



Estimation of Polychlorinated Biphenyls Intake through Fish Oil-Derived Dietary Supplements and Prescription Drugs in the Japanese Population

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HIGHLIGHTS

- Median polychlorinated biphenyls levels in fish oil products was 2.2 ng/g oil wt. with a range of <MDL-720 ng/g oil wt.
- Polychlorinated biphenyls in supplements containing shark liver oil and cod liver oil were higher than the other ones.
- Polychlorinated biphenyls exposure was negligible for Japanese adults through fish oil-derived products.

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Acronyms and abbreviations

MDL=Method Detection Limit
PCB=Polychlorinated Biphenyl
TDI=Tolerable Daily Intake

ABSTRACT

Background: Oily fish and their extracted oils may be a source of polychlorinated biphenyls (PCBs) which can induce toxic effects on the consumers. The main aim of this survey was estimation of PCBs intake through fish oil-derived dietary supplements and prescription drugs in the Japanese population.

Methods: PCBs levels were determined in 20 fish oil-derived dietary supplements and 6 oil-derived prescription drugs from the Japanese market using Gas Chromatography-Mass Spectrometry. Then, the daily exposure to PCBs was estimated. Data were statistically analyzed using JMP software suite.

Results: Totally, 17 of the 26 fish oil-derived products were contaminated with PCBs. The median PCB concentrations in the total set of fish oil-derived products was 2.2 ng/g oil wt. with a range of <MDL-720 ng/g oil wt. The average total daily intake of PCBs was estimated to be ranged from 770 to 2800 ng/day in the Japanese population.

Conclusion: PCBs intakes through fish oil-derived dietary supplements and prescription drugs in the Japanese adults were much lower than tolerable daily intake.

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Introduction

Around 2000, the global market for dietary supplements began to grow rapidly with the introduction of many new products (Dwyer et al., 2018; Greger, 2001; Stanton et al., 2001). Since then, the use of dietary sup-

plements has continued to increase among the general population, including children (Dwyer et al., 2013; Godwin et al., 2013; Huybrechts et al., 2010).

Recently, the popularity of fish oil supplements has

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increased in Japan. Fish oil is a source of long-chain n-3 polyunsaturated fatty acids, such as eicosapentaenoic acid and docosahexaenoic acid which decrease serum triglyceride levels (Breslow, 2006) and reduce the risk of developing cardiovascular disease and hypertension (Mori and Woodman, 2006; Mozaffarian and Wu, 2011). Some studies have also found that n-3 fatty acid supplementation by using fish oil products confers benefits on cognition (thinking, reasoning, memory), behavior, and school performance among healthy children (Al-Ghannami et al., 2019; Kuratko et al., 2013; Raine et al., 2015; Stonehouse, 2014); consequently, fish oil supplements have been marketed towards children with dyslexia, dyspraxia, attention-deficit hyperactivity disorder, and other similar disorders (Fernandes et al., 2006). Also, the popularity of fish oil products has increased concurrently with scientific research showing the benefits of fish oils in addressing a number of disease conditions, including hypertriglyceridemia, peripheral artery disease, cardiovascular disease, stroke, hypertension, renal injury, rheumatoid arthritis, and autoimmune disorders (Mason, 2000; Schmitz and Antony, 2002).

However, oily fish and their extracted oils may be a source of polychlorinated biphenyls (PCBs) on human (Jacobs et al., 2004; Shim et al., 2003; Storelli et al., 2004; Su et al., 2012). PCBs are included in the Stockholm Convention's list of persistent organic pollutants because they persist in the environment, bioaccumulate along the food chain, and are toxic to human and wildlife (UNEP, 2017). PCBs are ubiquitous pollutants and have been detected in fish all over the world due to the high potential of these chemicals to undergo atmospheric transport (Borgå et al., 2004; Green and Knutzen, 2003; Parera et al., 2013; Storelli et al., 2005; Ueno et al., 2003). Concern has been expressed about the high PCBs exposure of infants during pregnancy and nursing, because PCB exposure in infants and children is associated with adverse health effects including neurobehavioral disturbances (Jacobson et al., 1990; Nakai et al., 2004; Stewart et al., 2000, 2006), intellectual as well as developmental disabilities (Neugebauer et al., 2015; Tatsuta et al., 2014; Vreugdenhil et al., 2002), and increased risk of infection or allergy (Weisglas-Kuperus et al., 2000).

The contaminations of PCBs are the priority to investigate the quality of fish oil products. Indeed, several investigations have reported PCBs concentrations in fish oil supplement, so far. It was reported the concentrations of PCBs in supplements using shark liver oil in Japan (Akutsu et al., 2006), in fish and marine animal oil in Canada (Bourdon et al., 2010), UK (Fernandes et al., 2006), USA (Shim et al., 2003), and Italy (Storelli et al., 2004), and in fish and vegetable oil in UK (Jacobs et al., 2004) and Spain (Martí et al., 2010). Although PCBs

contaminations in fish oil supplements have been reported, those in "prescription drug" made from fish oil has not been available, yet.

Here, we determined and compared the concentrations of PCBs in fish oil-derived dietary supplements and oil-derived prescription drugs purchased on the Japanese market. We then conducted an exposure assessment of PCBs in the Japanese population, taking into account food consumption and the use of fish oil-derived dietary supplements or prescription drugs.

Materials and methods

Sample collection

Twenty fish oil-derived dietary supplements from 19 manufacturers and 6 fish oil-derived prescription drugs from 4 manufacturers were purchased from several retailers and pharmacies in Japan between September 2014 and January 2015 (Table 1). These products are generally in use. The oils in these products were made from shark liver, lamprey, cod liver, or mixed small fish (e.g., anchovy, sardine, mackerel). All the products were in capsule form. For each product, capsules equal to the proposed dose per day as indicated on the product label were cut open and the oils were pooled as one sample.

Chemical analysis

The concentrations of PCB isomers in the fish oil-derived products were determined as reported previously (Haque et al., 2017) with slight modifications. Briefly, 0.5 g of sample oil was mixed with a surrogate standard mixture containing $^{13}\text{C}_{12}$ -PCBs from mono- to deca-chlorinated biphenyl (Wellington Laboratory, USA). The oil/surrogate standard mixture was then subjected to Gel Permeation Chromatography (GPC) for clean-up. The GPC fraction containing the target compounds was concentrated and passed through an activated florisil-packed glass column for further clean-up. The eluate was micro-concentrated under nitrogen gas flow after adding an internal standard containing $^{13}\text{C}_{12}$ -PCB-105 (Cambridge Isotope Laboratories, Inc., USA) as a performance standard. PCBs quantification was performed by Gas Chromatography-Mass Spectrometry (GC-MS: 6890N/5973 inert; Agilent, USA) in selected ion monitoring mode with an HP-5ms column (30 m length, 0.25 mm i.d., 0.25 μm film thickness; Agilent, Inc., USA).

Quality control of PCBs analysis

The recoveries of the $^{13}\text{C}_{12}$ -PCB surrogate standards ranged from 70 to 120%. PCB congeners were quantified by using an isotope dilution method using the corresponding homologue of each $^{13}\text{C}_{12}$ -PCB. PCB

levels were determined as ng/g on an oil weight basis. The Method Detection Limit (MDL) was calculated as the threefold standard deviation of the background peak (or the threefold standard deviation of the signal-to-noise ratio on lowest concentration of the authentic standard peak when there was no background peak) for the procedural blank ($n=5$). The MDL for 3CBs and 4CBs were 0.05 ng/g oil wt. and the other PCBs were 0.1 ng/g oil wt.

A standard reference material (fish oil, EDF-2525; Cambridge Isotope Laboratories, Inc., USA) was also analyzed ($n=5$) by using the analytical procedure outlined above, and the data obtained from our laboratory showed acceptable agreement (tri-PCBs: $104\pm13\%$, tetra-PCBs: $107\pm15\%$, penta-PCBs: $101\pm16\%$, hexa-PCBs: $105\pm15\%$, hepta-PCBs: $104\pm12\%$, octa-PCBs: $96\pm2.8\%$, nona-PCBs: $86\pm20\%$, as well as deca-PCBs: $116\pm14\%$).

Estimation of daily intake of PCBs

The daily intake of PCBs in the Japanese population was estimated taking into account food consumption and the use of fish oil-derived dietary supplements and prescription drugs. First, we evaluated the daily exposure to PCBs through fish oil supplements and prescription drugs by multiplying the PCB concentrations determined in the present study with the proposed dose according to each product label, which afforded a range of <MDL to 2000 ng/day. Next, the daily exposure to PCBs through food consumption was determined. The Japanese population consumes a lot of fish; the average PCBs intake in the Japanese population through food consumption is 14 ng/kg body weight/day, with an estimated 80% of that

intake coming from the consumption of seafood (Tokyo Metropolitan Government, 2011). Also, an average adult body weight was assumed as 55 kg (Ministry of Health Labour and Welfare of Japan, 2011).

Statistical analysis

Values less than the MDL were considered as zero in the calculation of total concentration. Inter-group comparisons (Wilcoxon rank sum test) were conducted with the JMP software suite (V. 12; SAS Institute, Inc., USA).

Results

Totally, 17 of the 26 fish oil-derived products were contaminated with PCBs shown in Table 2. The median PCB concentrations in the total set of fish oil products was 2.2 ng/g oil wt. with a range of <MDL-720 ng/g oil wt. Also, the median PCB levels in the dietary supplements was 4.2 ng/g oil wt. ranged from <MDL to 720 ng/g oil wt., whereas in the prescription drugs it was 3.0 ng/g oil wt. with a range of <MDL-7.1 ng/g oil wt. However, no significant ($p>0.05$) difference was found regarding PCB levels between the dietary supplements and prescription drugs. PCBs concentrations in the supplements containing shark liver oil and cod liver oil were significantly higher ($p<0.05$) than those in the other supplements and also prescription drugs (Table 2).

The average intake of PCBs through food consumption was determined as 770 ng/day. Thus, the average total daily intake of PCBs in the Japanese population was estimated to be ranged from 770 to 2800 ng/day (Figure 1).

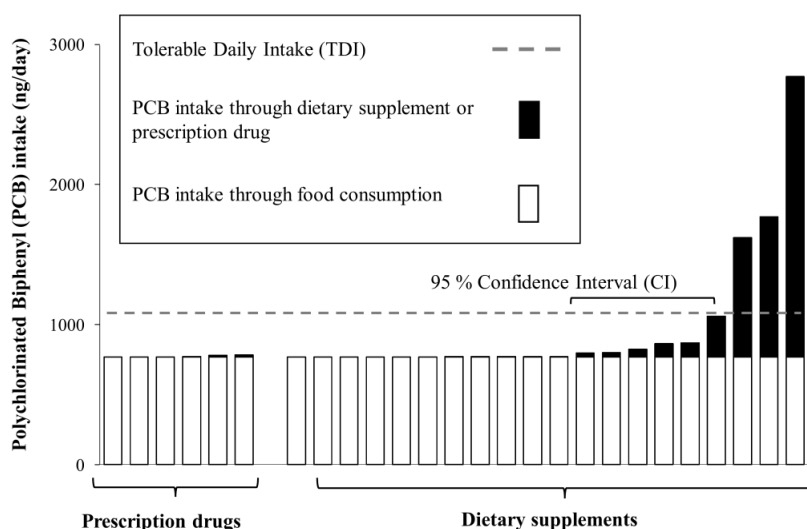


Figure 1: Exposure assessment of polychlorinated biphenyls intake through food consumption and fish oil-derived dietary supplements or prescription drugs in the Japanese population

Table 1: Characteristics of the fish oil products examined in the present study

Type	Ingredient	Sample ID	Country of origin	Proposed dose(g/day)**
Dietary supplement	Shark liver oil	SLO1	NA	1.5
		SLO2	New Zealand	2.3
		SLO3	NA	1.3
		SLO4	NA	1.3
		SLO5	NA	2.8
	Cod liver oil	CLO1	Japan	1.5
		CLO3	Japan	2.0
	Lamprey oil	LaO1	NA	1.3
		LaO2	NA	1.3
	Fish oil	FO5	Norway	0.5
		FO6	NA	0.4
		FO7	NA	1.4
		FO8	NA	1.7
		FO9	NA	2.2
		FO10-1*	Japan	1.7
		FO10-2*	Japan	1.7
		FO11	NA	1.9
		FO12	Chile	2.0
		FO13	NA	1.6
		FO14	NA	1.7
Prescription drug	Fish oil	FO1-1*	NA	4.0
		FO1-2*	NA	4.0
		FO2	Chile	2.7
		FO3	Chile	1.8
		FO4-1*	Chile	3.4
		FO4-2*	Chile	3.4

NA: Not Available

* Different lot number on the same product brand

** Proposed dose according to the label instruction of each product

Table 2: Polychlorinated biphenyls (PCBs) concentrations in the fish oil products examined in the present study

Type	Ingredient	Sample size	PCBs (ng/g oil wt.)		
			Median	Minimum	Maximum
Dietary supplement	Shark liver oil	5	69	23	720
	Cod liver oil	2	350	190	500
	Lamprey oil	2	73	<MDL	73
	Fish oil	11	2.2	<MDL	17
	All supplement	20	4.2	<MDL	720
Prescription drugs	Fish oil	6	3.0	<MDL	7.1
All samples		26	2.2	<MDL	720

<MDL: less than Method Detection Limit (0.1 ng/g oil wt.)

Discussion

In the present survey, the median PCBs concentrations in the total set of fish oil products was 2.2 ng/g oil wt. with a range of <MDL-720 ng/g oil wt. In comparison, supplements (fish and shark liver oil) analyzed in a pre-

vious Japanese study had PCBs concentrations range of 16-340 ng/g oil wt. (Akutsu et al., 2006). Another survey indicated that the supplements (fish and seal oil) purchased on the Canadian market in 2006 had a PCBs

concentrations range of <0.8-790 ng/g oil wt. (Bourdon et al., 2010); Martí et al. (2010) found PCBs concentrations range of 0.17-120 ng/g oil wt. in supplements (fish and vegetable oil) collected from Spanish market. The range of PCBs levels in supplements (fish oil) obtained from markets of USA (Shim et al., 2003), Italy (Storelli et al., 2004), and UK (Fernandes et al., 2006) markets were 10-280, 25-200, and <MDL-270 ng/g oil wt., respectively. This study is consistent with these previously reported values regarding dietary supplements in some other countries. However, since there are no previous reports on PCB contamination of fish oil-derived prescription drugs, a comparison could not be made.

The examined fish oil products in this study were manufactured using various marine species as raw materials. The supplements containing shark liver oil and cod liver oil showed higher PCB levels than the other supplements and prescription drugs examined in the current investigation. Information in the literature on shark liver is limited; however, higher concentrations of PCBs in shark than various small-fish have been previously reported by Borgå et al. (2004). Shark, cod, and lamprey are carnivorous and occupy higher trophic levels than small fish, which likely results in a higher bioaccumulation of PCBs.

According to the results of this research, that the concentration of PCBs in the dietary supplements was relatively higher than that in the prescription drugs, however, no significance difference was seen. This is likely due to differences in the manufacturing process used for the two types of product. The fish oil used in several brands of dietary supplements is manufactured by using a process that does not remove contaminants such as cold centrifugal extraction, mesh filtration, deoxygenation by vacuum, and deodorization using a nitrogen flow. In contrast, the prescription drugs most likely contained highly purified eicosapentaenoic acid and docosahexaenoic produced by a process that removes PCBs and other environmental pollutants such as heat separation, ethyl ether derivatization, vacuum separation, and column separation (Yazawa, 1994).

Finally, we conducted an exposure assessment of PCBs intake in the Japanese population (Figure 1). Assuming a TDI for PCBs of 20 ng/kg body weight/day (Faroon et al., 2003), a 55-kg person will have a TDI of 1100 ng/day. In this scenario, PCBs intake through food consumption (770 ng/day) accounts for 70% of the TDI, meaning that the TDI will be exceeded by the intake of an additional 240 ng/day of PCBs. As a result of this assessment, PCBs intake through prescription drugs with food consumption was much lower than those of TDI. Despite PCBs intake of some fish oil supplements (shark and cod liver oils) with food consumption exceeded of TDI, those values were outlier of the 95% Confidence Interval (CI) among supplements (Figure 1). These find-

ings suggest that the risk associated with fish oil-derived products is negligible for Japanese adults. In compassion, TDI values estimated in this survey was similar to those reported in Canada (Bourdon et al., 2010), UK (Fernandes et al., 2006), USA (Shim et al., 2003), and Italy (Storelli et al., 2004). However, it is assumed that many pregnant and nursing women in Japan often use dietary supplements. Therefore, fetuses and infants may be exposed to high levels of PCBs which can be transferred from mother to fetus and infant through the placenta and maternal breast milk (Aylward et al., 2014).

Conclusion

PCBs intakes through fish oil-derived dietary supplements and prescription drugs in the Japanese adults were much lower than TDI. However, since fetuses and infants are especially vulnerable to PCBs, the present data suggest that the Japanese pregnant and nursing women should avoid excessive consumption of fish oil-derived dietary supplements.

Author contributions

Y.M., K.N., I.S., K.A., and D.U. designed the study and wrote the manuscript; K.A., N.T., M.I., T.H., and N.R. conducted the experimental work and analyzed the data. All authors read and approved the final manuscript.

Conflicts of interest

There is no conflict of interest.

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