.6 (0.189–15.2)^{b}	–	–	2005–2007 [86]

Table 20.1 (continued)

	Median (range) concentrations (ng/g)				
	ΣPCBs (ng/g)	ΣOCPs (ng/g)	ΣDL-PCBs (pg WHO-TEQ/g)	ΣPCDD/Fs (pg WHO-TEQ/g)	
Legal limit (ng/g)	75	1,000	10	2	
Sample (origin of sample), N					Year (Reference)
FODS (mixed— including salmon), $N = 6$	25.1 (19.3–26.5)	11.1 (9.31–24.9)^{b}	–	–	2005–2007 [86]
FODS (salmon), $N = 7$	95.3 (36.1–170)	59.2 (4.76–250)^{b}	–	–	2005–2007 [86]
Shark liver oil (Japan), $N = 3^{d}$	320 (290–340)	–	–	–	2006 [87]
Shark liver oil (New Zealand), $N = 3^{d}$	22 (19–43)	–	–	–	2006 [87]
Shark liver oil, $N = 6$	18.5 (16–31)	–	–	–	2006 [87]
FODS (mainly Pacific fish, for Switzerland), $N = 6$	13 (0.23–17)	–	1.15 (0.038–1.3)	0.65 (0.32–0.83)	2006 [88]
FODS (mainly cod liver oil) (the United Kingdom), $N = 32$	–	–	9.4 (1.1–41.5)	0.9 (0.2–8.4)	2006 [89]
Fish oil (cod liver oil) (Spain), $N = 1$	–	13.2	–	–	2007 [90]
Fish oil (salmon) (Spain), $N = 2$	–	38.4 (25.6–51.3)	–	–	2007 [90]
Fish oil (Sweden), $N = 5$	–	0.74 (0.16–33)^{e}	0.17 (0.02–1.1)	0.57 (0.09–0.86)	2008 [91]
Seal Oil (Sweden), $N = 1$	–	210^{e}	4.9	2.3	2008 [91]

[a] Results were recalculated in ng/g using an average density of oil of 0.924 g/mL

[b] ΣOCPs are reported as ΣDDTs

[c] Denmark, South Africa, USA, France, and Sweden

[d] No heating step in the refining process

[e] ΣOCPs are reported as ΣHCHs + ΣDDTs

of polyvinyl chloride plastics [92]. Their toxicity was well established through various studies [93, 94] and therefore controlling emissions of these chemicals was of a high concern. Because of monitoring programs implemented by most of the countries, total environmental releases of dioxins from all quantifiable sources decreased by 90% between 1987 and 2000 [92]. The results presented in Table 20.1 shows that in case of PCDD/Fs, median concentrations measured in different FODS collected from various locations are well below the maximum tolerable limit. Only one study reported higher concentrations of PCDD/Fs, but the value is assigned to an oil sample obtained from seal [91].

2.1.3 Organochlorine Pesticides

The most important pesticides from this class which are usually measured in fish or fish oil samples are hexachlorocyclohexanes (HCHs) (usually present in their four isomers: α-, β-, γ-, δ-HCH), DDT and metabolites (DDTs), and chlordanes. Commercial DDT is actually a mixture of several closely related compounds where the major component (up to 77%) is the *p,p′* isomer. The *o,p′* isomer is also present in significant amounts (15%), the rest of the mixture being constituted from *p,p′*-dichlorodiphenyldichloroethylene (*p,p′*-DDE) and *p,p′*-dichlorodiphenyldichloroethane (*p,p′*-DDD). *p,p′*-DDE and *p,p′*-DDD are also the major metabolites and breakdown products of DDT in the environment [95]. The term "*total DDT*" or *ΣDDTs* is often used to refer to the sum of all DDT-related compounds (*p,p′*-DDT, *o,p′*-DDT, *p,p′*-DDE, and *p,p′*-DDD) in a sample.

From the pesticide formulations mentioned above, DDTs are by far the most abundant OCPs measured in fish and/or FODS. In fact, together with PCBs, DDTs constitute the main chlorinated contaminants found in general in marine samples. Therefore, the results from Table 20.1 related to the content of OCPs from FODS reported in the literature will often refer to the concentrations of ΣDDTs. Because of its ban in most of the countries, usually the main contributor to the ΣDDTs is the principal metabolite of *p,p′*-DDT, which is *p,p′*-DDE. However, none of the presented studies from Table 20.1 show concentration values for ΣDDTs higher than the EU regulatory limit (1,000 ng/g). Again, concentrations of ΣDDTs depend on the type of fish or organ used to produce FODS. As a consequence, oil supplements obtained from cod liver showed also for DDTs the highest median concentrations compared with other products [73, 82, 85].

2.1.4 Brominated Flame Retardants

Although several BFRs, such as polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCD), are found in quantifiable levels in wildlife and humans and have been extensively investigated in the last decade, we are still lacking information on the health effects caused by these compounds [70]. In humans, they are absorbed from the gastrointestinal tract and accumulate in fatty tissues [70]. It seems that they present acute toxicity at average doses, but their health effects from chronic exposure are of more concern, especially when they are related to the exposure of developing infants and wildlife. However, based on the available data, it is known that BFRs are associated with several health effects in animal studies, including neurobehavioral toxicity, thyroid hormone disruption, and possibly cancer, only for some PBDE congeners [70]. Even if limited information is available in the literature, there is some evidence that BFRs can cause developmental effects, endocrine disruption, immunotoxicity, reproductive, and long-term effects, including second-generation effects, reviewed by Birnbaum and Staskal [70] and Darnerud [96]. For PBDEs, there is some evidence available for estrogenic activity [96, 97], but more studies have to be undertaken to determine if low-dose exposures have estrogenic activity in humans or other species. However, their presence in fish in general and in FODS in particular is important and their monitoring should be carefully addressed for these new persistent contaminants.

Polybrominated Diphenyl Ethers

PBDEs are flame-retardant additives which are used in a wide array of household products in concentrations up to 30% by weight, typically between 2 and 6% (per weight) [98]. They are structurally related to PCBs and are produced commercially as mixtures. However, PBDE mixtures contain fewer congeners than the commercial PCB mixtures. The three commercial mixtures of PBDEs are penta-BDE, octa-BDE, and deca-BDE according to the number of bromine atoms in the dominating congeners of the mixtures. Since August 2004, the use of penta- and octa-BDE technical mixtures has been banned in the EU, followed in July 2008 by the ban on the use of deca-BDE mixture [98]. In USA, only California has banned the use of penta- and octa-BDE mixtures by the end of 2008, while other US states are currently in the phase-out legislation for PBDEs [98].

Even if PBDEs have been reported (sometimes in high levels) in marine environments [99], there are very few studies which monitored their presence in FODS. Generally, the most detected PBDE congeners in FODS are BDE 47, 99, and 100 (which usually contribute with >75% to the total PBDEs), while higher brominated congeners, such as BDE 153, 154, and 183, are in most of FODS below quantification limit [100], though reported levels of PBDEs are considerably lower than those of organochlorine contaminants, such as PCBs or OCPs [85]. This is probably due to improved selection of fish used for the FODS preparation and/or to the final purification methods used by different producers. Similar to PCBs and OCPs, the most contaminated samples were reported as FODS obtained from cod liver (Table 20.2) [73, 87, 101]. Interestingly, several FODS with an elevated PBDE content had also higher DHA content [100]. It is not clear whether this is due to the fish sources used for the preparation of FODS with high DHA content (e.g., tuna) or to the purification processes specific for DHA-enriched FODS.

Hexabromocyclododecane

HBCD is the third most widely used BFR in the world and on the second place in the EU [98]. It is mostly used in extruded and expanded polystyrene foams but also is used as insulation material in construction industry. HBCD is highly efficient so that very low levels are required to reach the desired flame retardancy. Other uses of HBCD are upholstered furniture, automobile interior textiles, car cushions and insulation blocks in trucks, packaging material, video cassette recorder housing, and electric and electronic equipment [98].

Table 20.2 Median and concentration range (ng/g oil) of polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), and total mercury (Hg + MeHg) in fish oil dietary supplements

Sample (origin of sample)	Median (range) concentrations (ng/g) ΣPBDEs	ΣHBCDs	Hg-MeHg	Year (Reference)
FODS (cod liver oil), $N = 7$	20 (15–35)	–	–	2001–2002 [73]
FODS (fish oil), $N = 6$	1.7 (0.8–2.6)	–	–	2001–2002 [73]
FODS (Belgium), $N = 27$	0.4 (<0.1–45)	–	–	2004–2006 [100]
FODS (The Netherlands), $N = 17$	0.5 (0.1–17)	–	–	2004–2006 [100]
FODS (the United Kingdom), $N = 12$	0.2 (0.1–2.8)	–	–	2004–2006 [100]
FODS (other countries)[a], $N = 13$	0.4 (0.1–7.5)	–	–	2004–2006 [100]
FODS (mainly Pacific fish, for Switzerland), $N = 6$	0.7 (0.069–3.8)	–	–	2006 [88]
Cod liver oil (North Sea), $N = 3$	28 (16–32)	5.4 (4–6.2)	–	2004–2008 [87, 101]
Shark liver oil (Japan), $N = 3$[b]	52 (49–53)	44 (44–45)	–	2004–2008 [87, 101]
Shark liver oil (New Zealand), $N = 3$[b]	0.6 (0.2–0.7)	<0.2	–	2004–2008 [87, 101]
Shark liver oil[c], $N = 6$	0.2 (0.1–15)	<0.2 (<0.2–7.3)	–	2004–2008 [87, 101]
Seal oil (Canada), $N = 2$	0.85 (0.8–0.9)	0.45 (0.4–0.5)	–	2004–2008 [87, 101]
Catfish-eggs oil (Venezuela), $N = 22$	–	–	2.16 (1.8–2.97)[d]	1998 [108]
FODS (fish oil), $N = 3$	–	–	38.8 (9.9–123)	2005 [109]

[a] Denmark, South Africa, USA, France, and Sweden
[b] No heating step in the refining process
[c] Origin (country of production) unspecified
[d] Results were recalculated in ng/g using a density value of 0.9 g/mL

The concentrations of HCHD in fish are usually strongly correlated with the contamination level of the area from which the samples are collected or with the proximity of industrial activity areas since there are several studies reporting high levels of HBCD in such samples [102]. Because of the increasing temporal trends of HBCD in various environmental compartments, especially in aquatic environmental samples [99], HBCD content of fish oils used to prepare FODS should also be monitored. The results presented in Table 20.2 show that the reported levels of HBCD in FODS are slightly lower compared to PBDEs measured in the same samples [101].

2.1.5 Mercury and Methyl Mercury

The forms in which mercury is present in the environment are various, namely elemental (metallic) mercury (Hg^0), inorganically bound mercury (Hg^{2+}), and organically bound mercury, for example, monomethyl mercury (MeHg) or dimethyl mercury (Me_2Hg). When assessing the risk for the human health, one has to consider that organically bound mercury species are much more toxic than elemental or inorganic species [103]. MeHg is formed in aquatic systems from inorganic mercury through a methylation process by the action of anaerobic organisms. Because MeHg is formed in aquatic systems and because it is not readily eliminated from organisms, it is biomagnified in aquatic food chains from bacteria, to plankton, through macroinvertebrates, to herbivorous fish, and further to piscivorous fish. Therefore, the concentration of MeHg in the top-level aquatic predators can reach a level a million times higher than the level in the water [103]. There are many factors which may influence Hg concentrations in any given fish, namely fish species, the age and size of the fish, and the type of water body in which the sample was collected [103].

Once entered in human body, MeHg is readily and completely absorbed by the gastrointestinal tract and afterward it reacts through a complexation process mostly with amino acids. MeHg is a risk factor for cardiovascular disease through a variety of mechanisms potentially involving pro-oxidant effects via the generation of radical species and the inactivation of cellular antioxidant systems such as glutathione peroxidase and catalase [104]. Mechanistic studies indicate that MeHg can exert toxic effects on the vascular endothelium by depletion of sulfhydryls, increased oxidative stress, and activation of phospholipases [105, 106]. Nevertheless, estimation of the benefits for $n - 3$ FA intake vs. MeHg risks should be carefully addressed for different fish species, according to their content in toxic/nontoxic compounds [107].

Therefore, even if the toxicity of Hg and its derivatives was shown in various studies involving aquatic environment, their monitoring in FODS was not as regular as it might be expected and there are very few reports of Hg content for such supplements (Table 20.2).

2.2 Naturally Produced Halogenated Compounds

Several recent studies have described the presence in marine environment of naturally produced halogenated compounds, such as methoxylated polybrominated diphenyl ethers (MeO-PBDEs) [110–112], polybrominated hexahydroxanthene derivatives (PBHDs) [113, 114], or halogenated dimethyl bipyrroles (HDBPs) [115, 116]. Their presence was already confirmed in some fish species used for the preparation of FODS [117, 118]. All mentioned classes of naturally produced compounds have been sometimes measured in concentrations higher than contaminants usually targeted in monitoring schemes, but not much is known about their occurrence, their dietary intake from fish and fish-derived products, or about the potential toxicological effects of these compounds.

2.2.1 Polybrominated Methoxylated Diphenyl Ethers

MeO-PBDEs are produced by algae, bacteria, or sponges (cyanobacteria and red algae—*Ceramium tenuicorne*) [112] and have previously been found in various marine organisms, including fish and marine mammals [110, 111]. The presence of elevated concentrations of these compounds found in the higher levels of the marine food chain demonstrates their bioaccumulative properties. However, little is known of their potential toxicological effects.

Covaci et al. [100] analyzed several FODS collected from various locations (Table 20.3), and MeO-PBDEs were found at elevated levels in most of the samples. Moreover, there was no significant correlation between PBDEs and MeO-PBDEs levels (namely between BDE 47 and 6-MeO-BDE 47, one of the most abundant compounds measured in fish samples usually) showing that these compounds could originate from other marine sources. However, some significant correlation between individual MeO-PBDEs (6-MeO-BDE 47 and 2-´MeO-BDE 68) shows that it is highly plausible that these compounds have both accumulated from the similar (natural) sources. The main difference between the results within the samples was based on the origin of fish included in FOD manufacture: fish from Pacific and Atlantic Oceans showed higher levels on MeO-PBDEs, similar results being reported for marine mammals from the Southern hemisphere [110].

Table 20.3 Median and concentration range (ng/g oil) of naturally produced brominated compounds: methoxylated polybrominated diphenyl ethers (MeO-PBDEs) and polybrominated hexahydroxanthenes (PBHDs) in fish oil dietary supplements

	Median (range) concentrations (ng/g)		
Sample (origin of sample)	ΣMeO-PBDEs	ΣPHBDs	Year (Reference)
FODS (Belgium), $N = 27$	4.6 (<0.2–1670)	3.8 (<1.3–98)	2004–2006 [100]
FODS (The Netherlands), $N = 17$	9.2 (<0.2–180)	22.9 (<1.3–158)	2004–2006 [100]
FODS (the United Kingdom), $N = 12$	14 (<0.2–315)	2.8 (<1.3–163)	2004–2006 [100]
FODS (other countries)[a], $N = 13$	4.1 (<0.2–230)	14.2 (<1.3–203)	2004–2006 [100]

[a] Denmark, South Africa, USA, France, and Sweden

2.2.2 Polybrominated Hexahydroxanthene Derivatives

PBHDs were recently identified by Hiebl et al. [113] as two congeners in fish and shellfish. Indeed, sponges of the *Cacospongia* genus, reported to occur in Australia, but also in the Mediterranean Sea, have been suggested as potential natural producers of PBHDs [113, 114]. In the fish oil survey by Covaci et al. [100], concentrations of PBHDs were similar to concentrations of MeO-PBDEs (Table 20.3), and in the most samples, higher than of PBDEs. Within the two mentioned classes of naturally produced compounds, the levels of ΣPBHDs did not correlate with ΣMeO-PBDEs ($R_s = 0.24$, $p > 0.01$), suggesting separate (natural) sources of their presence in fish/fish oil samples [100]. Similar concentrations of PBHDs were already determined in farmed fish from the Mediterranean Sea [113], in farmed mussels from New Zealand [113, 114], but also in bird eggs from Norway [119], indicating the transfer of these compounds throughout the marine food web.

2.2.3 Halogenated Dimethyl Bipyrroles

Specific sources of these compounds have not been yet identified, but radiocarbon analysis strongly suggests that halogenated dimethyl bipyrroles (HDBPs) are synthesized using a relatively recent source of carbon and thus likely have a biogenic origin [120, 121]. It was also assessed that they show persistency, have bioaccumulation potential, and are already globally distributed in marine environments. Due to similarities in physical properties and persistence, their environmental behavior has somewhat paralleled the behavior of persistent anthropogenic organohalogens, such as the higher chlorinated PCB congeners [115]. Although the geographical sources of HDBPs are poorly understood, these compounds seem to be more abundant in marine samples from the North Pacific Ocean rather than the Atlantic Ocean [122, 123]. The presence of HDBPs in FODS was not reported until now, but because of their levels in fish samples, it might be suggested that this is a matter of time. Moreover, it is important to report their levels in fish samples when discussion about comparison of risks/benefits of fish/FODS consumption is addressed, even if their potential toxicological effects are not yet elucidated.

3 Intake of Contaminants Through Consumption of FODS

Since FODS are intended to be consumed on a daily basis, several studies have also calculated the daily intake of organohalogenated compounds from FODS.

In a study by Covaci et al. [100], PUFA-rich FODS ($n = 69$) from 37 producers were collected in 2006 from products available for sale on the Belgian market, but also from The Netherlands, Ireland, the United Kingdom, and South Africa. Information on recommended dosage as provided on the product labels together with the EPA and DHA composition was used to calculate the daily intake in pollutants. In order to estimate the contaminant intake, daily recommended consumption of the supplements, as provided on the product labels, was multiplied by the corresponding concentrations. Intakes (ng/day) were calculated using lower bound (LB) and upper bound (UB) methods, where non-detects were replaced with a value equal to zero or LOQ, respectively.

The investigated FODS contained 200–800 mg/g EPA and DHA and the recommended dosing for human consumption ranged between 1 and 3 g/day [3]. Due to the low contamination levels in the FODS analyzed in this particular survey [85, 100], FODS do not appear to increase substantially the dietary intake of PCBs: median daily intake was 29 and 42 times lower than the intake from fish consumption alone or from total diet, respectively (Fig. 20.1).

Similarly, the median daily intake of PBDEs was 8 and 16 times lower than the intake from fish consumption alone or from total diet, respectively (Fig. 20.1). Although fish consumption is an important contributor to the total dietary intake of PCBs or PBDEs (Fig. 20.1), the low intake of these contaminants from FODS (<10% of that from fish) suggests that purification processes were present during the preparation of the vast majority of the investigated FODS. Since the PBDE intake from FODS covers yet a wide range of values (Fig. 20.1), some FODS brands are either produced from contaminated fish or are insufficiently purified.

The low intake of PCBs and PBDEs through FODS therefore makes these supplements a suitable alternative for populations with low consumption of PUFA-rich food or for which fish consumption recommendations have been issued (e.g., pregnant women). FODS also prove to be a powerful source of EPA and DHA compared with PUFA-containing vegetables oils, such as soybean and rapeseed oil, which have approximately 10 times less EPA and do not appear to provide an effective metabolic source of DHA for the average consumer [73]. This renders FODS an efficient, relatively clean, and low caloric source of PUFAs.

In the same survey by Covaci et al. [100], the presence of naturally produced halogenated compounds has been reported in FODS. Using a similar approach, it was calculated that the median daily intakes of MeO-PBDEs and PBHDs from FODS were, respectively, 3 and 6 times higher than the median intake of PBDEs (3 ng/day), respectively (Fig. 20.1). For some brands, the daily intake of MeO-PBDEs and PBHDs from FODS was even higher than the total dietary intake of PBDEs. This emphasizes that the presence of these scarcely investigated compounds should not be overlooked. Likewise, MeO-PBDEs and PBHDs showed a large variation of intake estimates, encompassing the range of PBDE values.

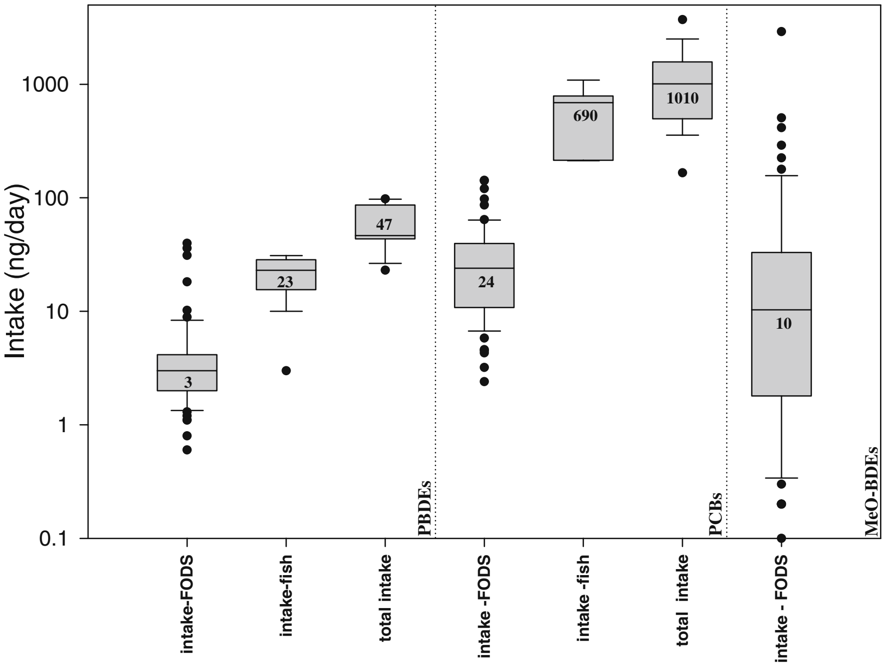

Fig. 20.1 Dietary intake (ng/day) of PCBs and PBDEs from fish oil dietary supplements, fish consumption, and total diet. The box plots show the median, 25th and 75th percentiles, the lines give the 10th and 90th percentiles, while the dots represent the outliers. Values in the *box* plots represent the medians for each category. Literature data used for the daily intake of PBDEs and PCBs from fish consumption and total diet are taken from references [124–144]

An estimation of the dietary intake of brominated FODS compounds for children has also been determined [100]. For each group of compounds, the intake was lower for children than for adults due to a combination of lower amounts needed to be daily ingested and lower concentrations of brominated compounds in the FODS used for children.

The dietary intake from fish and seafood has also been reported for other natural compounds, such as DBPs. The daily intake estimate for ΣDBPs was <3.5 ng/day [115], a lower result compared to the naturally produced compounds investigated by Covaci et al. [100].

4 Decontamination of Commercial Fish Oil Supplements

Previously, we showed that a large variety of both anthropogenic contaminants and naturally produced compounds are present in FODS at sometime considerable amounts. Most of the above-mentioned compounds are lipophilic and therefore they are mainly retained in the fatty tissues of fish used to produce the FODS. It is thus expected that such fish oils may incorporate a large variety of contaminants. If these fish oils are used as primary products directly obtained without any purification, they might represent a real risk to human health.

Fish oils are usually refined by neutralization, absorption, and distillation processes. The main refining techniques developed and published until now were focused on removing of mainly dioxins and DL-PCBs. The refining process is usually not an easy technique to be applied, many parameters being necessary to be rigorously optimized before its proper applicability [145].

The process optimization should consist of selecting purification parameters that would allow for maximum reduction of the toxic contaminants present in fish oil while retaining the favorable high fatty acid content. However, in many cases, the levels of contaminants following these refining processes are not adequately low for human consumption; furthermore, it is known that the removal of DL-PCBs from fish oil, particularly mono-*ortho* PCBs, is difficult [82, 146, 147].

The removal of contaminants from fish oil was applied using supercritical CO_2 extraction (SCE) and different adsorbents [148]. It was shown that when using SCE alone the removal efficiency was higher in case of DL-PCBs (70–90% efficiency), but lower for dioxins (some of PCDD/F congeners were removed only at an efficiency of 15%). In contrast, when using different adsorbent treatments, activated carbon showed high removal efficiencies (>90%) for PCDDs and PCDFs, but low (<30%) for DL-PCBs. A combination of both of these methods was suggested to be more effective in order to reduce the total TEQ value for dioxin-like contaminants [148].

These results were confirmed in 2007 when activated carbon adsorption on the reduction of POPs in fish oil was studied based on response surface methodology [149]. PCDD/Fs showed a rapid adsorption behavior and the TEQ levels could be reduced by 99%. Adsorption of DL-PCBs was less effective and depended on *ortho*-substitution, i.e., non-*ortho* PCBs were adsorbed more effectively than mono-*ortho* PCBs with a maximum of 87 and 21% reduction, respectively, corresponding to the DL-PCB-TEQ reduction of 73%.

In order to combine the best conditions for a proper purification of fish oils, refining techniques based on countercurrent supercritical CO_2 extraction (CC-SCE) and activated carbon treatment were developed [150]. This resulted in a 93% reduction in the sum of PCDD/Fs and DL-PCBs levels and by 85% reduction in the TEQ values. It was shown that CC-SCE is effective for the removal of DL-PCBs, whereas activated carbon treatment is effective for the removal of PCDD/Fs.

5 Conclusions

Diets rich in $n-3$ fatty acids present in fish offer a number of health benefits, from fighting heart disease to boosting immunity and neurological improvement. However, many noxious persistent contaminants, such as PCBs, OCPs, PCDD/PCDFs, and PBDEs, accumulate in fatty tissue of fish and, as a consequence, they may end up in commercial fish oils produced from these fishes. In general, the levels of contaminants measured in FODS are below the legal consumption norms. In some cases, very low contaminant levels (close to the detection limit) were measured indicating improved sourcing and advanced refining processes. Consequently, the daily intake of persistent contaminants through FODS represents only a small percentage (between 3 and 12%) of the intake resulting from consumption of fish. Another advantage is the “à la carte” preparation of FODS containing high and balanced custom-made amounts of DHA and EPA, sometimes in combination with other nutritional supplements, such as vitamins, minerals, or even other PUFAs.

However, some FODS products contain high levels of contaminants and this aspect needs to be better investigated. There are a number of general factors which can be linked to the purity of the fish oil capsules.

1. A high degree of purity has been seen in FODS prepared from the oil of fish caught in clean waters (open-ocean) compared to more polluted fish from coastal areas or closed seas.
2. Oil derived from smaller species, such as anchovy, typically contains fewer contaminants than oil from larger fish (cod or salmon). This is most probably due to the shorter life of smaller fish, which leads to a lower accumulation of contaminants.
3. In general, oil produced from fish body tends to have lower contaminant concentrations than from (cod) liver or from oil of marine mammals (e.g., seal).
4. Some companies go through a number of advanced chemical-stripping or refining processes to remove contaminants from fish oil and consequently, products from these suppliers tend to be clean. Yet, most companies selling fish oil supplements do not advertise about their processing or refining procedures, nor they do identify the source of their fish, much less what species they had tapped for its oil.
5. In general, companies that had labeled their supplements as being certified free of halogenated contaminants or methyl mercury should be given credit for their efforts to improve their products and for transparency toward the consumers.
6. There is a need for inclusion of a larger number of anthropogenic contaminants, e.g., PBDEs, but also naturally produced halogenated compounds, in monitoring schemes of marine products destined for human consumption. There is also a need for appropriate monitoring and legislation for FODS.

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