Assessing Human Polychlorinated Biphenyl Contamination for Epidemiologic Studies: Lessons from Patterns of Congener Concentrations in Canadians in 1992

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Humans are always exposed to mixtures of polychlorinated biphenyls (PCBs), so assessment of their health effects is complicated. Because the original sources are relatively standard mixtures that change in predictable ways while traversing the environment, there is substantial uniformity in the congener mixtures people carry. To the extent that concentrations are highly correlated, measuring multiple congeners within correlated groups would be unnecessary and estimation of separate biologic effects would be impossible. We examined correlation patterns in previously collected data on 38 congeners (and 14 other organochlorines) from 497 human milk samples from Canada from 1992. Congeners 138, 153, 156, 157, 170, 183, 187, 194, 199, and 203 were highly intercorrelated; 180 had slightly lower correlations with this group. Congeners 74, 105, and 118 were highly intercorrelated and moderately to highly correlated with the first group. Congener 99 had moderate correlations with both these groups, and congener 66 had lesser correlations with the primary group. In contrast, congeners 28, 44, 49, 60, 90/101, 128, 137, and 193 showed little correlation with any other congeners. The remaining 14 congeners were uninformative; they were quantified in fewer than 30% of samples, and varying lipid concentrations meant that those quantified were not necessarily at higher concentrations than those not quantified. In study of human health effects of PCBs, the congener pattern present in the population under study should be examined when deciding which congeners to measure; instead of solely redundant or uninformative congeners, attention should be given to other congeners that may be more useful in addressing the question of interest. *Key words:* **congeners, environmental monitoring, epidemiologic methods, organochlorine insecticides, polychlorinated biphenyls.** *Environ Health Perspect* **111:437–443 (2003). doi:10.1289/ehp.5858 available via** *http://dx.doi.org/* **[Online 21 November 2002]**

Polychlorinated biphenyls (PCBs) are industrial compounds whose production began in 1929 (ATSDR 2000). Their largest use by volume has been in electrical equipment such as capacitors and transformers, but the list of other uses is long and varied. Their extensive use and their stability led to their release into and persistence in the environment. The discovery of their widespread presence in the environment, together with information on their toxicity, led to limitations on their manufacture in many countries starting in the 1970s. However, the stability of these compounds ensures that many millions of kilograms remain in existence. Persons throughout the world have been exposed to these compounds, predominantly through the presence of trace amounts in diet, and measurable concentrations of some PCBs can be found in virtually everyone to this day (Schecter et al. 1994).

The toxicity of PCBs has been investigated actively for many years, with interest particularly spurred by accidental poisonings in Japan in 1968 and Taiwan in 1979 (Hsu et al. 1994; Masuda 1994). There was clear toxicity seen in these unfortunate accidents, but the nature and extent of toxicity of PCBs at concentrations encountered in the general human population are less clear and remain under study (Longnecker et al. 1997).

PCBs are a group of 209 compounds; the various members of the group are referred to as congeners. Commercial production involves mixing biphenyl with chlorine under various reaction conditions, and the result is always a complex mixture of congeners (plus chemically related impurities). As an example, an analysis of a typical sample of one product, Aroclor 1254, detected 112 congeners, none of which comprised more than 9.3% of the mixture (Frame 2001).

Studying the toxicity of such a large group of compounds is not simple. Although there are properties shared by many congeners, there are also clearly differences. In experiments, it is possible to administer single congeners or suitably chosen combinations. Such experiments have yielded insights and suggestions of some general patterns (Hansen 1998). For example, congeners with the highest dioxin-like activity (through binding to the aryl hydrocarbon receptor) tend to be congeners with no chlorines in *ortho* positions. On the other hand, certain neurologic effects tend to be more pronounced in *ortho* congeners. However, the overall picture of the toxicity of the 209 congeners remains quite incomplete.

Humans are always exposed to mixtures of congeners. Although the mixtures seen in the environment differ from those in commercial products because congeners differ in their rate of degradation, individual PCBs are not seen outside the laboratory. This complicates the assessment of human contamination. Chemical assay methods for PCBs have changed over the years (Erickson 1997). In the past, results were reported as single summary measures of PCB concentration, either as estimated Aroclor concentration or as total PCBs. More recently, it has become practical to assay individual congeners. Attention has generally been limited, particularly in large studies, to a relatively small number of congeners that are present in relatively high concentrations. Unfortunately, there is no guarantee that the congeners that are important for health are those that are present at high concentrations. Potencies for dioxin-like effects, for example, differ by orders of magnitude (Van den Berg et al. 1998), and congeners with high dioxin-like potency are generally present at quite low concentrations.

To help deal with this complexity, there have been proposals to group congeners, or at least congeners frequently detected in human tissues, into biologically similar categories (McFarland and Clarke 1989; Wolff et al. 1997). Another proposal developed lists of congeners to be measured based on combinations of concentrations seen in humans and in the environment and information on known toxicity (Jones 1988). These proposals, although representing reasonable approaches in principle, are based on incomplete information about toxicity and do not incorporate information on relative potency. For one group of health outcomes mediated through dioxin-like activity, an approach using sums of concentrations weighted by their potencies to bind to the aryl hydrocarbon receptor (called toxic equivalents) has been developed (Van den Berg et al. 1998); this is suitable for outcomes resulting from this specific mechanism of action but not for others acting through different pathways (Burgin et al. 2001; Kodavanti et al. 2001; Li and Hansen 1996a,

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1996b). A wholly satisfactory approach remains elusive.

In addition, another feature of human contamination needs to be considered. Because humans are generally exposed to similar mixtures, the patterns seen in different individuals tend to have many similarities. Previous investigations, many involving limited numbers of congeners or relatively small populations, have shown that concentrations of certain congeners in humans are positively correlated, with some of the correlations being quite high (DeVoto et al. 1997; Gladen et al. 1999a; Glynn et al. 2000, 2001; Longnecker et al. 2000; van den Berg et al. 1995). To the extent that high correlations exist among congeners, there is both no need to measure them separately and no ability to distinguish their biologic effects. It is therefore of interest to determine the correlation structure among larger numbers of congeners in larger populations, to see whether these kinds of findings hold more generally.

Here we have used previously assayed results on 38 congeners from 497 human milk samples taken from across Canada in 1992 (Newsome et al. 1995) to examine patterns of correlation among congeners. We have also examined correlations of PCBs with some other common organochlorines; although these have different origins, they may travel through the same environmental pathways.

Materials and Methods

The data used here have been described previously (Newsome et al. 1995). Briefly, human milk samples were obtained from 497 women 19–46 years old from five regions across Canada in 1992; women agreed to donate milk after receiving an introductory letter about the study. Concentrations of 38 PCB congeners (or coeluting congener pairs) and a number of other organochlorine compounds were measured by gas chromatography with election capture detection; spiked and unspiked control samples were included in each batch, and every tenth sample was confirmed semiquantitatively by mass spectrometry. Table 1 shows the PCB congeners measured, identifying them both by congener number and chlorine structure. Note that the congener identified as 201 in the original publication is called 199 in current nomenclature (Erickson 1997). PCBs and the other organochlorines measured here are lipophilic, and concentrations of milk lipids vary substantially over the short term, doubling over the course of a single feeding and exhibiting diurnal variation (Jensen et al. 1992). In our samples, the median percentage lipid was 3.1, with a range from 0.1 to 13.5. To eliminate this extraneous variability, we expressed concentrations as nanograms of compound per gram of milk lipid.

For all congeners, some samples were below the minimum quantitation limit. We converted limits originally expressed as nanograms per gram milk to nanograms per gram lipid by using the lipid content for each individual sample. Information on actual concentrations, where available, and on limits, for those not quantified, can be combined using censored data techniques. (Such techniques are more commonly used when large values are only partially known, e.g., when estimating survival times when some individuals are still alive. The principles are identical with small values that are only partially known.) We used standard life-table techniques, specifically the product-limit estimator, to estimate the median and other percentiles of the distributions (Kaplan and Meier 1958). For estimation of correlations, we assumed that all pairs of congeners had joint normal distributions on the logarithmic scale, and used maximum likelihood to estimate the correlation while accounting for the censored observations. As with estimation of percentiles, information on either actual concentrations or limits, whichever was available, was used in the calculation. That is, the likelihood contribution for each sample was either the probability of seeing the observed value (if the sample was quantified) or the probability of being below the quantitation limit (if the sample was not).

Table 1. Distribution of PCB congeners in 497 milk samples from Canada in 1992.

Congener number(s)	Chlorine structure	Percent quantified	Median (ng/g lipid)	90th percentile (ng/g lipid)	Maximum (ng/g lipid)
138	234-245	99.6	24.2	44.5	308
153	245-245	99.6	33.4	62.5	395
118	245-34	98.8	14.2	26.7	213
137	2345-24	98.8	10.0	23.0	736
170	2345-234	98.6	7.8	15.3	70
187	2356-245	98.2	7.2	14.4	51
49	24-25	98.0	9.5	24.0	294
156	2345-34	97.4	5.3	10.9	90
180	2345-245	97.4	17.9	35.9	132
74	245-4	97.2	12.1	21.6	130
203	23456-245	91.5	2.4	5.0	20
105	234-34	90.5	4.4	8.4	72
99	245-24	89.9	11.9	23.2	144
199	2345-2356	89.7	4.3	9.1	46
183	2346-245	88.3	3.6	6.5	75
194	2345-2345	85.9	3.1	6.6	102
28	24-4	84.5	4.1	8.6	96
66	24-34	72.6	3.0	5.7	24
60	234-4	53.1	1.8	8.8	318
157	234-345	51.7	1.4	3.2	28
44	23-25	50.7	2.1	11.2	258
193	2356-345	49.5	1.3	3.7	222
90/101	235-24/245-25	46.9	1.7	4.1	17
128	234-234	43.1	0.9	5.3	22
206	23456-2345	29.8	—	2.2	14
141	2345-25	25.8	—	1.9	12
191	2346-345	25.8	—	1.5	26
129	2345-23	23.7	—	2.5	14
189	2345-345	22.5	—	1.3	23
185	23456-25	22.3	—	1.3	7
52	25-25	21.7	—	3.7	24
110	236-34	19.3	—	5.1	34
151	2356-25	17.9	—	2.5	28
41	234-2	16.9	—	1.3	11
37	34-4	15.5	—	5.9	85
33	34-2	13.9	—	1.9	10
40	23-23	13.9	—	1.1	59
209	23456-23456	13.9	—	1.9	42

Median not shown for those with low percentage quantified because they are unreliably estimated.

Results

The distribution of PCB congeners in these samples has been described previously (Newsome et al. 1995), but some descriptive statistics are given here for convenience (Table 1). Twelve of the congeners were quantified in at least 90% of the samples. Another 12 were quantified in 40–90% of the samples.

The remaining 14 congeners were quantified in fewer than 30% of the samples. For these congeners, available information was quite limited. Among the samples that were quantified, concentrations were usually near the quantitation limit; most were less than twice the limit. When converted to concentration per lipid weight, the varying lipid content of the samples caused considerable overlap between the quantified amounts and the quantitation limits. Those not quantified

could, on a lipid basis, actually be as high as or higher than those quantified, if lipid content was low. For example, for congener 52, there were 108 quantified and 389 not. Those quantified had a median of 3.1 ng/g lipid; for those not quantified, the median quantitation limit was 3.2 ng/g lipid. Results for the other congeners in this group were similar. These 14 congeners were not considered further.

Tables 2 and 3 show correlations among the 24 congeners with at least 40% quantified. Many of the major congeners were highly intercorrelated; this is the case whether one defines major as meaning a high percentage quantified or as meaning a high median concentration. Congeners 138, 153, 156, 157, 170, 183, 187, 194, 199, and 203 formed a particularly tight group; each congener had at least one correlation of 0.90 or higher with another congener in the group, and all correlations among the group were at least 0.67. The mono-*ortho* congeners 74, 105, and 118 had correlations at least 0.80 with each other; correlations with the first group were at least 0.48 and generally much higher. Congener 180 showed moderate to high correlations with these two groups. Congeners 99 and 66 showed more modest correlations yet.

Except the correlations of congener 66 with 90/101 and 28, all other correlations were below 0.5. Two striking exceptions to the pattern of major congeners being highly intercorrelated were congeners 49 and 137. Congener 137 had only moderate correlations with any other congener, and 49 had very low correlations with virtually all other congeners.

We also looked at the correlations of PCBs with other major organochlorine compounds. Table 4 describes the distribution of the 14 compounds that were quantified in at least 40% of the samples. Correlations among these 14 were not generally high (Table 5); the two trichlorobenzenes were fairly highly correlated, as were the trio of *trans*-nonachlor, hexachlorobenzene, and oxychlordane. Most of these compounds showed low correlations with PCBs (Table 6); however, *trans*-nonachlor, *p,p′*-DDE (dichlorodiphenyldichloroethylene) and *o,p′*-DDT (dichlorodiphenyltrichloroethane) showed fairly high correlations with the major correlated PCB groups identified above.

Discussion

Most previous studies giving correlations among congeners involved fewer samples, fewer congeners, or both. However, the results are generally consistent with those found here. Some previous studies presented actual correlations, as we did here. At least five such studies with sample size greater than 100 exist, all with fewer congeners than were studied here (Table 7). There are studies of 9 congeners in 490 women, 4 congeners in 418 women, 18 congeners in 197 women, 4 congeners in 141 patients, and 10 congeners in 120 men. A number of similar smaller studies also exist; details are given in Table 7. Other authors have instead presented groupings suggested by principal components or factor analysis; such analyses provide less detail than the original correlation matrices, but the results are generally similar to those in the

Table 2. Correlations among PCB congeners in 497 milk samples from Canada in 1992, for those with at least 90% quantified.

Congener	153	138	118	137	170	187	49	180	156	74	203	105
153	1											
138	0.99	1										
118	0.83	0.86	1									
137	0.40	0.42	0.37	1								
170	0.94	0.91	0.73	0.43	1							
187	0.88	0.85	0.70	0.41	0.90	1						
49	0.27	0.28	0.27	0.29	0.22	0.25	1					
180	0.81	0.77	0.65	0.37	0.83	0.81	0.30	1				
156	0.95	0.95	0.80	0.41	0.92	0.83	0.24	0.78	1			
74	0.86	0.87	0.85	0.32	0.77	0.70	0.17	0.64	0.83	1		
203	0.80	0.75	0.60	0.40	0.87	0.89	0.16	0.76	0.78	0.62	1	
105	0.77	0.80	0.87	0.32	0.69	0.66	0.21	0.53	0.74	0.80	0.61	1
99	0.70	0.73	0.69	0.28	0.57	0.54	0.04	0.47	0.63	0.71	0.50	0.67
199	0.73	0.69	0.54	0.39	0.83	0.90	0.18	0.75	0.73	0.56	0.96	0.55
183	0.90	0.89	0.74	0.43	0.89	0.91	0.19	0.74	0.84	0.74	0.89	0.74
194	0.71	0.67	0.48	0.42	0.81	0.80	0.11	0.70	0.72	0.54	0.91	0.53
28	0.29	0.32	0.40	0.23	0.29	0.26	0.18	0.23	0.27	0.44	0.20	0.41
66	0.46	0.48	0.61	0.25	0.44	0.43	0.11	0.39	0.44	0.62	0.43	0.69
60	0.12	0.14	0.19	0.26	0.09	0.09	0.16	0.08	0.08	0.13	0.06	0.15
157	0.84	0.85	0.70	0.44	0.85	0.76	0.09	0.68	0.92	0.75	0.79	0.72
44	0.11	0.11	0.13	0.16	0.10	0.15	0.48	0.11	0.08	0.07	0.05	0.07
193	0.32	0.32	0.21	0.20	0.39	0.42	0.00	0.15	0.35	0.25	0.40	0.25
90/101	0.21	0.22	0.33	0.31	0.24	0.28	0.14	0.23	0.21	0.23	0.30	0.39
128	0.31	0.31	0.36	0.46	0.34	0.35	0.00	0.28	0.30	0.32	0.36	0.41

Entries are Pearson correlations on the logarithmic scale.

Table 3. Correlations among PCB congeners in 497 milk samples from Canada in 1992, for those with 40–90% quantified.

Congener	99	199	183	194	28	66	60	157	44	193	90/101	128
99	1											
199	0.40	1										
183	0.66	0.83	1									
194	0.39	0.89	0.78	1								
28	0.28	0.20	0.27	0.17	1							
66	0.49	0.39	0.51	0.35	0.57	1						
60	0.15	0.05	0.19	0.06	0.25	0.26	1					
157	0.58	0.74	0.84	0.72	0.26	0.49	0.07	1				
44	0.00	0.08	0.08	0.08	0.14	0.09	0.27	0.03	1			
193	0.22	0.43	0.43	0.47	0.12	0.19	0.00	0.47	0.05	1		
90/101	0.26	0.30	0.35	0.24	0.33	0.67	0.43	0.32	0.27	0.11	1	
128	0.30	0.35	0.38	0.29	0.23	0.38	0.19	0.38	0.00	0.11	0.31	1

Entries are Pearson correlations on the logarithmic scale.

Table 4. Distribution of other major organochlorine compounds in 497 milk samples from Canada in 1992.

Compound	Percent quantified	Median (ng/g lipid)	90th percentile (ng/g lipid)	Maximum (ng/g lipid)
p,p′-DDE	100.0	168.6	401.9	3,783
trans-Nonachlor	100.0	15.8	27.4	85
Hexachlorobenzene	100.0	13.0	20.3	323
p,p′-DDT	99.2	18.7	32.5	287
Oxychlordane	97.4	12.5	21.2	81
Dieldrin	94.4	8.5	16.9	103
β-Hexachlorocyclohexane	93.4	18.7	37.5	307
o,p′-DDT	82.1	2.8	5.0	39
Pentachlorobenzene	72.0	1.3	2.7	26
cis-Nonachlor	70.0	2.2	7.1	62
Heptachlor epoxide	68.4	2.6	8.4	67
Mirex	57.5	1.7	4.6	30
1,2,3-Trichlorobenzene	54.1	1.9	5.9	236
1,2,4-Trichlorobenzene	49.1	3.4	9.2	118

reports giving correlations. Larsen et al. (1994) measured six congeners; virtually all of the variance was explained by a single principal component, indicating a high degree of intercorrelation. Angulo et al. (1999) suggested a main group of six congeners, with three other groups involving five congeners. Moysich et al. (1999) suggested that 33 congeners should be split into five groups. Löffler and van Bavel (2000) suggested that four congeners be split into two groups.

We found congeners 138, 153, 156, 157, 170, 183, 187, 194, 199, and 203 to be highly intercorrelated, with congener 180 having somewhat lower but still high correlations with this group. This generally agrees with what has been seen in the literature cited above. Congener 180 was sometimes more highly correlated in previous literature than we found it to be; congeners 156 and 170 sometimes had less correlation than we saw. Correlations for congeners 194, 199, and 203 have not been studied previously to our knowledge. We found congeners 74, 105, and 118 to be highly intercorrelated and moderately to highly correlated with the first group. Again, this is in good agreement with the previous literature. We found congener 99 to have moderate correlations with both these groups; previous results show moderate to high correlations. We found congener 66 to have lesser correlations with the primary group; two previous studies of this congener have been inconsistent.

In addition to the congeners we studied, others have been found to be part of this highly intercorrelated group. Congeners 126 (chlorine structure 345-34) and 169 (structure 345-345), both present at much lower concentrations than those we studied, have repeatedly been shown to have moderate to high correlations with the main group (Dewailly et al. 1991; Gladen et al. 1999a; Glynn et al. 2001; Longnecker et al. 2000; van den Berg et al. 1995), as has 167 (structure 245-345) (Glynn et al. 2000, 2001; van den Berg et al. 1995). Furthermore, metabolites of major PCBs have usually been shown to be highly correlated with the parent compounds, as well as with other PCBs correlated with the parents (Newsome and Davies 1996; Sandau et al. 2002; Sjödin et al. 2000).

In contrast to the coherent picture presented by these congeners, congeners 28, 44, 49, 60, 90/101, 128, 137, and 193 showed little correlation with each other or with other congeners in our study. Most previous studies of congener 28 and 90/101 cited above show the same pattern of lack of correlation with other congeners. Correlations for congener 49

Table 5. Correlations among other major organochlorine compounds in 497 milk samples from Canada in 1992.

Compound	*p,p*′-DDE	*trans*-non	HCB	*p,p*′-DDT	Oxychlor	Dieldrin	β-HCH	*o,p*′-DDT	PnCB	*cis*-non	Hep epox	Mirex	1,2,3-TCB	1,2,4-TCB
p,p′-DDE	1													
trans-non	0.68	1												
HCB	0.58	0.72	1											
p,p′-DDT	0.56	0.46	0.54	1										
Oxychlor	0.50	0.76	0.73	0.57	1									
Dieldrin	0.32	0.37	0.28	0.30	0.30	1								
β-HCH	0.48	0.46	0.57	0.50	0.59	0.28	1							
o,p′-DDT	0.57	0.58	0.46	0.50	0.39	0.31	0.28	1						
PnCB	0.19	0.25	0.27	0.19	0.14	0.13	0.07	0.27	1					
cis-non	0.45	0.67	0.49	0.37	0.59	0.40	0.42	0.43	0.21	1				
Hep epox	0.33	0.36	0.31	0.25	0.31	0.65	0.42	0.22	0.27	0.42	1			
Mirex	0.23	0.37	0.26	0.26	0.23	0.16	0.13	0.31	0.27	0.26	0.18	1		
1,2,3-TCB	0.24	0.29	0.29	0.25	0.18	0.18	0.07	0.25	0.40	0.30	0.19	0.29	1	
1,2,4-TCB	0.26	0.35	0.28	0.21	0.27	0.19	0.06	0.28	0.43	0.35	0.26	0.34	0.77	1

Abbreviations: *cis*-non, *cis*-nonachlor; HCB, hexachlorobenzene; β-HCH, β-hexachlorocyclohexane; hep epox, heptachlor epoxide; oxychlor, oxychlordane; PnCB, pentachlorobenzene; 1,2,3-TCB, 1,2,3-trichlorobenzene; 1,2,4-TCB, 1,2,4-trichlorobenzene; *trans*-non, *trans*-nonachlor. Entries are Pearson correlations on the logarithmic scale.

Table 6. Correlations of PCB congeners with other major organochlorine compounds in 497 milk samples from Canada in 1992.

Congener(s)	*p,p*′-DDE	*trans*-non	HCB	*p,p*′-DDT	Oxychlor	Dieldrin	β-HCH	*o,p*′-DDT	PnCB	*cis*-non	Hep epox	Mirex	1,2,3-TCB	1,2,4-TCB
153	0.73	0.80	0.64	0.46	0.55	0.31	0.37	0.70	0.25	0.48	0.27	0.38	0.30	0.35
138	0.73	0.79	0.65	0.48	0.56	0.33	0.37	0.73	0.24	0.45	0.27	0.37	0.29	0.33
118	0.65	0.68	0.58	0.49	0.49	0.28	0.35	0.71	0.18	0.42	0.26	0.33	0.28	0.28
137	0.30	0.28	0.24	0.46	0.14	0.21	0.18	0.24	0.14	0.00	0.13	0.46	0.16	0.08
170	0.63	0.74	0.60	0.41	0.51	0.33	0.35	0.62	0.29	0.45	0.28	0.48	0.31	0.34
187	0.64	0.71	0.55	0.47	0.48	0.30	0.38	0.60	0.23	0.49	0.26	0.42	0.27	0.27
49	0.19	0.26	0.30	0.31	0.13	0.04	0.24	0.20	0.21	0.07	0.20	0.08	0.22	0.11
180	0.56	0.65	0.53	0.39	0.42	0.28	0.33	0.50	0.21	0.36	0.26	0.33	0.35	0.30
156	0.62	0.75	0.59	0.42	0.54	0.29	0.33	0.67	0.24	0.42	0.27	0.42	0.29	0.34
74	0.68	0.77	0.67	0.47	0.61	0.32	0.39	0.68	0.20	0.48	0.28	0.33	0.26	0.34
203	0.55	0.63	0.45	0.39	0.40	0.31	0.29	0.57	0.27	0.45	0.25	0.46	0.29	0.31
105	0.58	0.63	0.55	0.44	0.48	0.29	0.36	0.73	0.23	0.47	0.28	0.38	0.26	0.30
99	0.59	0.55	0.44	0.44	0.49	0.32	0.29	0.56	0.20	0.33	0.22	0.22	0.18	0.26
199	0.49	0.57	0.42	0.38	0.37	0.26	0.30	0.51	0.24	0.40	0.20	0.42	0.23	0.22
183	0.68	0.71	0.58	0.52	0.50	0.35	0.37	0.68	0.31	0.51	0.28	0.46	0.33	0.33
194	0.46	0.54	0.40	0.35	0.32	0.25	0.22	0.50	0.25	0.38	0.18	0.45	0.23	0.24
28	0.27	0.26	0.36	0.34	0.27	0.22	0.25	0.34	0.22	0.12	0.17	0.18	0.11	0.09
66	0.36	0.42	0.37	0.37	0.33	0.29	0.27	0.53	0.40	0.38	0.32	0.35	0.33	0.31
60	0.13	0.06	0.07	0.24	0.03	0.14	0.17	0.17	0.09	0.00	0.20	0.07	–0.16	0.00
157	0.54	0.62	0.53	0.46	0.49	0.24	0.26	0.64	0.24	0.43	0.22	0.48	0.28	0.35
44	0.06	0.18	0.15	0.17	0.05	0.00	0.10	0.15	0.25	0.07	0.21	0.13	0.14	0.13
193	0.23	0.20	0.18	0.29	0.13	0.02	0.02	0.29	0.14	0.21	0.02	0.22	0.18	0.16
90/101	0.16	0.18	0.18	0.26	0.12	0.26	0.24	0.34	0.33	0.24	0.35	0.28	0.17	0.18
128	0.23	0.25	0.26	0.32	0.28	0.16	0.34	0.29	0.07	0.20	0.15	0.32	0.01	0.03

Abbreviations: *cis*-non, *cis*-nonachlor; HCB, hexachlorobenzene; β-HCH, β-hexachlorocyclohexane; hep epox, heptachlor epoxide; oxychlor, oxychlordane; PnCB, pentachlorobenzene; 1,2,3-TCB, 1,2,3-trichlorobenzene; 1,2,4-TCB, 1,2,4-trichlorobenzene; *trans*-non, *trans*-nonachlor. Entries are Pearson correlations on the logarithmic scale.

were studied once previously; in that study, it was rarely detected, but the detection limit was quite high, so little real information was available (Moysich et al. 1999). The remaining congeners in this list are unstudied or were rarely found.

It would be useful if correlation patterns were related to structure in some predictable way. There is some tendency for more highly chlorinated congeners to be part of intercorrelated groups. For example, the group of 10 highly intercorrelated congeners we observed includes four hexachlorinated, three heptachlorinated, and three octachlorinated congeners. However, it is unwise to rely on this pattern; the eight congeners we identify as having essentially no correlation with others include one trichlorinated, three tetrachlorinated, one pentachlorinated, two hexachlorinated, and one heptachlorinated congener. The position of the chlorines present might also be thought to be a useful predictor. We observed a grouping of three congeners with chlorines in *ortho* positions on only one ring. However, the behavior of the mono-*orthos* is not consistent; of the six other mono-*ortho* congeners examined, two are part of the main highly correlated group, one has modest correlations with the main group or the mono-*ortho* cluster, and three have little correlation with any other congeners.

The results demonstrated here have implications for epidemiologic studies relating PCB concentrations to health outcomes in the general population. In older epidemiologic studies, the practical available technologies produced only measures of total PCBs. The increasing development of realistic methods to measure many individual congeners has opened the door to other possibilities, although relatively few studies have made use of this information. In thinking about appropriate ways to proceed, one may consider congeners as roughly being of three kinds, for which different considerations apply.

One group is a set of highly intercorrelated congeners, including most of the major congeners. The high degree of correlation consistently seen among this group means that their biologic effects cannot realistically be separated in human studies. Studying the relationship of each of these congeners to the health outcome in question might possibly suggest associations, especially if there is supporting evidence from laboratory experiments to guide interpretation. However, it would be, at best, difficult for epidemiologic studies to distinguish congeners or metabolites truly related to the outcome from those that are simply fellow travelers through the environment. The difficulty is inherent in the available data and represents intractable confounding that cannot be overcome by use of alternate statistical analysis methods. Measurement of multiple congeners from this group would add little information regarding their separate health effects; this has led to the suggestion of using a single congener, usually 153, to represent the whole group when studying associations with health outcomes (Brouwer et al. 1995).

Another group of congeners will be defined partly by the assay methods used in or proposed for a study. It consists of those that are quantifiable in only a small fraction of the population when using those methods. Measurement of such congeners will generally be uninformative for epidemiologic studies. Some of these congeners could certainly be of

Table 7. Other studies examining correlation patterns among PCB congeners.

Study	Samples	Results presented
Holford et al. (2000)	Breast adipose tissue from 490 women, case–control study of breast cancer, 40–79 years old, United States, 1994–1997	Pearson correlations (eliminating one outlier) among congeners 74, 118, 138, 153, 156, 170, 180, 183, 187
Koopman-Esseboom et al. (1994)	Milk, plasma, cord plasma from 418 new mothers, mean age 29 years old, Netherlands,1990–1992	Spearman correlations among congeners 118, 138, 153, 180
Gladen et al. (1999b)	Milk from 197 new mothers, 16–45 years old, Ukraine, 1993–1994	Spearman correlations among congeners 8/5, 18/17, 28, 44, 52, 66, 101/90, 105, 118, 128, 138/160, 153/132, 170/190, 180, 187, 195/208, 206, 209
Daniel et al. (2001)	Blood from 141 male and female patients with varying complaints, 8–74 years old, Germany, 1992–1998	Spearman correlations among congeners 101, 138, 153, 180
Glynn et al. (2000)	Serum from 120 men, 40–74 years old, Sweden	Spearman correlations among congeners 28, 52, 101, 105, 118, 138, 153, 156, 167, 180
DeVoto et al. (1997)	Serum from 98 male and female fishing boat captains, 20–71 years old, United States, 1991	Pearson correlations (logarithmic scale) among congeners 138, 153, 180
DeVoto et al. (1997)	Plasma from 66 women, controls from breast cancer study, 28–74 years old, United States, 1993–1995	Pearson correlations (logarithmic scale) among congeners 74, 99, 118, 138, 153, 180
Longnecker et al. (2000)	Plasma from 63 male and female blood donors, 17–67 years old, Canada, 1994	Pearson correlations (logarithmic scale) among congeners 99, 118, 126, 138, 153, 156, 169, 170, 180, 187
Luotamo et al. (1991)	Adipose tissue from 59 autopsies, 15–83 years old, Finland (28 serum samples from those 57–83 years old)	Pearson correlations among congeners 18, 28, 33, 47, 66, 74, 101, 138, 153, 156, 171, 183
DeVoto et al. (1997)	Serum from 56 male and female anglers, 29–77 years old, United States, 1991	Pearson correlations (logarithmic scale) among congeners 138, 153, 180
Gladen et al. (1999a)	Blood from 44 male veterans, 41–66 years old, United States, 1991–1992	Spearman correlations among congeners 28, 74, 77, 99, 105, 118, 126, 138, 153, 156, 169, 170, 180, 187
Van den Berg et al. (1995)	Milk from 32 new mothers, Netherlands	Correlations of congeners 118, 153 with 105, 126, 156, 157, 167, 169
Glynn et al. (2001)	Milk from 27 new mothers, 22–35 years old, Sweden, 1996–1999	Spearman correlations among congeners 28, 105, 118, 126, 138, 153, 156, 167, 169, 180
Bush et al. (1985)	Milk from 20 new mothers, United States, 1979	Pearson correlations of congeners 1, 8, 28 with 23 congeners, and of congeners 82, 180 with 32 congeners
Bush et al. (1985)	Milk from 13 new mothers, United States, 1979	Pearson correlations of congeners 1, 8, 28 with 23 congeners, and of congeners 82, 180 with 32 congeners
Larsen et al. (1994)	Milk from 64 new mothers, Italy, some samples pooled prior to analysis	Interpretation of principal components of congeners 28, 74, 118, 153, 180, 194
Angulo et al. (1999)	Milk from 100 new mothers, 15–47 years old, Spain, 1993–1994	Interpretation of principal components as four groups: (congeners 138, 153, 180, 183, 170, 187), (28, 52), (101, 188), (118)
Moysich et al. (1999)	Serum from 192 postmenopausal women, 45–81 years old, United States, 1986–1991	Interpretation of factor analysis as five groups: (congeners 156/171, 172, 180, 187, 194, 195, 203/196, 206), (105/132, 118, 138, 147, 153, 188), (6, 7/9, 47/48, 87, 134, 177), (22, 31/28, 66/95, 101, 128, 129, 141/179, 174/181), (77/110,176, 183, 201 [called 200 in original], 205)
Löffler and van Bavel (2000)	Blood from 309 male and female patients with unspecified symptoms, Germany, 1992–1995	Interpretation of principal components as two groups: (138, 153, 180), (101)

biologic interest, depending on the health outcome under study (Hansen 1998; Rose et al. 2002). However theoretically interesting these congeners may be, studies of their biologic effects will normally yield little if they are present at concentrations too low for the assay methods to reliably distinguish samples with large and small concentrations, or if only a few individuals can be clearly distinguished from those whose concentrations are unquantifiable. Results involving such congeners should be scrutinized carefully; samples that have quantifiable amounts may differ from those not quantifiable simply by having larger sample volume or greater lipid content. If the aim of a particular epidemiologic study requires measurement of such congeners, alternate assay methods may be needed.

Finally, there are congeners that fall into neither of these groups. They are quantifiable in a reasonable fraction of samples and they do not correlate highly with the bulk of major congeners. Measurement of such congeners is neither redundant nor uninformative and will add to the picture of contamination. These congeners are prime candidates for inclusion in epidemiologic studies.

Of course, which congeners should be measured in any specific epidemiologic study will depend on the purpose of the study. If the question being investigated involves a specific congener or set of congeners, then the decision is simple. If the question is broader based, the decision becomes correspondingly less clear. Decisions about which congeners to measure will then depend partly on the concentrations and patterns seen in the particular population under study. This may well require pilot studies. Some patterns appear to be nearly universal; for example, all the evidence to date suggests that congeners 138 and 153 may safely be assumed to be major congeners, highly correlated with each other, in all populations. Other patterns vary considerably; for example, congeners such as 49 and 137, both major congeners in this population, were present in much lower concentrations in other populations (DeCaprio et al. 2000; Humphrey et al. 2000).

We also examined the relationships between PCBs and other organochlorine compounds. The source of these other organochlorines would, of course, be different from PCBs. However, they tend to travel the same pathways as PCBs once they enter the environment, so similar concerns about whether health effects can be distinguished arise. There have been previous examinations of relationships of PCBs and other organochlorines, with quite disparate results. For example, in a study of 858 American infants born in 1978–1982, the correlation of PCBs and *p,p′*-DDE was only 0.23 (Rogan et al. 1987). In samples taken in 1993–1995 from a group of 180 U.S. residents, about half of whom ate presumably contaminated fish, PCBs and *p,p′*-DDE had a Spearman correlation of 0.64 (Schantz et al. 1999). In a recent study of 120 Swedish men, correlations between *p,p′*-DDE and seven major PCBs ranged from 0.37 to 0.76 (Glynn et al. 2000). Generalizations do not seem feasible here, and the correlations seen in each individual population would need to be examined.

In summary, PCB patterns seen in humans are complex, partly predictable, and partly unpredictable. Studies of the relationship of PCBs to health outcomes need to be designed, where feasible, to accommodate these patterns. The congeners examined in most epidemiologic studies to date provide little more information than would measurement of a single representative congener. Consideration should be given to measurement of other congeners less correlated with these, as long as assay methods adequate to allow quantitation are used.

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