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Half-lives of serum PCB congener concentrations in environmentally exposed early adolescents

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ABSTRACT

The aim was to determine half-life of six most abundant PCB congeners in the body of early adolescents. In 304 environmentally exposed children, PCB serum concentration was determined at the age of 8 and 12 years. Half-life was determined for each child assuming exponential decrease or for the whole cohort using multiple regression. Results obtained by both approaches were in agreement. PCB reuptakes corrupting half-life estimates for each child and each congener were evaluated. If one of the serum PCB concentration values fell below the level of detection (LOD) the pair was excluded and if PCB half-life value exceeded the arbitrary value of 30 years. The following median half-lives in years 4.46, 10.59, 9.7, 4.7, 9.1 and 9.8 were obtained for PCB congeners 118, 138^{+163}, 153, 156^{+171}, 170 and 180, respectively. The elimination half-life values were not systematically related to PCB serum concentration at any examination age. Between half-life values, percentage of children with significant reuptakes and PCB congener abundance in serum were found significant associations.

1. Introduction

A formal description of the kinetics of polychlorinated biphenyls (PCBs) in humans is in focus of interest for many decades in view of assessment of risk for the population exposed to this important member of the persistent organic pollutants (POPs) family (Matthews and Dedrick, 1984; Yakushiji, 1988; Phillips et al., 1989; Rogan and Ragan, 1994; Shirai and Kissel, 1996; Lotti, 2003; Larsen, 2006). Most recently were published extensive literature searches and new data on human PCBs half-lives in environmentally and occupationally exposed populations (Grandjean et al., 2008; Milbrath et al., 2009; Seegal et al., 2010). In spite of the accumulating knowledge on this topic, it has been stressed that further study into the causes of interindividual and intraindividual elimination rate variability would refine half-life estimation accuracy (Milbrath et al., 2009).

The industrial production of PCBs in Michalovce, eastern Slovakia, resulted in massive environmental pollution of a vast densely populated area (Kočan et al., 2008) and created a unique opportunity to study human toxicokinetics of PCBs in various age groups (Hertz-Picciotto et al., 2003). Due to scarce human PCB exposure data for this region, a study was initiated in 2002 within which a cohort of 434 8–9-year old children was examined on PCB exposures (Kočan et al., 2004; Petrík et al., 2006). When 4 years later children reached the age of 12 years, 304 of them were reexamined with the aim to evaluate PCB elimination rate from their bodies assuming that their PCB body burdens were built up mainly during the breast feeding period as already shown elsewhere (Burns et al., 2009; Grimalt et al., 2010; Windham et al., 2010). Quantitative characterization of the PCB elimination rate from the human body is difficult due to (Milbrath et al., 2009): 1. Reuptakes of PCBs that may lead to unrealistic long half-life estimates. 2. Great variability of physiological factors governing the distribution and elimination of PCBs from the human body.

The aim of our work was to assess variability of elimination half-lives of six most abundant PCB congeners from the body of early adolescents and to eliminate as much as possible the influence of PCB reuptakes on estimated half-life values.

2. Material and methods

2.1. Study population

The study population involved 434 children, 221 boys and 213 girls, aged 8–9-years at the time of the first examination. Written informed consent was obtained from parents. The study was approved by the Ethics Committee of the Slovak Medical University. The mothers of children should have permanently lived in the area for at least 5 years before the child's birth. We have examined the

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children in year 2002 and 4 years later we have been able to re-examine 304 children, 155 boys and 149 girls. Blood was withdrawn from the cubital vein and processed as described (Kočan et al., 2004).

2.2. Laboratory measurements

The concentration of 15 PCB congeners (PCB IUPAC (International Union of Pure and Applied Chemistry) nomenclature #28, #52, #101, #105, #114, #118, #123, #138^{+163}, #153, #156^{+171}, #157, #167, #170, #180, and #189) were determined in the sera samples by high-resolution gas chromatography with electron capture detection (Kočan et al., 1994; Čonka et al., 2005). Total serum lipids were estimated using enzymatic summation method (Akins et al., 1989). Only congeners with the highest detection rate (PCB 153, 138^{+163}, 170, 180, 156^{+171}, 118) were taken into account. When a serum concentration was <LOD (level of detection) for a particular PCB congener, both paired values for the years 8 and 12 were excluded.

2.3. Data analysis

Two independent approaches for assessment of the PCB half-life values were used. The first approach assumed that the decrease in each set of paired serum PCB concentrations behaves by first order kinetics and may be described by a simple equation:

$$k_i = (\ln A_i(t_1) - \ln A_i(t_2))/(t_2 - t_1) \quad (1)$$

where k_i is the elimination rate constant (1/time), A_i stands for total amount of a PCB congener (denoted as i) in body fat and A_i can be estimated as

$$A_i = V\text{fat} \cdot C_i \quad (2)$$

where Vfat is the total amount of body fat and C_i is the measured lipid-adjusted PCB serum concentration (ng g^{-1} lipids) at 8 and 12 years, respectively and $(t_2 - t_1)$ is 4 years. The half-life ($T_{1/2}$) has been calculated as

$$T_{1/2} = -\ln(0.5)/k \quad (3)$$

for each child and each congener and no cofactors were taken into account. The amount of body fat was calculated for each child using formula published previously (Deurenberg et al., 1991). The second approach was using regression model as described (Grandjean et al., 2008). Parameter k was estimated from Eq. (1) by nonlinear regression (SPSS 16.0 for Windows produced by SPSS Inc., Chicago, IL).

3. Results

The statistics describing the serum concentration of PCB congeners in 304 children at 8 (upper part) and 12 (lower part) years of age are presented in Table 1.

It can be seen for all PCB congeners that their mean and median serum concentration values decreased during the 4-year period. From these aggregate values the respective reuptakes could not be recognized.

3.1. First approach of half-life determination

In order to obtain information on significant reuptakes of PCBs during the 4-year period between the first and second examination we constructed frequency diagrams of elimination rate constants k for each PCB congener shown in Fig. 1. It can be seen that PCB reuptakes, signaled by values of $k < 0$, occurred with all congeners studied, but the shape of the diagrams between PCB congeners widely differs. The value of $k < 0$ in the diagram marks children in which the PCB serum concentration at the age of 12 years exceeded PCB serum concentration at the age of 8 years. It is obvious that $k < 0$ or a value slightly higher than 0 would compromise the net PCB elimination rate estimates. To avoid this not only children with $k < 0$, but also children with $k < 0.023$ were excluded from further statistical treatment. This k value corresponds to $T_{1/2} = 30$ years. The vertical lines in frequency diagrams in Fig. 1 divide children with an arbitrary half-life ($T_{1/2}$) < 30 years and ⩾30 years. The value of 30 years seems to be in the upper region of realistic estimates of individual PCB half-life values and compares well with the recently published data (Grandjean et al., 2008; Milbrath et al., 2009). Statistic data on half-lives after exclusion of children with obvious reuptakes from further statistical treatment, identified in a way just described, are shown in Table 2.

Table 1
Descriptive statistics on serum concentration of PCB congeners (ng g^{-1} lipids) measured at the age of 8 years (upper part) and 12 years (lower part).

PCB congener	118	138^{+163}	153	156^{+171}	170	180
Examination at 8 years						
Number of samples	167	301	303	200	283	302
% of detection	54.9	99	99.7	65.8	93.1	99.3
Minimum	5.7	11.8	17.7	3.8	5.8	11.1
Maximum	118.0	1011.2	1757.1	239.2	1056.0	2285.6
5th Percentile	6.5	22.0	33.2	6.4	11.6	23.1
25th Percentile	11.5	45.7	74.3	10.6	23.6	54.3
50th Percentile	16.5	72.6	191.6	17.1	42.3	94.6
75th Percentile	29.6	142.6	231.4	30.9	79.5	184.2
95th Percentile	61.8	342.5	537.2	72.8	229.7	581.9
Mean	23.4	120.2	190.5	25.2	74.2	169.3
SD	18.8	139.7	216.9	26.5	101.7	229.0
Geometric mean	18.4	70.5	127.9	18.4	45.8	101.8
Examination at 12 years						
Number of samples	192	302	304	249	301	303
% of detection	63.2	99.3	100	81.9	99	99.7
Minimum	0.5	7.9	6.2	0.6	0.8	3.1
Maximum	106.0	1038.8	1451.6	105.8	800.5	2033.9
5th Percentile	0.8	13.4	20.3	1.1	4.4	13.9
25th Percentile	2.8	29.9	47.1	2.5	13.1	34.9
50th Percentile	2.4	53.4	81.1	4.0	25.8	64.7
75th Percentile	12.5	99.6	148.9	11.6	48.7	123.0
95th Percentile	44.1	276.6	415.2	24.5	163.0	375.4
Mean	11.3	91.2	137.1	8.8	47.6	121.7
SD	15.5	120.0	177.0	11.2	74.4	188.8
Geometric mean	5.9	57.1	86.4	5.4	25.9	68.4

3.2. Second approach of half-life determination

The data on elimination half-lives obtained using regression are in Table 3. Included were data from children which passed the same reuptake criteria as applied in the first approach. The half-lives calculated by the two independent approaches compared well.

With regard to the possible dose dependent elimination kinetics of PCBs from the human body (Brown et al., 1989; Phillips et al., 1989; Ryan et al., 1993; Seegal et al., 2010) we examined the relationship between the elimination half-lives and PCB serum concentration, either at the time of first or second sampling. We were not able to find such an association for the given set of congeners and sampling times except for PCB congeners 118 for which at the age of 12 years the serum concentration was associated with a significant increase of elimination half-life (Table 4).

4. Discussion

The estimation of elimination half-lives of PCBs and organohalogen compounds in general, especially under environmental exposure scenario, is connected with many methodical problems

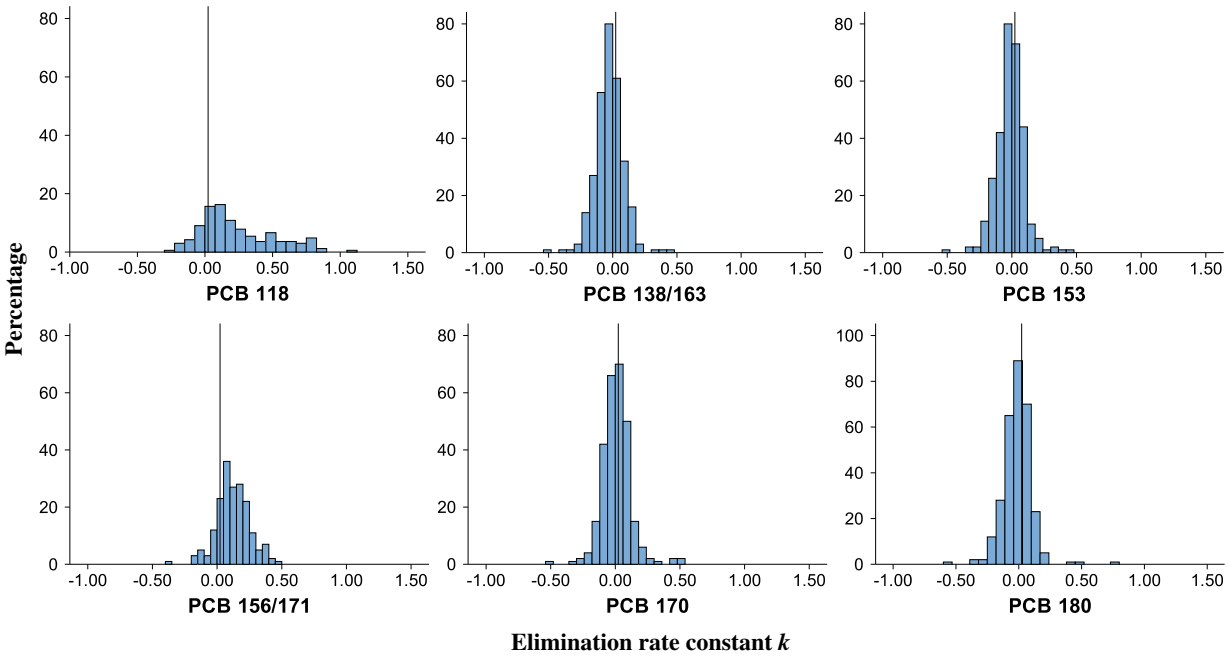

Fig. 1. Frequency diagrams of PCB elimination rate constants k_i from body fat of children for each congener evaluated. The vertical lines mark k value that corresponds to a half-life of 30 years.

Table 2
Descriptive statistics on half-lives (years) of children complying inclusion criterion: half-life ($T_{1/2}$) < 30 years.

PCB congener	118	138^{+163}	153	156^{+171}	170	180
N	99	93	107	154	119	109
Minimum	0.97	1.48	1.51	1.54	1.3	0.93
Maximum	27.33	28.75	29.88	22.51	28.69	29.45
5th Percentile	1.34	3.22	2.97	1.88	2.55	3.56
25th Percentile	2.45	5.87	6.39	3.17	5.99	6.08
50th Percentile	4.46	10.59	9.7	4.7	9.1	9.8
75th Percentile	7.92	15.14	15.16	8.17	15.52	13.7
95th Percentile	17.54	26.25	27.71	17.52	26.34	26.16
Mean	6.02	11.68	11.48	6.46	11.12	11.1
SD	5.07	7.11	6.87	4.68	6.93	6.44
Geometric mean	4.46	9.56	9.52	5.15	9.01	9.32

Table 3
Descriptive statistics on half-lives (years) of children determined by regression.

Half-life estimate by regression			
PCB congener	Lower bound	Half-life estimate	Upper bound
118	3.14	3.63	4.28
138^{+163}	7.7	9.0	11.0
153	7.97	9.37	11.18
156^{+171}	4.01	4.41	4.92
170	7.15	8.35	10.05
180	7.53	9.0	11.18

(Phillips, 1989; Shirai and Kissel, 1996). It is not surprising therefore that there is no systematic information on half-life of all PCB congeners in humans. In general, the elimination rate of PCBs from the body decreases with increasing chlorination, and values of half-life have been estimated to range from <1 year to 71 years (Yakushiji et al., 1984; Steele et al., 1986; Phillips et al., 1989; Masuda et al., 1991, 1995, 2007; Ryan et al., 1993; Shirai and Kissel, 1996; Ogura, 2004; Seegal et al., 2010). However, the most common congeners to which the general population is exposed are characterized by half-lives of 2–6 years (Shirai and Kissel, 1996; Ogura, 2004; Milbrath et al., 2009).

A direct comparison of our half-life values with those published by other authors is difficult for the following reasons. 1. Elimination kinetics of PCBs is dose (Phillips et al., 1989; Ryan et al., 1993; Seegal et al., 2010) and age (Masuda et al., 2007; Milbrath et al., 2009) dependent. This complicates the situation as information on dosages is lacking and in view of the latter issue it is important that much of the published data is based on observations on adults, whereas our results concern adolescents. 2. Many authors report data for sum of PCB congeners (Steele et al., 1986; Taylor et al., 1991; Wolff and Schecter, 1991; Taylor and Lawrence, 1992; Wolff et al., 2000), whereas our data are congener specific. The overlap of our congener data with those in published PCB half-life databases (Ogura, 2004; Milbrath et al., 2009) is rather poor. Congeners evaluated and age of subjects of our study matches at best those published by Grandjean et al. (2008), however for most congeners they report longer half-lives than we.

Table 4
Association between elimination half-life of PCB serum concentration and PCB serum concentration at the age of 8 or 12 years.

PCB congener			118	138^{+163}	153	156^{+171}	170	180
PCB serum concentration at	8 years	β	0.046	−0.015	−0.006	−0.02	0.063	−0.013
		R^2	0.025	0.002	0.003	0.002	0.002	0.008
		p	0.067	0.667	0.559	0.557	0.629	0.301
	12 years	β	0.121	−0.004	0.0026	0.005	0.255	−0.012
		R^2	0.066	0.000	0.000	0.000	0.011	0.003
		p	0.002	0.946	0.901	0.909	0.186	0.521

The discrepancy may be related to the fact that in the two studies compared, different measures for elimination of reuptakes were applied.

Factors determining elimination kinetics of PCB congeners and other organochlorines have been studied thoroughly (Milbrath et al., 2009). In this work we did not find any signs of dose dependent elimination rate except PCB congener 118. A similar relationship was already described (Brown et al., 1989).

We have found that there are associations between half-life values, percentage of children with $k < 0$ and PCB congener abundance in serum. The bivariate correlations between these three variables are as follows:

$$\text{Percentage of children with } k_i < 0 = 8.143 \cdot T_{1/2,i} - 21.98 \quad R^2 = 92.8\%$$

$$\text{Percentage of children with } k_i < 0 = 1.32 \cdot \text{Abundance}_i + 19.8 \quad R^2 = 71.0\%$$

$$T_{1/2,i} = 0.156 \cdot \text{Abundance}_i + 5.24 \quad R^2 = 70.6\%$$

where i is ith congener. For $T_{1/2,i}$ geometric means and for abundance of ith congener arithmetic means were used.

A 3D display of the three variables is in Fig. 2. The penta-chlorinated PCB congener 118 is marked by yellow, the hexa-chlorinated PCB congeners 138^{+163}, 153 and 156^{+171} by red and the hepta-chlorinated PCB congeners 170 and 180 by blue color. It can be seen that the two congeners with short half-lives, PCB 118 and PCB 156^{+171}, and medium half-life, PCB 170, are less abundant in the serum samples and for them the percentage of children with $k_i < 0$ is lower. On the other hand the PCB congeners 138^{+163}, 153 and 180 with longer half-lives are more abundant in serum samples and for them the percentage of children with $k_i < 0$ is higher. The chlorination degree does not seem to be related to any of the parameters.

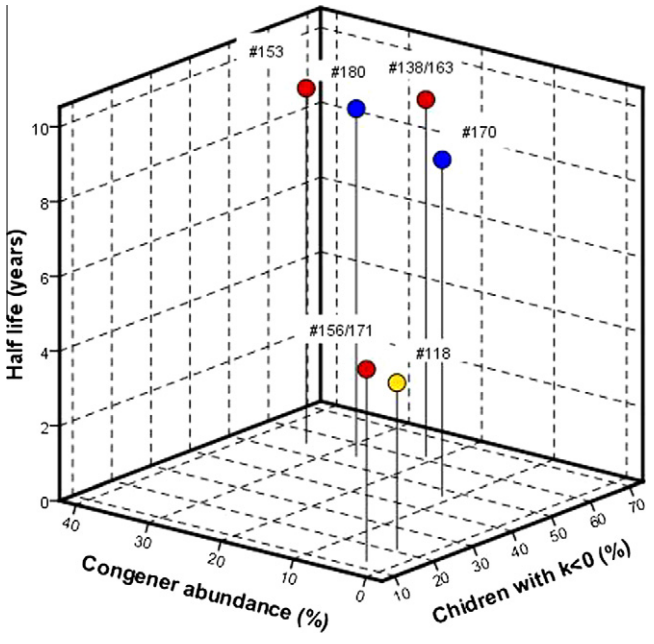

Fig. 2. A 3D display of association between half-life values, percentage of children with $k_i < 0$ and PCB congener abundance in serum. The penta-chlorinated PCB congener 118 is marked by yellow, the hexa-chlorinated PCB congeners 138^{+163}, 153 and 156^{+171} by red and the hepta-chlorinated PCB congeners 170 and 180 by blue color. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The strength of our half-life estimates is that they are based on relatively great number of subjects. The weakness of the study is the high occurrence of PCB reuptakes during the observation period.

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