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REGULAR ARTICLE

Paradoxical increases in serum levels of highly chlorinated PCBs in aged women in clear contrast to robust decreases in dietary intakes from 1980 to 2003 in Japan

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Abstract
Objective Exposure to polychlorinated biphenyls (PCBs) is considered to have culminated between 1950 and 1970 in Japan, and exposure through diet, the major exposure route, has decreased significantly over the last 10 years. The primary goal of the present study was to investigate the long-term trends and congener profiles of serum and dietary levels of PCBs using historical samples.

Methods Using banked samples collected in 1980, 1995, and 2003 surveys, we determined the daily intakes and serum concentrations of 13 PCB congeners (#74, #99, #118, #138, #146, #153, #156, #163, #164, #170, #180, #182, and #187) in women.

Results The total daily PCB intake [ng/day, geometric mean (geometric standard deviation)] decreased significantly from 523 (2.5) in 1980 to 63 (3.2) in 2003. The

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serum total PCB level (ng/g lipid) in women <40 years of age decreased significantly from 185 (1.8) in 1980 to 68 (1.8) in 2003. In contrast, the level in women >50 years of age increased significantly from 125 (1.7) in 1980 to 242 (1.7) in 2003. Specifically, the serum concentrations of hexa (#138, #146, #153, #156, #163, and #164) and hepta (#170, #180, #182, and #187) congeners increased significantly. A comparison of the serum PCB levels of women born from 1940 to 1953 revealed that their serum total PCB level was significantly higher in the 2003 survey [242 (1.7), $n = 9$] than in the 1995 [128 (2.0), $n = 17$] surveys. This increase in the total PCB level was attributable to increases in the hepta congener groups.

Conclusion Present results suggest a decreased rate of elimination of hepta congeners with aging in females, rather than a birth-generation phenomenon.

Keywords Polychlorinated biphenyl · Congener profiles · Diet · Serum · Aging · Decrease in metabolism

Introduction

Polychlorinated biphenyls (PCBs), which were produced from 1930 to the 1970s, are still found in the environment. Although human exposure to PCBs has been persistent, it has recently decreased significantly [1, 2]. Although the mechanisms of this reduction are still unknown, it is speculated to be due to degradation and/or diffusion under the control of global dynamics [3].

We recently established a human specimen bank for monitoring long-term exposure to persistent organic pollutant (POPs). The seeds of the sample bank were collected by Prof. Ikeda and his colleagues in the 1980s and 1990s [4, 5]. Samples newly collected in 2003–2004 have now been added to expand the quantities available in the bank.

Using samples in the human specimen bank from the 1980s and 1990s, we previously showed that exposure to PCBs through the dietary route decreased significantly in the mid-1990s [6]. However, it remains unanswered whether there are long-term decreasing trends for the serum and daily intake levels of PCBs.

The human PCB body burden reflected by the serum congener profile is an integrated function of various factors, including the source, route, timing of exposure, and individual determinants of metabolism and clearance [7]. An age-associated increase in the PCB body burden has been emerging as a common phenomenon in many countries in recent studies [8–11]. However, most of the observations have been based on samples collected at a single time point. Exposure to PCBs is considered to have culminated between 1950 and 1970 in Japan. Therefore, generations born between 1940 and 1960 are considered to have been exposed to PCBs from childhood to young adulthood, while generations born after 1970 are thought to have experienced less exposure to PCBs due to the banning of PCB production and use in Japan in the 1973. However, it remains uncertain whether the observed age-associated changes in the levels and profiles of serum PCBs represent a generation phenomenon or are associated with decreased elimination or food preferences.

PCBs are known to be metabolized to their phenolic counterparts through dehalogenation and hydroxylation by P450s [12–15]. These counterparts are generally more hydrophilic than the parent compounds and are therefore more easily eliminated from the body than the parent PCB congeners [12]. The metabolic activity mediated by P450 is known to decrease with age [16]. Therefore, there might be a possibility that the timing of exposure, metabolism, and dietary profiles of PCB congeners are major factors that determine the serum levels of PCBs.

The primary goal of the present study was to investigate the long-term trends and congener profiles of the serum and dietary levels of PCBs using historical samples. The samples analyzed were collected in three surveys of different periods between 1980 and 2003. All three surveys contained generations that were born between 1940 and 1953. These generations are expected to provide further insights into the long-term trend for the human body burden of PCBs.

Materials and methods

Target population, serum samples, and food samples

Serum and food samples collected from 1977 to 1981 (the 1980 survey) [5], 1991 to 1997 (the 1995 survey) [4], and 2003 to 2004 (the 2003 survey) have been stored in our sample bank. The protocol for sample collection in the 1980 and 1995 surveys has been documented previously [6]. Samples were collected from both males and females. In the 1980 and 1995 surveys, serum and food samples were collected from 1977 to 1981 and 1991 to 1997, respectively, in eight prefectures in eight districts: Hokkaido, Miyagi (Tohoku), Gunma (Kanto), Ishikawa (Chubu), Shimane (Chugoku), Kochi (Shikoku), Kagoshima (Kyushu), and Okinawa. In these surveys, the participants donated serum as well as duplicate portions of the food that they had consumed over the previous 24 h. In the 2003 survey, we collected serum samples and meals in eight prefectures in six districts: Akita and Miyagi (Tohoku), Fukui and Gifu (Chubu), Osaka and Kyoto (Kansai), Yamaguchi (Chugoku), Kochi (Shikoku), and Okinawa. Serum samples were donated when the subjects attended an annual health checkup. Information was

limited to age and gender. We collected trios of meals (breakfast, lunch, and dinner) with water (1.5 L) each day in the spring and fall seasons. The combination of breakfast, lunch, and dinner was arranged so that the food menus followed the most common consumption patterns of subjects aged between 30 and 60 years in the local community areas in the season of sampling. A total of 50 trios and water were purchased from a local commercial vendor in each sampling site. Each trio of meals was carefully homogenized with the 1.5 L of water to prevent contamination and a portion of the homogenate was stored at −20°C in two 1-L polypropylene tubes.

Blood samples were taken from a cubital vein late in the morning. Serum samples were separated by centrifugation at 1,500×g for 15 min, and stored at −20°C. All samples have been stored in the Department of Health and Environmental Sciences, Kyoto University Graduate School of Medicine. Quality controls for contamination monitoring were checked as previously described [6].

The study population of the present study was limited to female participants because sampling in the 2003 surveys was limited to females. We randomly selected participants from each sampling site.

A verbal form of informed consent was obtained for the 1980 and 1995 surveys and written informed consent was obtained for the 2003 survey. Participation in the surveys was completely voluntary. In 2003, we obtained approval for delivery and analysis of the serum samples from the Ethics Committee of the Kyoto University Graduate School of Medicine on 14 November 2003 (E25).

Determination of PCBs

We determined the concentrations of 13 PCB congeners (IUPAC #74, #99, #118, #138, #146, #153, #156, #163, #164, #170, #180, #182, and #187) in the serum and food homogenates. In the present study, we classified the tetra congener (#74) and penta congeners (#99 and #118) as penta CBs, hexa congeners (#138, #146, #153, #156, #163, and #164) as hexa CBs, and hepta congeners (#170, #180, #182, and #187) as hepta CBs. These congeners were selected because they represent the most predominant congeners in the environment [2, 17, 18]. Determination of these congeners was carried out as previously reported [19]. Briefly, 1 mL serum was used to determine the serum levels of the PCBs. For PCBs in food, 2 g food homogenate was used. For sample blanks and tube extracts, five samples were used for each preparation. High-resolution gas chromatography/high-resolution mass spectroscopy (HRGC/HRMS), which consisted of an AutoSpec-Ultima (Micromass, UK) and a HP-6890 Series gas chromatograph (Agilent Technologies, Inc., USA), was used for analysis. The column used was a HT8-PCB capillary column (0.25 mm I.D. × 60 m; Kanto Chemical Co., Inc., Japan). The analytical conditions used were described previously [19].

All analyzes were quantified by the isotope dilution method. The recovery of spiked internal standards was calculated against the spikes. The limit of detection (LOD) and the limit of quantification (LOQ) for each PCB congener were 0.02 and 0.2 pg/ml, respectively.

The serum levels of PCBs are expressed as ng/g lipid [20]. The serum total cholesterol and triglyceride levels were measured using an aliquot of each serum sample [21]. The daily intakes of PCBs in food per person are expressed as ng/day.

Statistical analysis

The concentrations of PCBs showed log-normal distributions and were log-transformed for all analyzes. The PCB concentrations are presented as geometric mean (GM) with geometric standard deviation (GSD). Where appropriate, arithmetic mean ± standard deviation (M ± SD), range, medians, 25th percentile, and 75th percentile are also shown.

Database management and all statistical analyzes were performed with SAS software (version 8.2; SAS Institute). Analysis of variance (ANOVA) was used for all analyzes. A p value of less than 0.05 was considered to be statistically significant.

Results

Sampling time and demographic features of the participants

Variation of sampling periods is shown in Table 1. A total of 40 serum samples from each of the 1980 and 1995 surveys and 90 serum samples from the 2003 survey were analyzed. For the 1980 and 1995 surveys, the samples were randomly selected for five participants per sampling site. For the 2003 survey, ten serum samples were randomly selected for each sampling site. We failed in the preparation of one serum sample for determination, collected in Hokkaido in 1980.

The mean ages (SD) and birth years (SD) are shown in Table 1. Height, body weight, and BMI were available only for the 1980 and 1995 surveys. The mean birth years were 1937.9 (9.8), 1942.1 (9.7), and 1966.8 (9.9) in the 1980, 1995, and 2003 surveys, respectively. The sample recoveries were more than 97 ± 2% ($n = 5$). All five sample blanks and tube extracts were found to be less than the LOD.

Table 1 Demographic factors of the study participants

Survey year	1980	1995	2003	Total
No.	39[a]	40	90	169
Sampling period				
Mean ± SD	1980.4 ± 0.7	1995.3 ± 0.8	2003 ± 0	1987.8 ± 7.5
Range	1979–1981	1994–1997	2003	1979–2003
Q1	1979	1994	–	1980
Q2	1981	1995	–	1988
Q3	1981	1996	–	1995
Age (years)				
Mean ± SD	42.4 ± 9.9	53.2 ± 10.1	36.2 ± 9.9	41.7 ± 12.0
Range	24–65	37–76	20–58	20–76
Q1	37	44	29	32
Q2	41	55	35	40
Q3	51	61	44	50
Birth year				
Mean ± SD	1937.9 ± 9.8	1942.1 ± 9.7	1966.8 ± 9.9	1954.1 ± 16.7
Range	1916–1957	1920–1958	1945–1983	1916–1983
Q1	1930	1935	1959	1941
Q2	1940	1941	1969	1954
Q3	1944	1951	1974	1969
Height (cm)				
Mean ± SD	150.5 ± 6.6	152.5 ± 5.6	NA	NA
Range	136.7–164.5	138.6–162.5	NA	NA
Q1	136.7	138.6	NA	NA
Q2	150.0	152.7	NA	NA
Q3	154.9	157.1	NA	NA
Body weight (kg)				
Mean ± SD	53.4 ± 7.1	57.6 ± 9.8	NA	NA
Range	43.5–72.0	42.8–78.2	NA	NA
Q1	43.5	42.8	NA	NA
Q2	52.0	55.6	NA	NA
Q3	59.0	62.2	NA	NA
BMI (kg/m^2)				
Mean ± SD	23.6 ± 2.8	24.8 ± 4.2	NA	NA
Range	19.5–31.8	18.0–33.6	NA	NA
Q1	24.8	27.0	NA	NA
Q2	23.9	23.9	NA	NA
Q3	21.9	21.6	NA	NA

[a] One sample was lost during preparation

NA not available

Daily intakes of PCBs through food

Five diet samples paired to serum samples were chosen from the eight sampling sites in the 1980 and 1995 surveys. In the 2003 survey, ten diet samples were randomly selected for each sampling site, with the exception of Yamaguchi (Chugoku) in which no diets were collected during the survey.

The total amount of PCBs in the diet was smaller in the 2003 survey than in the 1980 and 1995 surveys (Table 2). Specifically, the level in the 2003 survey was 12% and 38% of the levels in the 1980 and 1995 surveys, respectively. The distribution patterns of the three isomer groups were similar among the three surveys and the ratios of hexa/penta (about 2) and hepta/penta (about 0.8) congeners remained unchanged among the three periods.

Age and congener patterns of PCBs in serum during 1980 and 2003

The total PCB levels in the serum did not differ according to age group in either the 1980 or 1995 survey. In contrast, a significant age-associated increase became evident in the 2003 survey, since the PCB level increased from 68 to 242

Table 2 Intake of PCBs in diet per day

Survey year	1980				1995				2003	Total
No. Age group (years)	40	(17) (<40)	(13) (40–50)	(10) (>50)	40	(2)[a] (<40)	(17) (40–50)	(21) (>50)	80	160
Total PCBs (ng/g lipid)										
GM (GSD)	523 (2.5)*	467 (2.7)	703 (2.3)	431 (2.4)	166 (3.3)*	138 (13.3)	215 (2.4)	137 (3.8)	63 (3.2)*	137 (4.1)
Range	105–3412	112–3412	227–3206	105–1707	5.7–1548	22–863	32–1548	5.7–1026	5.5–1102	5.5–3412
Q1	283	219	344	255	85	–	158	55	30	41
Q2	510	503	603	468	196	–	215	154	52	139
Q3	925	865	1205	737	408	–	368	432	129	450
CB-74 (ng/g lipid)										
GM (GSD)	19 (2.6)*	16 (2.6)	29 (2.4)	14 (2.4)	6.4 (2.6)*	6.3 (7.7)	8.0 (1.8)	5.9 (3.1)	2.6 (3.1)*	5.4 (3.8)
Range	3.1–165	3.1–79	9.4–165	4.2–54	1.0–43	1.5–27	2.4–19	1.1–43	0.1–38	0.1–165
Q1	10.1	8.1	13	5.7	3.5	–	5.0	2.5	1.4	2.2
Q2	20	16	28	17	7.3	–	7.6	6.6	2.6	5.0
Q3	32	32	40	31	13	–	13	14	4.7	14
CB-99 (ng/g lipid)										
GM (GSD)	35 (2.5)*	30 (2.5)	53 (2.3)	28 (2.5)	15 (2.5)*	–	16 (2.0)	13 (2.8)	5.6 (3.4)*	11 (3.8)
Range	7.0–263	7.0–134	18–263	8.3–118	ND–66	ND–66	3.3–59	ND–61	ND–116	ND–263
Q1	19	13	23	11	6.5	–	10.5	4.1	2.8	4.2
Q2	39	36	53	34	17	–	18	15	5.2	11
Q3	68	59	84	52	26	–	26	26	10.8	29
CB-118 (ng/g lipid)										
GM (GSD)	66 (2.7)*	55 (2.9)	96 (2.3)	56 (2.6)	21 (3.4)*	19 (16.6)	29 (2.3)	16 (3.7)	8.3 (3.4)*	18 (4.2)
Range	8.4–438	8.4–354	37–438	123–256	0.7–139	2.6–139	3.5–139	0.7–114	0.5–160	0.5–438
Q1	37	22	42	28	9.7	–	20	5.2	4.2	5.6
Q2	74	76	94	63	29	–	32	20	7.0	16
Q3	125	106	164	106	47	–	47	47	16	57
CB-138 (ng/g lipid)										
GM (GSD)	78 (2.5)*	68 (2.7)	106 (2.3)	65 (2.4)	25 (3.5)*	23 (12.8)	34 (2.5)	19 (4.1)	9.4 (3.2)*	20 (4.2)
Range	13–461	13–461	34–435	15–273	0.6–255	3.7–137	4.9–255	0.6–175	1.1–143	0.6–461
Q1	44	32	53	35	12	–	24	9	4.2	5.9
Q2	80	82	92	69	30	–	33	23	7.3	21
Q3	152	128	201	111	69	–	57	67	20	69
CB-146 (ng/g lipid)										
GM (GSD)	20 (2.6)*	17 (2.8)	28 (2.3)	17 (2.6)	6.4 (3.9)*	5 (20.1)	8 (3.1)	4.9 (4.2)	2.2 (4.4)*	5.0 (5.0)
Range	2.9–147	4.0–137	9.0–147	2.9–65	0.4–81	0.6–41	0.8–81	0.4–55	ND–61	ND–147
Q1	9.8	8.1	14	9.3	2.9	–	5.6	2.0	1.0	1.5
Q2	21	15	27	21	8.1	–	8.3	5.7	1.7	5.2
Q3	35	32	46	30	18	–	18	18	5.0	19
CB-153 (ng/g lipid)										
GM (GSD)	135 (2.6)*	121 (2.8)	182 (2.3)	110 (2.4)	44 (3.5)*	36 (13.9)	57 (2.6)	37 (3.9)	16 (3.4)*	35 (4.3)
Range	23–944	23–944	58–836	26–443	2.0–468	5.7–235	7.6–468	2.0–296	0.6–297	0.6–944
Q1	73	58	89	66	20	–	42	16	6.8	10.1
Q2	127	124	154	120	51	–	56	43	13	35
Q3	244	238	330	189	114	–	106	113	33	115
CB-156 (ng/g lipid)										
GM (GSD)	10 (2.4)*	9 (2.6)	13 (2.4)	8 (2.3)	3.9 (2.4)*	3.8 (8.3)	4.1 (2.1)	2.9 (2.5)	0.8 (5.9)*	2.3 (5.8)
Range	1.8–70	1.8–70	3.2–52	2.4–34	ND–19	1.1–19	0.8–18	ND–13	ND–16	ND–70
Q1	5.9	4.3	6.9	4.8	1.8	–	3.4	1.4	0.7	1.0

Table 2 continued

Survey year	1980				1995				2003	Total
No. Age group (years)	40	(17) (<40)	(13) (40–50)	(10) (>50)	40	(2)[a] (<40)	(17) (40–50)	(21) (>50)	80	160
Q2	10.1	10.0	11	9.1	4.2	–	4.6	2.4	1.1	2.5
Q3	17	16	24	13	7.8	–	6.8	7.9	2.1	7.7
CB-163 & 164 (ng/g lipid)										
GM (GSD)	31 (2.7)*	29 (2.8)	42 (2.5)	24 (2.8)	10.3 (3.4)*	9.1 (11.0)	12 (2.9)	9.0 (3.7)	3.2 (4.1)*	7.5 (4.9)
Range	4.7–222	7.8–195	12–222	4.7–102	ND–117	1.7–51	1.2–117	ND–86	0.1–74	ND–222
Q1	14	13	20	9.1	3.9	–	7.8	3.2	1.2	2.0
Q2	31	29	34	28	12	–	13	8.8	2.7	7.8
Q3	61	57	80	49	27	–	25	27	7.0	28
CB-170 (ng/g lipid)										
GM (GSD)	17 (2.4)*	16 (2.6)	21 (2.4)	15 (2.2)	6.4 (2.6)*	–	7.2 (2.4)	6.1 (2.8)	1.6 (5.1)*	4.1 (5.3)
Range	4.3–148	4.4–148	5.1–89	4.3–50	ND–53	ND–24	1.4–53	ND–33	ND–25	ND–148
Q1	9.0	7.7	12	8.3	2.8	–	4.5	2.3	1.1	1.4
Q2	18	18	21	18	6.1	–	6.4	4.6	1.7	4.7
Q3	30	26	37	26	12	–	10.8	14	3.8	13
CB-180 (ng/g lipid)										
GM (GSD)	60 (2.4)*	57 (2.6)	73 (2.3)	52 (2.3)	16 (3.1)*	15 (9.1)	21 (2.5)	13 (3.5)	5.8 (3.1)*	13 (4.2)
Range	14–554	16–554	22–306	14–182	1.0–175	3.2–72	3.3–175	1.0–90	0.7–89	0.7–554
Q1	32	30	38	28	7.8	–	14	5.4	2.7	3.9
Q2	60	57	75	66	18	–	22	13	4.9	14
Q3	114	91	130	88	37	–	33	44	11	43
CB-182 & 187 (ng/g lipid)										
GM (GSD)	42 (2.7)*	39 (2.9)	53 (2.4)	34 (2.6)	13 (3.3)*	11 (9.4)	15 (3.1)	12 (3.4)	5.1 (4.0)*	11 (4.5)
Range	5.7–369	10.9–369	14–268	5.7–130	ND–165	2.2–52	1.4–165	ND–122	0.1–105	ND–369
Q1	20	16	25	21	6.1	–	10	4.1	2.2	3.3
Q2	43	32	52	42	13	–	16	11	4.1	12
Q3	83	73	100	61	31	–	28	39	11	38
Penta CBs (ng/g lipid)										
GM (GSD)	122 (2.6)*	102 (2.7)	179 (2.3)	99 (2.5)	41 (3.1)*	31 (17.3)	54 (2.1)	34 (3.5)	17 (3.2)*	35 (3.9)
Range	18–853	18–559	64–853	24–427	1.8–232	4.1–232	10.4–215	1.8–188	0.6–313	0.6–853
Q1	70	44	82	45	20	–	36	10.5	8.7	12
Q2	134	130	181	113	53	–	54	48	15	33
Q3	228	195	278	185	85	–	84	84	33	105
Hexa CBs (ng/g lipid)										
GM (GSD)	275 (2.5)*	246 (2.8)	371 (2.3)	224 (2.4)	88 (3.5)*	78 (13.1)	116 (2.6)	72 (4.0)	32 (3.3)*	71 (4.3)
Range	55–1788	56–1788	116–1691	55–917	3.0–939	13–483	15–939	3.0–624	2.7–590	2.7–1788
Q1	146	116	182	123	41	–	83	32	14	21
Q2	266	265	316	242	103	–	119	85	26	73
Q3	502	469	670	390	237	–	215	231	69	238
Hepta CBs (ng/g lipid)										
GM (GSD)	120 (2.5)*	113 (2.7)	147 (2.3)	102 (2.4)	33 (3.4)*	28 (10.4)	43 (2.6)	28 (3.9)	13 (3.3)*	29 (4.3)
Range	25–1065	32–1065	41–662	25–362	1.0–393	5.4–148	6.3–393	1.0–237	0.8–209	0.8–1065
Q1	60	55	72	67	17	–	30	12	6.3	8.3
Q2	112	107	148	120	36	–	43	26	10.5	31

Table 2 continued

Survey year	1980				1995				2003	Total
No. Age group (years)	40	(17) (<40)	(13) (40–50)	(10) (>50)	40	(2)[a] (<40)	(17) (40–50)	(21) (>50)	80	160
Q3	221	187	266	175	76	–	71	97	27	93

In 1980 and 1995, diets were collected in Hokkaido, Tohoku, Kanto, Chubu, Chugoku, Shikoku, Kyushu, and Okinawa

In 2003, diets were collected in Tohoku, Kanto, Chubu, Kansai, Shikoku, and Okinawa

[a] This group was excluded from statistical comparison due to small number participants

GM geometric mean, *GSD* geometric standard deviation, *Q1* 25th percentile, *Q2* median, *Q3* 75th percentile

* In all congeners and total PCBs, there are significant differences in log-transformed daily intakes between three survey years [$p < 0.05$ by Tukey's honestly significant difference (HSD) test]. There were no significant differences among the three age groups within the same survey year ($p > 0.05$)

(ng/g lipid) according to the age group (Table 3). Furthermore, individual congener groups showed similar increasing trends.

Among the same age groups in the three eras, the serum total PCB level in the younger generation (<40 years) was lower in the 2003 survey than in the 1980 survey. In the age groups of <40 years and 40–50 years, penta CBs were significantly lower in the 2003 survey than in the 1980 survey. The hexa and hepta CBs groups were significantly lower in the <40 year age group, but significantly higher in the >50 year age group, in the 2003 survey compared with the 1980 survey. These results indicate that hexa and hepta CBs may have accumulated in the >50 year age group, whereas all the congeners decreased in the <40 year age group, in the 2003 survey compared with the 1980 survey.

Long-term changes in the total PCB levels and congener profiles in participants born from 1940 to 1953

The above results suggested that the age-dependent increases in serum PCB concentrations may be attributable to the accumulation of more highly chlorinated PCBs than lower-chlorinated PCBs. However, testing this hypothesis is not easy because the participants born before 1960 have had more extensive exposure to PCBs than participants born after 1960. Therefore, we compared the serum total PCB levels and congener profiles among the generations born from 1940 to 1953. Since these birth-year generations were part of all three surveys, the exposure histories can be evaluated. Specifically, females born from 1940 to 1953 ($n = 17$) were <40 years of age in the 1980 survey, 42–55 years of age in the 1995 survey ($n = 17$), and 50–63 years of age in the 2003 survey ($n = 9$). The proportions of these serum donors of this generations living in different districts over the three surveys were: Tohoku–Hokkaido, about 20%; Kanto–Hokuriku–Chubu, about 40%; Chugoku–Shikoku, about 20%; and Kyushu–Okinawa, about 20%.

The serum concentrations and congener profiles are shown in Fig. 1. The serum total PCB levels were significantly increased in 2003. This increase was attributable to a significant increase in the hepta CBs group. This increase in the hepta CBs group was in contrast with the decrease in the penta CBs group over the 23-year period. These data indicate that the effects of intensive exposure from 1950 to 1970 may have disappeared by 1995, and therefore may not contribute the large PCB body burden observed in these generations in 2003.

Discussion

We found age-associated increases in serum PCB levels in females born between 1940 and 1953 in retrospective long-term trend study, although daily intakes have been consistently decreasing. This paradoxical phenomenon has never been reported.

With the advantages of using our samples stored in the specimen bank, the higher serum PCB levels observed in the older generations were found to be correlated with elevation of hepta CBs.

The changes in the congener distribution patterns in serum were in sharp contrast with those in diet. In diet, the congener patterns were almost constant at 1:2:1 (penta:hexa:hepta), despite the fact that total PCB intake decreased significantly from 523 to 63 (ng/day). Since our diet samples covered various kinds of food items, these congener patterns represent the patterns in the modern Japanese diet. Therefore, the age-specific accumulation of hepta CBs in serum is unlikely to be explained by differences in food preferences among generations.

There are at least two possibilities that may explain the age-specific accumulation of hepta CBs in the older

Table 3 Time era- and age-specific total PCB and congener concentrations in serum

Survey year	1980			1995			2003			Total
Age (years)	<40	40–50	>50	<40	40–50	>50	<40	40–50	>50	
Birth year (group)	1946 (group C)	1936 (group B)	1924 (group A)	1957 (group D)	1950 (group C)	1934 (group B)	1972 (group E)	1958 (group D)	1948 (group C)	
No.	17	12	10	2[a]	17	21	59	22	9	169
Total PCBs (ng/g lipid)										
GM (GSD)	185 (1.8)	170 (1.4)	125 (1.7)	83 (2.3)	128 (2.0)	164 (1.9)	68 (1.8)A	110 (1.6)B	242 (1.7)C*	113 (2.0)
Range	60–414	97–306	55–282	46–148	42–714	67–895	18–282	49–221	84–570	18–895
Q1	105	118	76	–	72	95	43	68	191	66
Q2	195	180	128	–	115	163	65	112	236	114
Q3	311	220	175	–	181	222	106	157	356	182
#	a	ns	ns	–	ns	ns	b	ns	ns	
CB-74 (ng/g lipid)										
GM (GSD)	18 (1.9)	17 (2.0)	12 (1.9)	5.4 (2.0)	7.4 (1.9)	11 (2.1)	3.0 (1.9)A	4.8 (1.7)B	11 (1.8)C*	6.5 (2.5)
Range	6.0–40	6.2–40	7.3–67	3.4–8.8	2.6–33	3.0–51	0.8–12	2.0–12	3.8–29	0.8–67
Q1	10.7	8.8	8.1	–	4.4	6.8	1.9	2.8	8.1	3.3
Q2	17	15	10.5	–	7.1	11	3.0	5.3	9.4	6.6
Q3	33	35	12	–	12	18	5.0	7.6	19	12
#	a	a	ns	–	b	ns	b	b	ns	
CB-99 (ng/g lipid)										
GM (GSD)	10.0 (1.9)	9.2 (1.5)	5.9 (1.6)	4.1 (1.8)	5.0 (2.2)	6.0 (2.0)	2.8 (1.8)A	3.9 (1.8)A	7.4 (2.1)B*	4.7 (2.2)
Range	2.9–26	4.7–16	3.6–18	2.7–6.1	1.1–35	1.2–29	0.9–13	0.9–9.8	1.8–22	0.90–35
Q1	5.6	6.3	4.6	–	3.0	3.7	1.7	2.7	4.4	2.7
Q2	10.6	9.2	4.9	–	4.1	6.2	2.5	4.4	7.9	4.7
Q3	18	13	7.5	–	8.6	8.7	4.4	5.7	13	7.9
#	a	a	ns	–	b	ns	b	b	ns	
CB-118 (ng/g lipid)										
GM (GSD)	26 (2.0)	22 (1.3)	17 (1.8)	8.8 (1.7)	12 (2.1)	14 (2.1)	5.8 (1.8)A	8.9 (1.6)B	17 (2.1)C*	10.7 (2.2)
Range	8.4–64	15–37	8.6–53	6.0–13	3.7–107	3.5–79	1.8–16	3.3–17	4.8–56	1.8–107
Q1	13	16	10.8	–	8.2	10.2	3.7	5.8	10.1	5.8
Q2	28	23	15	–	10.9	14	5.6	10.2	18	10.9
Q3	52	28	23	–	17	20	9.1	13	31	16
#	a	a	ns	–	b	ns	b	b	ns	
CB-138 (ng/g lipid)										
GM (GSD)	24 (1.9)	23 (1.4)	15 (1.6)	11 (2.1)	15 (2.1)	19 (2.0)	8.3 (1.8)A	13 (1.7)B	27 (1.8)C*	14 (2.1)
Range	7.8–84	13–45	7.5–33	6.3–18	4.6–121	7.2–167	2.3–31	4.0–27	8.9–64	2.3–167
Q1	13	16	11	–	9.2	12	5.4	8.1	20	7.9
Q2	24	24	15	–	13	18	7.8	14	23	14
Q3	42	29	22	–	24	23	12	20	42	22
#	a	a	ns	–	ab	ns	b	b	ns	
CB-146 (ng/g lipid)										
GM (GSD)	6.1 (1.8)	6.0 (1.4)	4.2 (1.7)	3.1 (2.3)	5.1 (2.1)	6.6 (2.0)	2.6 (2.0)A	4.3 (1.7)B	9.7 (1.8)C*	4.2 (2.1)
Range	2.2–18	3.3–12	1.8–7.3	1.7–5.6	1.7–32	2.5–45	0.5–13	1.5–11	2.8–22	0.5–45
Q1	3.2	4.4	2.6	–	2.9	3.5	1.6	2.9	7.5	2.6
Q2	6.5	5.9	4.9	–	4.7	6.3	2.5	4.4	9.9	4.5
Q3	9.6	8.0	7.1	–	7.4	9.5	4.5	6.2	15	7.2
#	a	ns	a	–	ns	ab	b	ns	b	
CB-153 (ng/g lipid)										
GM (GSD)	41 (1.8)	40 (1.4)	28 (1.6)	21 (2.3)	33 (2.1)	42 (2.0)	19 (1.9)A	30 (1.6)B	65 (1.7)C*	29 (2.0)
Range	15–115	25–81	11–53	12–39	11–188	18–295	4.9–85	12–64	23–152	4.9–295

Table 3 continued

Survey year	1980			1995			2003			Total
Age (years)	<40	40–50	>50	<40	40–50	>50	<40	40–50	>50	
Birth year (group)	1946 (group C)	1936 (group B)	1924 (group A)	1957 (group D)	1950 (group C)	1934 (group B)	1972 (group E)	1958 (group D)	1948 (group C)	
No.	17	12	10	2[a]	17	21	59	22	9	169
Q1	24	28	18	–	20	24	12	19	50	18
Q2	40	41	29	–	32	39	18	30	65	29
Q3	65	51	43	–	46	57	28	43	95	47
#	a	ns	a	–	ns	ab	b	ns	b	
CB-156 (ng/g lipid)										
GM (GSD)	5.4 (2.0)	4.7 (1.4)	3.4 (1.6)	2.7 (2.6)	4.3 (2.3)	5.2 (2.0)	1.9 (2.0)A	3.3 (1.7)B	8.1 (1.8)C*	3.3 (2.2)
Range	1.9–18	2.6–08	1.5–6.6	1.4–5.4	1.7–48	1.7–39	0.3–6.8	1.5–7.0	2.7–19	0.3–48
Q1	3.0	3.6	2.3	–	2.2	3.4	1.1	1.8	5.8	1.9
Q2	5.0	4.9	3.7	–	3.8	5.0	1.9	3.6	8.4	3.6
Q3	9.1	6.3	5.3	–	6.5	7.5	3.1	4.6	12	5.5
#	a	ns	a	–	ns	ab	b	ns	b	
CB-163 & 164 (ng/g lipid)										
GM (GSD)	10.3 (1.9)	10.3 (1.4)	7.2 (1.6)	4.9 (2.3)	8.2 (2.2)	10.7 (2.0)	4.1 (2.0)A	6.9 (1.6)B	16 (1.7)C*	6.9 (2.1)
Range	3.4–34	6.6–20	3.0–13	2.7–9.0	2.9–60	4.1–92	0.8–17	3.0–15	5.2–31	0.8–92
Q1	5.3	7.2	4.4	–	4.5	6.9	2.5	4.6	13	4.1
Q2	10.2	10.8	7.8	–	7.8	9.2	4.1	7.0	16	7.4
Q3	18	14	11	–	12	17	7.7	9.4	25	11
#	a	ns	a	–	ns	ab	b	ns	b	
CB-170 (ng/g lipid)										
GM (GSD)	5.8 (1.7)	5.0 (1.4)	4.1 (1.7)	3.4 (2.8)	5.2 (2.0)	6.3 (1.8)	2.8 (1.9)A	5.1 (1.5)B	11 (1.6)C*	4.4 (2.0)
Range	1.9–11	2.8–10	1.5–6.9	1.6–6.9	2.2–22	2.2–23	0.5–12	2.6–10	4.3–22	0.5–23
Q1	3.5	3.5	2.5	–	2.7	3.9	1.9	3.3	9.4	2.7
Q2	6.0	5.3	5.1	–	4.8	6.1	2.9	5.5	10.6	4.9
Q3	9.4	6.0	5.9	–	8.2	10.2	5.0	6.7	16	6.8
#	a	ns	a	–	ns	a	b	ns	b	
CB-180 (ng/g lipid)										
GM (GSD)	21 (1.7)	19 (1.5)	16 (1.8)	12 (2.9)	19 (1.9)	24 (1.8)	11 (1.9)A	20 (1.5)B	46 (1.6)C*	17 (2.0)
Range	7.3–42	10.3–39	5.7–28	5.9–26	7.6–74	8.7–69	2.8–49	10.4–44	20–101	2.8–101
Q1	14	13	8.6	–	10.2	16	7.2	15	35	10.6
Q2	24	19	20	–	17	23	10.7	20	46	19
Q3	31	25	25	–	31	42	20	28	59	26
#	a	ns	a	–	ns	a	b	ns	b	
CB-182 & 187 (ng/g lipid)										
GM (GSD)	10.0 (1.7)	9.6 (1.5)	7.2 (1.7)	5.1 (2.7)	8.6 (1.9)	11 (1.9)	5.3 (2.0)A	9.3 (1.7)B	21 (1.9)C*	8.0 (2.0)
Range	3.7–20	5.4–23	2.8–12	2.5–10.3	2.7–39	4.9–42	0.9–32	3.1–27	6.0–58	0.9–58
Q1	6.5	6.5	4.1	–	5.1	6.4	3.5	7.2	15	4.9
Q2	10.2	9.6	9.2	–	8.7	11	5.2	8.9	21	8.7
Q3	16	12	11	–	14	18	9.7	13	31	13
#	a	ns	a	–	ns	a	b	ns	b	
Penta CBs (ng/g lipid)										
GM (GSD)	55 (1.9)	50 (1.5)	27 (1.8)	18 (1.8)	25 (2.1)	32 (2.0)	12 (1.8)A	18 (1.6)B	36 (2.0)C*	22 (2.3)
Range	17–122	26–86	10–47	12–28	7.4–175	8.8–126	3.6–36	6.3–35	10.4–108	3.6–175
Q1	29	33	15	–	16	22	7.2	10.9	23	11
Q2	68	47	34	–	23	35	11	19	38	23
Q3	101	76	42	–	39	46	18	26	63	36

Table 3 continued

Survey year	1980			1995			2003			Total
Age (years)	<40	40–50	>50	<40	40–50	>50	<40	40–50	>50	
Birth year (group)	1946 (group C)	1936 (group B)	1924 (group A)	1957 (group D)	1950 (group C)	1934 (group B)	1972 (group E)	1958 (group D)	1948 (group C)	
No.	17	12	10	2[a]	17	21	59	22	9	169
#	a	a	ns	–	b	ns	b	b	ns	
Hexa CBs (ng/g lipid)										
GM (GSD)	87 (1.9)	84 (1.4)	58 (1.6)	43 (2.3)	66 (2.1)	84 (2.0)	36 (1.9)A	57 (1.6)B	127 (1.7)C*	58 (2.0)
Range	30–265	52–164	25–113	24–77	22–448	35–636	8.9–153	22–119	43–282	8.9–636
Q1	48	58	38	–	39	48	23	34	99	35
Q2	87	89	59	–	61	79	33	56	129	56
Q3	145	106	89	–	93	109	54	83	192	92
#	a	ns	a	–	ns	ab	b	ns	b	
Hepta CBs (ng/g lipid)										
GM (GSD)	37 (1.7)	34 (1.5)	35 (1.8)	21 (2.8)	33 (1.9)	42 (1.8)	19 (1.9)A	35 (1.6)B	78 (1.6)C*	30 (2.0)
Range	13–70	19–71	20–138	10–43	13–131	16–134	4.2–94	18–76	31–181	4.2–181
Q1	24	23	23	–	18	27	13	24	63	18
Q2	39	35	30	–	30	39	19	35	75	34
Q3	58	44	42	–	53	70	35	45	106	45
#	a	ns	a	–	ns	a	b	ns	b	

GM geometric mean, *GSD* geometric standard deviation, *Q1* 25th percentile, *Q2* median, *Q3* 75th percentile

[a] This group was excluded from statistical comparison due to small number participants

* There were significant differences among the three age groups within the same survey year ($p < 0.05$ by Tukey's HSD test). Values with a different capital letter differ significantly from each other. For example, a value indicated by A differs from the corresponding values indicated by B or C

[#] Comparison among the three surveys within the same age group. Values with a different lower-case letter differ significantly from each other

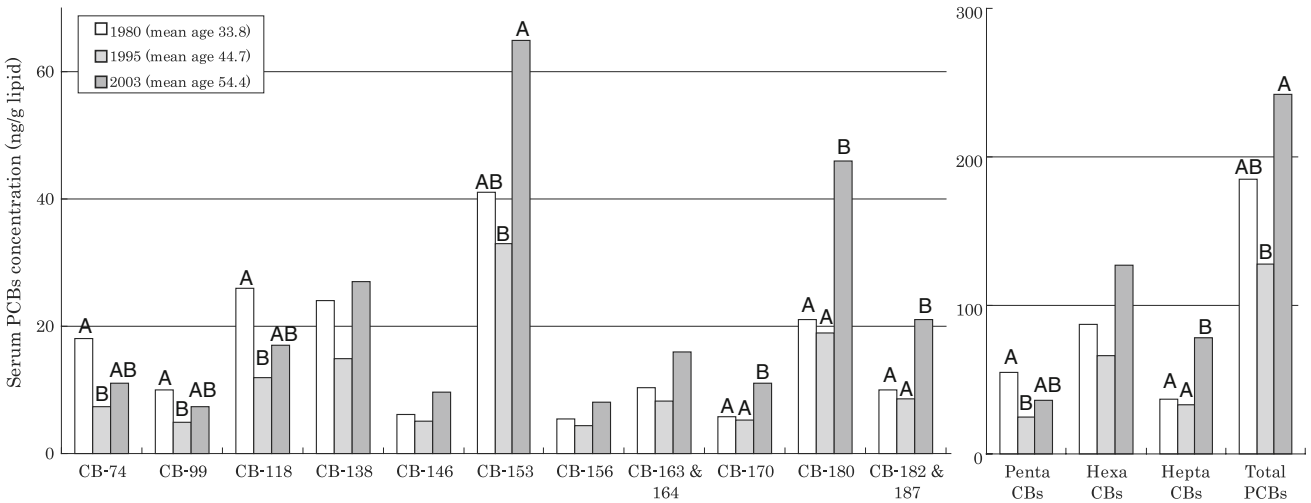

Fig. 1 Serum concentrations of PCBs (ng/g lipid) in females born from 1940 to 1953 in the three different surveys (1980, 1995, and 2003). The *letters* indicate the results of statistical analyzes by ANOVA. When the ANOVA was significant, Tukey's post hoc tests were conducted. The letters *A* and *B* indicate that the corresponding values differ significantly at $p < 0.05$, while *A* and *AB* or *AB* and *B* do not

generations. The first hypothesis assumes a birth-year generation phenomenon, involving generation-specific exposure histories to PCBs. Since highly chlorinated PCBs are more lipophilic and have longer half-lives [22], the apparent accumulation of highly chlorinated PCBs in the older generation may be associated with past intense exposure from 1950 to 1970. Alternatively, the second hypothesis assumes a decrease in elimination of highly

chlorinated PCBs with age. It is well established that PCB metabolic activity is mediated by P450s [12–15], which is depressed with aging [16].

The two hypotheses were tested by long-term observations in generations born from 1940 to 1953 in various geographic locations. The results indicated preferential increases in the hexa and hepta concentrations in 2003 compared with the corresponding levels in 1995 and 1980. Although these generations had been extensively exposed to PCBs, an effect of this high exposure history was only discernible in the 1980 survey and had disappeared in the 1995 survey. Thus, the recent preferential increases in hepta CBs despite large decreases in dietary PCB intake suggest that the accumulation of these congener groups is probably due to decreased elimination with aging, rather than a birth-generation phenomenon or preferred consumption of fish.

The present findings may raise a new issue for risk assessment of PCBs. Neonates and children have been postulated to be the most susceptible to exposure to PCBs [23]. However, since it is well known that exposure to PCBs is associated with various cancers [24–29], older generations may need to be considered as a high-risk population due to their tendency for higher accumulation of PCBs than younger generations.

The present study has several limitations. First, it was not a cohort study. Thus, the present observations may be confounded by both individual and geographical differences. The present population was, however, free from occupational exposure. The second limitation is the absence of individual background data concerning number of pregnancies, number of breast feeding, body mass index (BMI), age of menopause, and consumption of fish, which are known to be determinants for serum PCB levels: number of pregnancies [30], breastfeeding [31, 32], BMI [33], age of menopause [30], and consumption of fish [34]. The third limitation is uncertainty about the sources of the PCBs. We assumed that the major source of PCBs is diet. However, inhalation is well known to be another important exposure route [35], and we did not evaluate exposure through this route. Our neglect of routes other than food may be justifiable because more than 90% of exposure occurs via food [36].

In conclusion, the advantages of using historical samples superseded the various limitations of this study. The versatile evidence, although indirect, strongly suggests preferential accumulation of highly chlorinated PCBs in the older generation. Such generation-specific accumulation warrants further investigation.

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