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Review

CONTAMINANTS IN FISH: RISK-BENEFIT CONSIDERATIONS*

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Fish provide a healthful source of dietary protein and are high in nutrients such as omega-3 fatty acids. There is evidence of beneficial effects of fish consumption in coronary heart disease, stroke, age-related macular degeneration, and growth and development. Yet, benefits may be offset by the presence of contaminants, such as methylmercury (MeHg), dioxins, polychlorinated biphenyls (PCBs) and several other halogenated persistent organic pollutants. MeHg is a known developmental neurotoxicant, as evidenced by several animal studies and episodes of human intoxication in Japan and Iraq. Fish represent the main source of exposure to MeHg for the general population, and large predatory fish (swordfish, tuna) have the highest levels of MeHg contamination. Provisional tolerable weekly intakes of 0.7 μg kg^{-1} to 1.6 μg kg^{-1} have been set by regulatory agencies. Concern for contamination of fish with dioxins and dioxin-like PCBs stems from their reported carcinogenicity, immunotoxicity, and reproductive and developmental toxicities. Farmed and wild-caught fish appear to have similar levels of contaminants. Advisories are in place that recommend limited consumption of certain fish in children, pregnant women and women of childbearing age. Careful risk-benefit considerations should foster fish consumption while minimizing exposure to toxic contaminants.

KEY WORDS: *coronary heart disease, developmental neurotoxicity, dioxins, fish, methylmercury, polychlorinated biphenyls, risk-benefit analysis*

Fish is good for you", so claims an old saying. Fish is a generally widely available food that indeed contains a number of nutrients shown to have beneficial effects on human health. Yet, fish may contain several contaminants, such as metals and organohalogenated compounds, that are known to cause adverse effects in humans, both during development and in adulthood. This requires that the consumer balances benefits and risks of fish and seafood consumption. This brief overview discusses current knowledge on the benefits of fish consumption for human health, and the potential risks associated with exposure to fish contaminants. It also argues for intervention measures that may shift the balance toward beneficial effects of fish. Additionally, it also addresses recent controversies on the levels of contaminants in wild-caught fish versus farmed fish. These topics have lately been a matter of notable interest and debate, as evidenced by several recent publications (1-6).

NUTRITIONAL COMPOSITION OF FISH

Fish is an excellent source of important nutrients, including proteins, vitamins, minerals and fatty acids.

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Fish proteins have high biological value, are easily digestible, and are rich in essential amino acids. Fish are a good source of some vitamins, especially vitamin A, D and B_{12}. All species of fish contain considerable amounts of selenium, and shellfish are a good source of iodine. Fish, especially fatty fish, are rich in lipids, which can contribute up to 60 % of their total energy value. In particular, fish lipids are high in long chain n-3 polyunsaturated fatty acids (LC-n-3 PUFA or omega-3 fatty acids), in which eicosapentaenoic acid, EPA (C 20:5 n-3) and docosahexaenoic acid, DHA (C 22:6 n-3) predominate. For several fish, 18 % to 28 % of total lipid may be omega-3 fatty acids. Humans do not synthesize omega-3 fatty acids, and they are thus provided solely through the diet. In addition to fish, omega-3 fatty acids are found in certain marine algae, in certain plants (e.g. soybean, canola), and, importantly for newborns, in human milk.

Farmed fish (e.g. trout, salmon) have higher whole body lipids levels than their wild counterparts. The fatty acid composition of body fat in farmed fish can be influenced by the lipid composition of the feed. The relative omega-3 content of farmed fish tends to be lower than that of wild-caught fish, but the amount provided per portion is likely to be similar, due to higher fat content (2).

BENEFICIAL EFFECTS OF FISH CONSUMPTION

Beneficial effects of fish are primarily ascribed to omega-3 fatty acids, and have been studied in particular in regard to coronary heart disease, stroke, age-related maculopathy and growth and development. Indeed, omega-3 fatty acids have been shown to affect a variety of biological processes, including growth, neurological development, vascular health and immune responses.

Coronary heart disease

The first suggestion that fish consumption may have beneficial effects on coronary heart disease (CHD) came from studies in Greenland Inuits, who had a low rate of death from CHD and a high consumption of fish (7). Since then, several large epidemiological studies have investigated the association between fish consumption and CHD, and these have been recently summarized (6, 8-10). The overall evidence strongly indicates that fish consumption significantly lowers CHD mortality rate. Moderate consumption (250 mg to 500 mg per day of EPA and DHA, corresponding to 1 to 2 portions of fish per week) lowers the relative risk by 20 % to 30 %, with higher intakes having no substantial additional effects. Lower risk appears to be more strongly correlated with the consumption of fatty fish (e.g. salmon, herring, sardines) than lean fish (e.g. cod, catfish, halibut) (6). Such beneficial effects may be ascribed to the reported antiarrhythmic effects of omega-3 fatty acids (11, 12) and to their ability to reduce formation of atherosclerotic plaques (13, 14).

Stroke

More limited evidence also suggests that fish consumption is associated with the lower risk of stroke. Ischemic stroke, which comprises almost 90 % of all strokes, is caused by blocking of arteries leading to the brain. Fish consumption has been shown to reduce the risk of stroke by 12 % to 30 %, as evidenced by various epidemiological studies (6, 15-17). Underlying biological mechanisms for such protective effects may reside in the ability of omega-3 fatty acids to reduce platelet aggregation, to inhibit the 5-lipoxygenase pathway, and to reduce plasma levels of fibrinogen (18-20).

Age-related maculopathy

Two recent studies indicate that fish consumption decreases the risk of age-related macula degeneration, a leading cause of severe visual impairment and blindness among the elderly population. One study of 681 elderly American men showed that those who ate fish twice a week had a 36 % lower risk of macular degeneration (21). In another study, which followed more then 2000 Australian men and women over five years, people who ate fish just once a week reduced their risk by 40 % (22). Possible mechanisms include the ability of omega-3 fatty acids to neutralize free radicals in the eye, to prevent the formation of blood vessels, or to reduce inflammation.

Growth and development

Several lines of evidence in both animals and humans indicate that fish consumption, and omega-3 fatty acid in particular, play an important role in growth and development. Omega-3 fatty acids are essential for normal brain development, and demand is highest in the last trimester of pregnancy. Pre-and post-natal deficiencies of omega-3 fatty acids in rhesus monkeys

have been shown to affect visual acuity and dark-adapted retinograms (23). Conversely, in humans, DHA supplementation improved visual acuity in a dose-related manner (24). Various studies have also observed a positive effect on cognitive development. Daniels et al. (25) found that fish intake during pregnancy and by the infant postnatally was associated with higher developmental scores in a number of behavioral tests (e.g. the McArthur comprehension score). Fish consumption during pregnancy was found to be associated with higher infant cognition, as assessed by the percent novelty preference on visual recognition memory testing at six months of age (26). Maternal supplementation with omega-3 fatty acids during pregnancy and lactation was reported to increase children's intelligence quotient (IQ) at four years of age (27). Supplementation of the maternal diet with fish oil has been shown to increase DHA levels in breast milk and to slightly increase early language development (28). A quantitative analysis of eight randomized clinical trials estimated that increasing maternal DHA intake by 100 mg per day increases child IQ by 0.13 points (29). Finally, supplementation with omega-3 fatty acids has been shown to prevent pre-term birth, though findings were not consistent among studies (30), while no effects were seen in the growth of term infants (31).

CONTAMINANTS IN FISH

Fish can also contain a number of toxic contaminants, with metals and organohalogenated compounds being the most relevant. Among metals, methylmercury is the compound of most concern, but fish may also contain arsenic, cadmium, lead, and organotin compounds (2). Among organohalogenated contaminants, most notable are polychlorinated dioxins and furans, polychlorinated biphenyls (PCBs), various brominated flame retardants such as polybrominated diphenyl ethers, and various organochlorine insecticides. Only methylmercury and dioxin-like compounds are discussed here, as model contaminants.

Methylmercury

Most fish contain mercury as a contaminant, and almost 100 % of the mercury present in fish is methylmercury. Most fish have mercury levels below 0.5 mg kg^{-1}, but in several species, particularly large, old predatory fish such as sharks, swordfish, tuna and pike, mercury levels can exceed 1.0 mg kg^{-1}. A list of mercury levels in selected fish is given in Table 1. Methylmercury in fish meat is bound to proteins; skimming, trimming of fish, or cooking does not significantly reduce its concentration. Dietary methylmercury is readily absorbed and easily crosses the placental barrier and the blood-brain barrier. Significant concentrations can be found in blood, brain, toenails and hair, with the latter two utilized as indicators of long-term mercury exposure in population studies (32, 33).

Concerns for methylmercury are based primarily on its developmental neurotoxicity, but recent studies have also addressed the possibility that this metal may represent a risk factor for cardiovascular disease. The developmental neurotoxicity of methylmercury became evident in the 1950s in Japan, where a large number of cases of a new syndrome (Minamata disease) were seen in children born to mothers who had consumed fish from contaminated waters (34). The syndrome was characterized by spasticity, blindness, and mental retardation. The cause was identified as methylmercury that had accumulated in fish in the bay, after its discharge (as inorganic mercury compounds) by a local factory, and its biomethylation by microorganisms in aquatic sediments. A similar outbreak of poisoning occurred several years later in Iraq, where grains treated with alkylmercury fungicides and destined to planting, were erroneously consumed (35).

More recent studies have focused on prenatal exposures to lower doses of methylmercury, in populations with high fish consumption. Two studies in New Zealand and in the Faroe Islands reported small decrements in IQ and impairments of memory, attention, language and visuospatial perception in exposed children (36-38). On the other hand, a third study in the Seychelles Islands found no evidence of an association between methylmercury exposure through fish consumption and neurodevelopmental effects in children (39). These differences may be ascribed to different dietary patterns (e.g. whale meat and whale bubbler consumption in the Faroe Island, with concomitant exposure to PCBs), and/or to the higher nutrient content in fish from the Seychelles (40). Based on positive results found in the two studies, the US National Academy of Sciences has concluded that evidence exists for fetal neurotoxicity of methylmercury even at low doses (33). Exposure limits for methylmercury have been established; the

provisional tolerable weekly intake (PTWI) ranges from 0.7 μg kg^{-1} (33) to 1.6 μg kg^{-1} (41, 42).

Recent studies have also examined the possible association between mercury exposure and the risk of cardiovascular disease. Evidence so far appears to suggest that mercury may increase the risk of cardiovascular disease (43-45), though negative findings have also been reported (46). Mercury may promote atherosclerosis and hence increase the risk of myocardial infarction in several ways. Among these, mercury promotes the formation of free radicals, binds to thiol groups and may inactivate the antioxidant properties of glutathione, and may induce lipid peroxidation. It also binds to selenium and reduces bioavailability of selenium for incorporation into glutathione peroxidase (47).

Dioxin-like compounds

Humans are exposed to dioxins and dioxin-like PCBs (DL-PCBs) primarily through the diet, and though meat and dairy products are the largest contributors to total intake (48), these contaminants are also present in fish. Levels of dioxins and dioxin-like PCBs in fish are highly variable, and depend mainly upon the lipid in the fish diet. A survey of fish in the European Union showed levels of these compounds ranging from 1.4 ng kg^{-1} to 1.5 ng kg^{-1} (2). A recent study found significant concentrations of dioxins and dioxin-like PCBs in salmon, particularly in farmed salmon from Europe (49). Fish oil and fish meal contribute to 98 % of these contaminants in the diet of carnivorous fish (2). As these compounds are lipophilic, high levels are found in fatty fish such as salmon and herring. Removal of skin and associated fat has been shown to reduce levels of these contaminants in fish.

There are 210 different congeners of chlorinated dibenzo-*p*-dioxins and furans (referred here as dioxins), and 209 congeners of PCBs; among the latter, several exhibit toxicological effects similar to dioxins (mediated by activation of the aryl hydrocarbon receptor), and are thus called dioxin-like PCBs. All these compounds are standardized against the most potent dioxin, TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin), and potential toxicities are calculated using toxic equivalency factors.

TCDD is classified as a group I carcinogen, i.e. carcinogenic to human (50), and cancer risk is the greatest toxicological concern for all dioxins and dioxin-like PCBs. Additional adverse effects of these compounds include immunotoxicity (51), reproductive toxicity, endocrine disruption, and developmental neurotoxicity (52). Dioxin exposure may also be associated with an increased risk of diabetes (53).

RISK-BENEFIT CONSIDERATIONS

As with most life choices, the consumer needs to balance the benefits of eating fish with the risk of potential adverse health effects due to the presence of contaminants. With regard to methylmercury, developmental neurotoxicity is the major concern. Advisories from various national and international agencies recommend that women who might become pregnant, and who are pregnant, nursing mothers, and young children, do not consume fish such as shark, swordfish and tilefish, which generally contain high levels of mercury. However, they should consume fish (1 to 2 servings per week), that is low in methylmercury content (see Table 1). Furthermore, because of similar considerations, they should choose canned light tuna over albacore (white) tuna. In adults, methylmercury contamination of fish may modestly reduce the beneficial cardiovascular effects of fish intake, but overall benefits of moderate fish consumption seem to outweigh the risks (6).

Contamination of fish, particularly fatty fish, with dioxin-like compounds poses another challenge,

Table 1 *Mercury levels in fish*

Fish	Mercury / mg kg^{-1}	
	Mean	Max.
Anchovy	0.04	0.34
Sardines	0.02	0.03
Herring	0.04	0.13
Salmon	0.01	0.19
Flounder	0.04	0.18
Cod	0.10	0.42
Carp	0.14	0.27
Halibut	0.25	1.52
Tuna	0.38	1.30
Swordfish	0.98	3.22
Shark	0.99	4.54
Shrimp	ND	0.05
Clam	ND	ND
Oyster	0.01	0.25
Scallop	0.05	0.22

Data from the US Food and Drug Administration (http://www.cfsan.fda.gov/~frf/sea-mehg.html)

particularly because of the long half-life of these compounds in the human body. As dioxins and dioxin-like PCBs are present in meats and dairy products, substituting fish with these food products would not reduce exposure to these compounds, while negating beneficial effects of fish (2). Consumption of dioxin-contaminated fish may increase overall cancer risk, particularly if high levels of these contaminants are present (54, 55). However, it has also been estimated that cardiovascular benefits outweigh cancer risks by 10 to 1000 fold, depending on the level of contamination (6).

Results from a study by Hites et al. (49) indicated that farmed salmon, particularly from Europe, had higher levels of dioxins than wild-caught Pacific salmon or farmed salmon from South America. However, other data indicate that there are no consistent differences between wild and farmed fish, and in some cases (e.g. wild herring from the Baltic Sea) contaminant levels may be higher in wild-caught fish (2).

THE WAY FORWARD

Moderate fish consumption (1 to 2 servings per week) should be included in a balanced diet, as it provides sufficient intake of omega-3 fatty acids recommended for benefits to health. Levels of contaminants in wild fish can only be reduced by long-term control of emissions of pollutants in the environment. On the other hand, fish farming offers the possibility of controlling contaminant levels in fish in order to minimize the risks while maintaining its benefits. Fish oil and fish meal are the most important sources of contamination of farmed fish feed with dioxin-like compounds. Replacement of fish oil with vegetable oil significantly reduces levels of dioxin and dioxin-like PCBs in fish. However, a marked reduction of EPA and DHA is also observed (Table 2), thus reducing the beneficial component of fish. Bell et al. (56) recently showed that when farmed salmon is fed vegetable oil followed by fish oil, loss of omega-3 fatty acids is kept to a minimum, while contaminant levels are substantially reduced (Table 2). This example indicates that novel aquaculture strategies can be developed to ensure ample fish supply that maintains high omega-3 fatty acid levels, while reducing those of harmful contaminants.

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Table 2 *Effect of replacement of fish oil with vegetable oil in feed on contaminants and omega-3 fatty acid content of salmon*

Diet	Dioxins	DL-PCBs	EPA	DHA
Fish oil (FO)	100	100	100	100
Vegetable oil (VO)	25	36	25	25
VO+FO	40	53	80	80

Results are expressed as percentage of content in fish oil-fed salmon. Adapted from: Bell et al. (56)
DL-PCBs = dioxin-like polychlorinated biphenils
EPA = eicosapentaenoic acid
DHA = docosahexaenoic acid

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Sažetak

ZAGAĐIVALA U RIBAMA: RAZMATRANJA RIZIKA I DOBROBITI

Ribe su zdravi izvor prehrambenih proteina te su bogate hranjivim tvarima poput omega-3 masnih kiselina. Dokazano je blagotvorno djelovanje konzumacije ribe pri koronarnim srčanim bolestima, moždanom udaru, makularnim degeneracijama uzrokovanim dobi te rastom i razvojem. Međutim, ovakvo djelovanje može osujetiti prisutnost zagađivala poput metilžive (MeHg), dioksina, poliklorbifenila (PCB-a) te drugih halogeniranih perzistentnih organskih zagađivala. MeHg je znana po neurotoksičnome djelovanju tijekom razvoja, na što su upozorila neka istraživanja na životinjama te slučajevi otrovanja ljudi u Japanu i Iraku. Riba je glavni izvor izloženosti opće populacije metilživi, a veliki grabežljivci (sabljarka, tuna) sadržavaju najveće razine ovog zagađivala. Regulacijske su agencije stoga odredile privremeni podnošljivi tjedni unos od 0.7 μg kg^{-1} do 1.6 μg kg^{-1}. Zabrinutost zbog zagađenja ribe dioksinima i PCB-ima nalik dioksinu proizlazi iz njihove kancerogenosti, imunotoksičnosti te reprodukcijske i razvojne toksičnosti. Izgleda da uzgojene i ulovljene neuzgojene ribe imaju podjednake razine zagađivala. Stoga valja imati na umu preporuke za ograničenje potrošnje pojedinih vrsta riba u djece, trudnica i žena u reprodukcijskoj dobi. Promišljanja koja pažljivo odvaguju rizike i dobrobit trebaju promicati konzumaciju ribe uz smanjenje izloženosti toksičnim zagađivalima.

KLJUČNE RIJEČI: *dioksini, koronarna srčana bolest, metilživa, poliklorbifenili, razvojna neurotoksičnost*

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