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Polychlorinated biphenyl (PCB) exposure assessment by multivariate statistical analysis of serum congener profiles in an adult Native American population ☆

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Abstract

The major determinants of human polychlorinated biphenyl (PCB) body burden include the source and route of exposure and the toxicokinetic processes occurring after uptake. However, the relative importance of each factor for individual subjects cannot currently be determined. The present study characterizes levels and patterns of PCB congeners in a large cohort of adult Akwesasne Mohawks with historical PCB exposure. Total serum PCB ranged from 0.29 to 48.32 ng/g and was higher in adult men than in women (median of 3.81 vs. 2.94 ng/g). The mean serum congener profile for the full cohort was dominated by persistent penta- to hepta-chlorinated biphenyls; several labile congeners were also prominent. In order to provide additional information on individual body burden determinants, multivariate exploratory data analysis techniques were applied to the congener-specific serum PCB data. A self-training receptor model, polytopic vector analysis (PVA), was employed to determine the number, composition, and relative proportions of independent congener patterns that contributed to the overall serum PCB profile for each Mohawk subject. PVA identified five such patterns, each of which was characterized by a unique mix of congeners. One pattern observed in a limited number of Mohawks was similar to those reported for air sampled near contaminated sediment deposits at Akwesasne and for volatilized Aroclor 1248 and is hypothesized to reflect recent inhalation exposure in these subjects. A second pattern was consistent with unaltered Aroclor 1254. A third pattern, resembling Aroclor 1262 but without labile congeners, was correlated with age and is interpreted as representing a lifetime PCB accumulation profile. The final two patterns were dominated by subsets of major persistent congeners and are hypothesized to reflect intermediate bioaccumulation profiles and/or differences in individual toxicokinetics. The results confirm the utility of a multivariate exploratory analysis approach to

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congener-specific PCB data and provide additional insight into the exposure and individual factors that determine PCB body burden in this population.

Keywords: Polychlorinated biphenyls; Native American; Exploratory data analysis; Exposure assessment; Body burden; Congener-specific PCB analysis

1. Introduction

Polychlorinated biphenyls (PCBs) are important members of the group of environmental contaminants known as persistent organic pollutants (POPs) (Johnson et al., 1998; Vallack et al., 1998). These compounds contribute to the POP body burden present in individuals of all species (Jones and de Voogt, 1999; Rodan et al., 1999; Mackay and Fraser, 2000). PCB body burden has historically been characterized by measuring total PCB levels in the lipid portion of the blood. However, this approach provides little information regarding source, route, or timing of exposure or of individual subject factors that could alter body burden. In contrast, these determinants can be reflected in the relative proportion of individual congeners, and congener-specific PCB analyses of biota and human tissue are increasingly reported for this purpose (Hansen, 1998). Full characterization of a subject's PCB body burden at a given point in time requires determination of the absolute and relative levels of up to 150 individual congeners that have been detected in commercial PCB mixtures, environmental media and biota, and human foodstuffs (Jones, 1988; McFarland and Clarke, 1989; Frame, 1997) and that therefore may be present in the lipid portion of blood and fatty tissue.

The route and source of exposure are important determinants of PCB body burden (Hansen, 2001). Diet (in particular ingestion of contaminated fish) is widely regarded as the primary exposure route/source for these pollutants in humans (Humphrey, 1983; Fiore et al., 1989; Asplund et al., 1994; Feeley, 1995; Chiu et al., 2004). In contrast, dermal and inhalation uptake are considered minor routes and most nonaquatic foodstuffs, air, water, and soil as less important sources of PCBs for the general population (Duarte-Davidson et al., 1994a; Laden et al., 1999). While diet is clearly a dominant exposure source for many individuals, direct exposure routes may assume greater significance for sites at which PCB contamination of local environmental media is considerable (Hansen et al., 2003; Orloff et al., 2003). In addition to exposure, toxicokinetic factors will also influence an individual's PCB body burden (Sipes and Schnellmann, 1987; Brown, 1994; Hansen, 1998; van Birgelen and van den Berg, 2000). Biological persistence of specific PCBs and their relative contribution to the body burden varies with chemical structure and depends on tissue affinity and physiological clearance rate. Highly chlorinated (i.e., six or more chlorines) congeners and those with *para*- (i.e., 4,4′-) chlorine-ring substitution generally persist in lipid-rich tissues (Safe, 1994). Because of these complicating factors, it is not possible with currently available exposure assessment tools to quantitate route- and source-specific PCB intake or to predict the resultant body burdens for individual subjects.

While a number of large congener-specific datasets are now available, their analysis has primarily involved descriptive statistics and correlation studies. With these methods, limited success in evaluating congener patterns with respect to contributing sources and modifying factors has been achieved. A promising alternative approach is the application of multivariate exploratory data analysis (EDA). Such "data-mining" techniques can provide important insights into the underlying structure of a complex dataset. In particular, certain EDA methods known as self-training receptor models (also called mixing models) allow contributing chemical fingerprints to be resolved in complex environmental systems without a priori assumption of contributing patterns and with minimal knowledge of source, toxicokinetics, or data structure distribution (Johnson et al., 2002). As applied to congener-specific PCB datasets for biota or human tissue, the goal of EDA would be to extract contributing congener profiles that might be related to specific source patterns, physicochemical alteration mechanisms occurring prior to exposure, or toxicokinetic processes that further modify the patterns following uptake. Such congener patterns could ultimately represent useful route-, source-, or toxicokinetic-dependent exposure markers for these contaminants.

The Mohawk Nation at Akwesasne is a Native American community of about 10,000 people located at the juncture of New York State and the Canadian provinces of Ontario and Quebec on the St. Lawrence River (Santiago-Rivera et al., 1998; Schell and Tarbell, 1998; Hwang et al., 1999). Akwesasne directly abuts a US federal Superfund site, the General Motors Central Foundry Division site. Two New York State Superfund sites, the Reynolds Metal Co. and ALCOA aluminum smelters, are located immediately upriver. These facilities have contaminated the St. Lawrence River and three local tributaries with PCBs, primarily Aroclor 1248 (A1248) (Sokol et al., 1994). Sediments in several locations downstream of these sites are highly contaminated with PCBs. In addition, fish and other

aquatic and terrestrial wildlife have accumulated PCBs and other POPs from past and continuing discharges to local environmental media at Akwesasne (Fitzgerald et al., 1996; Akwesasne Task Force on the Environment Research Advisory Committee, 1997).

The Akwesasne Mohawks have historically depended upon fish as a major source of protein in their diet, and fishing was previously the major occupation of the community (Santiago-Rivera et al., 1998). In the 1980s the St. Regis Mohawk Environmental Health Service and the New York State Department of Health imposed advisories against eating any fish from these waters. The reduction in the consumption of locally caught fish has resulted in a gradual decrease in mean PCB levels in breast milk and serum over the past decade (Fitzgerald et al., 1995, 1999), although recent data indicate that some Mohawks continue to exhibit elevated (i.e., >10 ppb) total serum PCBs (DeCaprio et al., 2000, 2001). While individual body burdens are no longer generally elevated, there are still many important questions among the community regarding the impact of past and current PCB contamination on Mohawk health (Akwesasne Task Force on the Environment Research Advisory Committee, 1997). Over a decade of research involving the Akwesasne Mohawks has been conducted by the State University of New York at Albany (UAlbany) in partnership with the Akwesasne Task Force on the Environment (Santiago-Rivera et al., 1998; Schell and Tarbell, 1998). A large amount of exposure, health, and clinical data has been obtained for more than 1000 Mohawk adults and children. For each participant, data on levels of 91 serum PCB analytes have been collected, making this perhaps the largest congener-specific PCB database available for a Native American population.

The present report characterizes serum PCB congener levels, prevalence, and patterns in adult Akwesasne Mohawks. In addition, an EDA self-training receptor model, polytopic vector analysis (PVA), was employed to explore congener profiles in these subjects. The objectives of the PVA were to determine whether distinct PCB patterns could be detected in the database, to identify a set of independent congener patterns that contribute to the overall serum congener profile for each subject, and to compare the identified patterns with specific PCB exposure sources potentially relevant to the Akwesasne population. This work represents the first reported application of self-training receptor models to human congener-specific PCB data.

2. Materials and methods

2.1. Subject population

The data were generated as part of the UAlbany Superfund Basic Research Program from 1995 to 2000 in support of two epidemiological projects within the program. Sampling and recruitment into the human health studies were performed on a household basis. This process minimized any potential disruptive effects, maximized recruitment efforts, and capitalized upon available environmental sampling data. A listing of all households was constructed by Mohawk field staff with the aid of detailed maps of the Akwesasne Reserve. Once the listing was complete, a simple random sample of households (of a total list of 2089 units) was selected, providing a one-stage cluster sample with respect to individuals in the population. Selected households were visited by project staff, who explained the study objectives and procedures to the family, answered questions, and determined the composition of the family and study eligibility. Detailed explanations were provided regarding the interview process, procedures for obtaining blood samples, and the schedule of incentives. Those who agreed to participate were required to sign a consent form. All human study protocols and consent forms were approved by the UAlbany institutional review board prior to the initiation of the project.

2.2. Blood collection and PCB analysis

Congener-specific serum PCB data were obtained for 753 adult Akwesasne Mohawks (489 women and 264 men) within the age range of 18–95 years. The sample consisted of individuals with varied exposure histories, including those with a range of consumption of locally contaminated fish and wildlife. Data for the present study were collected during 1998–2000. Blood was collected by trained Mohawk staff either at a project laboratory located within the Akwesasne Reserve or at study participants' homes. Subjects were asked not to eat or drink anything after 10 PM on the preceding evening. For PCB analysis, approximately 20 mL of blood was collected from each adult participant by venipuncture into two 10-mL red-top (no additive) Vacutainer tubes. Blood samples were accessioned and processed as previously described (DeCaprio et al., 2000).

An ultratrace analytical method using dual-column gas chromatography with electron-capture detection was employed to determine 91 analytical peaks (representing a total of 100 PCB congeners) in 5-g serum specimens. An analysis was performed concurrently on DB-5 and Apiezon-L capillary columns configured in parallel. Details on sample processing, the analytical method for quantitation of individual congeners, and laboratory quality assurance/quality control procedures have been previously published (DeCaprio et al., 2000; Schell et al., 2003). Method detection limits (MDLs) for individual congeners were generally in the range of 0.01–0.04 ng/g serum, based on a 5-g serum sample (Table 1).

Table 1
Summary statistics for congener-specific serum PCB data; 753 adult Akwesasne Mohawks

Congener[a]	IUPAC No.	MDL[b]	Mean (SD)[c]	Mean (SD)[d]	ROD (%)[e]	% of ∑PCB[f]	Percentiles[g]					Max	CD[h]
							5	25	50	75	95		
∑PCB			***4.39(4.18)***				***0.78***	***1.78***	***3.18***	***5.67***	***12.13***	***48.32***	
236/345 + 234/245 + 2356/34	**138[i] + 164 + 163**	**0.02**	**0.53(0.54)**	**0.52(0.54)**	**100.0**	**12.2**	**0.09**	**0.20**	**0.36**	**0.68**	**1.48**	**5.92**	**0.72**
245/34	**118**	**0.02**	**0.30(0.38)**	**0.29(0.33)**	**99.9**	**6.5**	**0.05**	**0.09**	**0.17**	**0.35**	**0.96**	**5.16**	**0.76**
2345/245	**180**	**0.02**	**0.46(0.48)**	**0.47(0.64)**	**99.9**	**10.2**	**0.06**	**0.15**	**0.32**	**0.60**	**1.34**	**4.48**	**0.66**
245/245	**153**	**0.02**	**0.62(0.61)**	**0.63(0.60)**	**99.7**	**14.6**	**0.11**	**0.24**	**0.44**	**0.82**	**1.68**	**6.68**	**0.62**
245/4	**74**	**0.02**	**0.30(0.45)**	**0.30(0.52)**	**98.1**	**5.6**	**0.02**	**0.06**	**0.15**	**0.37**	**0.99**	**4.79**	**0.66**
235/24 + 245/25	**90 + 101[i]**	**0.02**	**0.07(0.06)**	**0.07(0.06)**	**97.7**	**2.5**	**0.02**	**0.04**	**0.06**	**0.09**	**0.19**	**0.65**	**0.89**
2356/245	**187**	**0.02**	**0.18(0.23)**	**0.19(0.25)**	**97.3**	**3.8**	**0.02**	**0.05**	**0.11**	**0.23**	**0.56**	**2.52**	**0.42**
245/24	**99**	**0.02**	**0.23(0.27)**	**0.24(0.30)**	**96.0**	**5.4**	**0.03**	**0.09**	**0.15**	**0.29**	**0.68**	**2.58**	**0.50**
236/34	**110**	**0.02**	**0.07(0.06)**	**0.07(0.06)**	**96.0**	**2.5**	**0.02**	**0.03**	**0.06**	**0.09**	**0.18**	**0.55**	**0.85**
2345/2356	**199**	**0.01**	**0.11(0.14)**	**0.12(0.19)**	**94.7**	**2.4**	**—**	**0.03**	**0.07**	**0.15**	**0.35**	**1.54**	**0.62**
2345/234	**170**	**0.02**	**0.12(0.13)**	**0.12(0.15)**	**94.6**	**2.5**	—	**0.04**	**0.08**	**0.16**	**0.34**	**1.44**	**0.68**
234/25	**87**	**0.02**	**0.05(0.03)**	**0.05(0.03)**	**93.9**	**1.7**	—	**0.03**	**0.04**	**0.06**	**0.11**	**0.33**	**0.84**
235/245	**146**	**0.02**	**0.09(0.11)**	**0.09(0.11)**	**91.5**	**1.9**	—	**0.03**	**0.06**	**0.11**	**0.27**	**1.17**	**0.41**
2346/245	**183**	**0.01**	**0.05(0.06)**	**0.05(0.08)**	**87.6**	**1.1**	—	**0.01**	**0.04**	**0.06**	**0.15**	**0.75**	**0.31**
234/34	**105**	**0.02**	**0.07(0.11)**	**0.07(0.08)**	**86.3**	**1.5**	—	**0.02**	**0.04**	**0.08**	**0.24**	**1.55**	**0.63**
2356/234	**177**	**0.01**	**0.04(0.06)**	**0.04(0.06)**	**85.4**	**0.8**	—	**0.01**	**0.02**	**0.05**	**0.13**	**0.70**	**0.40**
2345/34	**156**	**0.02**	**0.10(0.12)**	**0.10(0.15)**	**84.6**	**2.0**	—	**0.03**	**0.06**	**0.13**	**0.31**	**1.08**	**0.51**
2345/2346	196	0.01	0.03(0.04)	0.03(0.04)	82.3	0.7	—	0.01	0.02	0.04	0.10	0.37	
2345/2345	**194**	**0.02**	**0.09(0.13)**	**0.10(0.15)**	**82.2**	**1.8**	—	**0.02**	**0.06**	**0.12**	**0.28**	**1.56**	**0.66**
23456/245	**203**	**0.02**	**0.06(0.08)**	**0.06(0.07)**	**78.6**	**1.1**	—	**0.02**	**0.03**	**0.08**	**0.18**	**0.98**	**0.59**
236/25	**95**	**0.02**	**0.03(0.03)**	**0.03(0.03)**	**74.9**	**1.0**	—	—	**0.02**	**0.04**	**0.10**	**0.32**	**0.65**
25/25	**52**	**0.02**	**0.03(0.04)**	**0.04(0.03)**	**73.2**	**1.1**	—	—	**0.03**	**0.05**	**0.11**	**0.24**	**0.78**
234/235	130	0.01	0.02(0.02)	0.02(0.02)	69.6	0.4	—	—	0.01	0.03	0.06	0.24	
24/34	**66**	**0.02**	**0.04(0.06)**	**0.04(0.04)**	**68.0**	**0.7**	—	—	**0.02**	**0.04**	**0.12**	**0.91**	**0.54**
345/24 + 236/245	**123 + 149[i]**	**0.02**	**0.03(0.03)**	**0.03(0.03)**	**67.9**	**0.8**	—	—	**0.02**	**0.04**	**0.08**	**0.25**	**0.57**
2346/2356	**201**	**0.02**	**0.04(0.12)**	**0.04(0.05)**	**65.9**	**0.7**	—	—	**0.02**	**0.05**	**0.11**	**2.69**	**0.24**
236/23	84	0.02	0.02(0.02)	0.02(0.01)	61.8	0.6	—	—	0.02	0.03	0.05	0.22	
23456/2345	206	0.02	0.06(0.16)	0.06(0.12)	61.6	1.0	—	—	0.02	0.07	0.20	3.24	
23456/34	190	0.02	0.03(0.04)	0.03(0.03)	61.2	0.6	—	—	0.02	0.04	0.10	0.55	
2345/4	114	0.02	0.04(0.07)	0.05(0.07)	60.0	0.7	—	—	0.03	0.06	0.14	0.57	
2345/235	172	0.02	0.03(0.04)	0.03(0.03)	57.2	0.5	—	—	0.02	0.04	0.09	0.48	
23/25	**44**	**0.02**	**0.02(0.03)**	**0.03(0.02)**	**56.0**	**0.7**	—	—	**0.02**	**0.03**	**0.08**	**0.19**	**0.52**
2345/24	137	0.02	0.03(0.03)	0.03(0.03)	55.6	0.5	—	—	0.02	0.04	0.09	0.26	
2356/25	151	0.02	0.02(0.02)	0.02(0.01)	54.4	0.4	—	—	0.02	0.02	0.05	0.14	
2346/34	158	0.01	0.01(0.02)	0.01(0.01)	53.3	0.2	—	—	0.01	0.02	0.03	0.22	
25/34	**70**	**0.02**	**0.02(0.03)**	**0.03(0.02)**	**48.7**	**0.6**	—	—	—	**0.03**	**0.06**	**0.25**	**0.60**
24/4	**28**	**0.02**	**0.03(0.06)**	**0.04(0.08)**	**47.4**	**0.9**	—	—	—	**0.04**	**0.16**	**0.46**	**0.54**
235/25	92	0.02	—	0.02(0.01)	45.8	0.3	—	—	—	0.02	0.04	0.24	
23456/234	195	0.02	0.02(0.03)	0.02(0.02)	44.8	0.3	—	—	—	0.03	0.06	0.27	
2345/25	141	0.02	—	0.02(0.01)	40.1	0.3	—	—	—	0.02	0.04	0.13	
2345/236	174	0.01	0.01(0.02)	0.01(0.01)	39.2	0.2	—	—	—	0.01	0.03	0.47	
24/24 + 236/3	47[i] + 59	0.02	0.02(0.03)	0.02(0.04)	31.3	0.5	—	—	—	0.03	0.08	0.28	
245/23	97	0.02	—	0.02(0.01)	31.3	0.3	—	—	—	0.02	0.04	0.17	
23/34	56	0.02	—	0.02(0.01)	29.7	0.2	—	—	—	0.02	0.03	0.08	
2346/234	171	0.02	—	0.02(0.03)	29.5	0.2	—	—	—	0.02	0.06	0.44	
234/234	128	0.02	—	0.02(0.01)	28.7	0.2	—	—	—	0.02	0.04	0.35	
25/4	**31**	**0.02**	—	**0.02(0.04)**	**27.8**	**0.4**	—	—	—	**0.02**	**0.08**	**0.19**	**0.60**
25/2	**18**	**0.02**	—	**0.02(0.01)**	**27.2**	**0.3**	—	—	—	**0.02**	**0.05**	**0.09**	**0.53**
234/236	132	0.02	—	0.02(0.01)	25.9	0.3	—	—	—	0.02	0.04	0.23	
245	29	0.01	—	0.01(0.01)	23.5	0.2	—	—	—	—	0.03	0.20	
236/236	136	0.03	—	—	22.2	0.2	—	—	—	—	0.05	0.16	
2/4	**8**	**0.02**	—	—	**21.8**	**0.3**	—	—	—	—	**0.05**	**0.44**	**0.35**
34/2	**33**	**0.02**	—	**0.02(0.03)**	**21.0**	**0.3**	—	—	—	—	**0.06**	**0.36**	**0.32**
2346/25	144	0.02	—	—	18.6	0.1	—	—	—	—	0.03	0.25	
24/25	49	0.03	—	—	18.5	0.4	—	—	—	—	0.10	0.22	
23456/236	200	0.02	—	—	18.2	0.1	—	—	—	—	0.04	0.13	
2356/236	179	0.01	—	—	18.1	0.1	—	—	—	—	0.02	0.06	
2356/23	134	0.01	—	—	17.4	0.1	—	—	—	—	0.02	0.17	
23/24	42	0.01	—	—	16.6	0.1	—	—	—	—	0.02	0.03	

Table 1 (*continued*)

Congener[a]	IUPAC No.	MDL[b]	Mean (SD)[c]	Mean (SD)[d]	ROD (%)[e]	% of ∑PCB[f]	Percentiles[g]					Max	CD[h]
							5	25	50	75	95		
34/34	77	0.02	—	—	16.3	0.2	—	—	—	—	0.04	0.22	
26/34	71	0.02	—	—	15.5	0.2	—	—	—	—	0.06	0.28	
25/26	53	0.02	—	—	13.5	0.1	—	—	—	—	0.02	0.09	
23/23	40	0.02	—	—	12.6	0.1	—	—	—	—	0.02	0.29	
2346/236	176	0.01	—	—	12.2	0.1	—	—	—	—	0.01	0.15	
2/2 + 3	4[i] + 2	0.02	—	—	11.3	0.3	—	—	—	—	0.09	0.32	
26/4 + 23/2	**32 + 16**	**0.04**	—	—	**11.0**	**0.2**	—	—	—	—	**0.06**	**0.12**	**0.24**
26/2	19	0.03	—	—	10.9	0.1	—	—	—	—	0.05	0.28	
236 + 26/3	24 + 27	0.02	—	—	10.8	0.1	—	—	—	—	0.03	0.19	
25/3	26	0.03	—	—	9.7	0.1	—	—	—	—	0.04	0.41	
4/4	15	0.03	—	—	8.9	0.1	—	—	—	—	0.03	0.41	
24/2	17	0.03	—	—	8.9	0.1	—	—	—	—	0.03	0.40	
235/23	83	0.02	—	—	8.9	0.1	—	—	—	—	0.02	0.07	
24/3	25	0.01	—	—	6.2	0.0	—	—	—	—	0.02	0.03	
24	7	0.02	—	—	5.8	0.0	—	—	—	—	0.02	0.19	
3/4	13	0.02	—	—	5.8	0.1	—	—	—	—	0.03	0.30	
23/4	22	0.04	—	—	5.7	0.1	—	—	—	—	0.05	0.16	
23/26	46	0.02	—	—	5.6	0.0	—	—	—	—	0.02	0.06	
2356/24 + 235/34	147 + 109[i]	0.03	—	—	5.6	0.0	—	—	—	—	0.03	0.25	
2/6	10	0.02	—	—	5.4	0.0	—	—	—	—	0.02	0.05	
236/4	64	0.02	—	—	4.4	0.0	—	—	—	—	—	0.06	
236/24	91	0.03	—	—	4.2	0.0	—	—	—	—	—	0.19	
25	9	0.02	—	—	4.0	0.0	—	—	—	—	—	0.06	
2345/23	129	0.02	—	—	2.4	0.0	—	—	—	—	—	0.07	
24/26	51	0.05	—	—	1.7	0.0	—	—	—	—	—	0.13	
2/3	6	0.02	—	—	1.5	0.0	—	—	—	—	—	0.60	
23456/25	185	0.02	—	—	1.2	0.0	—	—	—	—	—	0.11	
245/3	67	0.02	—	—	1.1	0.0	—	—	—	—	—	0.51	
236/2	45	0.04	—	—	0.7	0.0	—	—	—	—	—	0.10	
235/4	63	0.01	—	—	0.7	0.0	—	—	—	—	—	0.04	
2	1	0.15	—	—	0.1	0.0	—	—	—	—	—	0.32	
4	3	0.04	—	—	0.1	0.0	—	—	—	—	—	0.05	

[a]Chlorine positions on ring A/chlorine positions on ring B. Congeners in bold are those selected for PVA (see text).
[b]Method detection limit (ng/g serum).
[c]Mean (SD) (ng/g serum) of all samples with zero substituted for nondetects. Results using one-half MDL substitution were virtually identical and are not shown.
[d]Mean (SD) (ng/g serum) of all samples with MLE substitution for nondetects as described under Materials and methods.
[e]Rate of detection of analyte (number of samples above detection limit/total number of samples).
[f]Arithmetic mean of congener concentration/mean total serum PCB × 100%.
[g]Percentile distribution of each analyte concentration (ng/g); zero substituted for nondetects.
[h]Miesch coefficient-of-determination for analyte (see text).
[i]Expected major congener in coeluting peak based on biological persistence and other relevant data (Brown, 1994; Hansen, 1998).

2.3. Descriptive statistics and data visualization

Total serum PCB levels were calculated as the sum of the concentrations of all PCB analytes above the MDL. Since all subjects were fasted prior to blood collection and as only within-cohort comparisons were planned, PCB data were expressed and analyzed on a whole-weight (ng/g serum; ppb) basis (Phillips et al., 1989; Hebert and Keenleyside, 1995). Descriptive statistics included the mean, standard deviation (SD), maximum, percentile ranges (with median), rate-of-detection (ROD; percentage of samples above the MDL), and mean percentage of total PCBs for each analyte. Most congeners were detected in only a subset of the samples, a finding that can bias the calculation of descriptive statistics and the calculation of central tendencies. Means and SDs were calculated using two common substitution methods for nondetected analytes, i.e., substitution with zero and with one-half the MDL (USEPA, 1998). In addition, the maximum likelihood estimation (MLE) method of Helsel and Cohn (1988) was used to calculate these summary statistics for congeners that were detected in at least 20% of the samples. As described by these authors, results are unreliable for analytes with an ROD of $<20\%$; thus, means and SDs for such congeners were not calculated by the MLE method.

2.4. Exploratory data analysis

Initial EDA efforts utilized two-dimensional bar graphs, which have been usefully employed for the examination of congener-specific PCB data from multiple samples (Fitzgerald et al., 1995, 1998). To facilitate visual and statistical comparability with the present data, PCB patterns from analyses conducted by other investigators are shown using the same selection of congeners and elution order as reported in the current study. Statistica Version 6.1 software (StatSoft, Inc., Tulsa, OK, USA) was used to generate these plots and for general statistical analysis. Significance testing was performed by ANOVA and post hoc comparisons by a Newman–Keuls test using the appropriate modules of Statistica. PCB congeners were numbered according to the IUPAC convention (Ballschmiter et al., 1993; Guitart et al., 1993).

PVA was the primary EDA approach for the identification of contributing congener patterns in the Mohawk cohort data. PVA is a self-training receptor modeling method used to determine three parameters of interest in an environmental/biological system: (1) the number of patterns (i.e., "end-members" in PVA terminology) contributing to the system, (2) the chemical composition of each end-member, and (3) the relative contribution of each end-member in each sample. PVA utilizes principal components analysis (PCA) as an intermediate step to reduce the dimensionality of a dataset, followed by rotation of the reduced data matrices to give an oblique solution using an iterative process with explicit nonnegativity constraints (Full et al., 1981, 1982; Johnson et al., 2002). For the present study, the output of PVA modeling consisted of a set of independent serum PCB congener patterns (end-members) and the relative proportion of each pattern present in the overall congener profile for each study subject. By definition, the mixing proportions for all end-members must sum to 100% for each subject.

PVA was conducted using software written in the MATLAB high-level programming language (The Mathworks, Natick, MA, USA). The PVA algorithm as implemented in this study (including data transformations and goodness-of-fit diagnostics) was based on original published algorithms (Klovan and Imbrie, 1971; Klovan and Miesch, 1976; Miesch, 1976a; Full et al., 1981, 1982) and is presented in its entirety by Johnson et al. (2002). A commercial version of the PVA software is available through Tramontane, Inc. (available at URL http://www.etramontane.com). Data screening and outlier identification were conducted in accordance with methods also described by Johnson et al. (2002). The evaluation of goodness-of-fit included Miesch coefficients-of-determination (CD) and associated scatter plots (Miesch, 1976b; Johnson et al., 2000) as well as other indices.

After the number of end-members was determined through goodness-of-fit analysis, end-member chemical compositions and mixing proportions were resolved using the DENEG algorithm of Full et al. (1981). DENEG is an iterative algorithm that alternately adjusts mixing proportions and composition matrices such that neither matrix contains negative values. PVA allows for slight negative mixing proportions (i.e., end-member proportions of $<0\%$) in the model solution to account for noise or error in the system, with a typical default negativity tolerance of -5% (Full et al., 1981). Such nonnegativity constraints and tolerances are a common feature of all receptor model methods. In the present study, tolerance had to be relaxed to -12% in order for the model to converge. The potential implications of this observation are discussed later in this report. Similarity between congener patterns was assessed quantitatively using the cosine θ metric (Davis, 1986), which compares two patterns by treating each as a multidimensional vector and calculating the cosine of the angle between those two vectors. This metric is a geometric calculation between two vectors and thus does not carry any inherent implications of regression diagnostics (as do Pearson and Spearman correlation coefficients) or data distribution.

The full adult Mohawk serum PCB dataset consisted of 753 samples with 91 analytes (chromatographic peaks) per sample (DeCaprio et al., 2000). Many analytes were not detectable in many of the subjects. Because statistical treatment of nondetect data can influence the results of PVA and other multivariate analyses, selection criteria (see below) were established to limit the number of analytes retained in the initial PVA model. The handling and evaluation of nondetects in receptor models (and in particular in PVA models) is discussed in detail by Johnson et al. (2002). With regard to the PVA model, MLE-based substitutions for nondetects are not applicable. This approach takes into account the MDL and number of nondetects for an analyte in the calculation of means and does not require the assignment of a proxy value for each and every censored data point. In contrast, methods such as PVA do require substitution for censored data elements. The most commonly used schemes are substitution with zero or substitution with one-half the MDL. Both approaches were evaluated for use in the present study.

As the primary goal of this study was to identify the major contributing end-members in the Mohawk serum PCB dataset, initial analyses included only the most prevalent analytes (i.e., those in the upper tertile based upon the ROD; see Table 1). In addition, due to the high proportion of chlorinated biphenyls (CBs) 8, 18, 16 + 32, 28, 31, 33, 44, and 70 in Aroclor 1248, the major PCB mixture contaminating the Akwesasne Mohawk Reserve (ATSDR, 1999), these congeners were added back into the model. Although not generally prevalent in Mohawk

serum, these congeners were measured at relatively high levels when present (Table 1). Subjects characterized as gross outliers based on the results of a Miesch CD plot analysis were removed from the dataset prior to PVA (see below). While the anomalous PCB profiles of these individuals are important and are the subject of continuing investigation, the focus in the present study was to determine the most common and consistent contributing end-member patterns present in the Mohawk population. Based on the data-screening procedure, the final dataset submitted for the PVA consisted of 32 analytical peaks (a total of 37 PCB congeners) for 702 subjects.

3. Results

3.1. Descriptive statistics and serum PCB congener profiles

Total serum PCB in all 753 Mohawk adults ranged from 0.29 to 48.32 ng/g. This wide range was consistent with the subject age span and the inclusion of both local fish consumers and nonconsumers in the sample. Based on zero and one-half MDL substitution for nondetects, mean total serum PCB levels for the full cohort were 4.39 ± 4.18 and 5.04 ± 4.13 ng/g, respectively, while median total PCB was 3.18 ng/g (Table 1). Total PCBs and levels of individual congeners were log-normally distributed. Consequently, the MLE-based substitution method was also employed for the calculation of individual analyte means. However, only minor differences were noted between mean congener levels calculated using the various nondetect substitution approaches (Table 1).

The median total serum PCB level in adult men was higher than that in adult women (i.e., 3.81 vs. 2.94 ng/g, respectively). A significant correlation ($r^2 = 0.41$; $P < 0.05$) between age and total serum PCB was noted for all subjects combined. While this correlation was significant, considerable scatter about the regression line was observed, suggesting that age is not the sole determining factor for PCB body burden in this cohort. Highly elevated (>20 ng/g) serum PCB levels were also noted in a subset (3%) of Mohawk men.

Table 1 presents individual serum PCB congener prevalence data for all 753 Mohawk participants. The congener content was dominated by penta- to octa-CBs. The highest concentration analytes were the persistent CBs 153, 138 + 163 + 164, 180, and 118 (means of 0.63, 0.52, 0.47, and 0.29 ng/g, respectively, based on MLE substitution), which were observed in virtually all subjects. Other major congeners included persistent CBs 99 and 187. In addition, the tetra-CB 74 was present in high proportions in many subjects. Several labile congeners, including CBs 52, 47 + 59, 95, 90 + 101, 110, and 151, were also routinely detected. A number of di- and tri-CBs were detected in limited number of individuals.

Fig. 1A shows the mean serum congener profile (the level of each congener normalized to the mean percentage of total PCB) for the 32 analytes and 702 subjects selected for PVA modeling (see below). Fig. 1B compares mean congener profiles for the youngest and oldest 5% (age ranges of 18–24 and 72–95, respectively) Mohawk subjects. Significant age-dependent differences in the relative proportions of a number of congeners were detected (Fig. 1B). In general, older subjects exhibited higher proportions of hepta- and higher chlorinated congeners and of CB 74, while younger individuals exhibited increased proportions of tetra- and penta-CBs.

3.2. Characteristics of the PVA model

In PVA, the determination of the number of end-members (i.e., independent contributing patterns) in a model is accomplished by an evaluation of the number of significant principal components (PCs) in the model. For the adult Mohawk serum PCB dataset, initial analyses demonstrated that five PCs were sufficient to account for 90.5% of the variance. As discussed previously, goodness-of-fit in PVA is also evaluated by more stringent criteria, i.e., the calculation and inspection of Miesch CDs and scatter plots. CD scatter plots evaluate goodness-of-fit on a congener-by-congener basis. For each scatter plot, the reported CD describes the variance for that congener with respect to the 1:1 fit line for each plot. In preliminary PVA models for the present dataset, options using either zero or one-half the MDL for nondetect substitution were evaluated. The zero-substitution option resulted in a PVA model with a minimum CD of 0.24 rather than 0.06. In addition, the substitution method did not change either the interpretation of the end-member congener patterns or the relative contributions of those patterns for each sample. Consequently, the final PVA model employed zero substitution for all analyte concentrations below the MDL.

The CD values shown in Table 1 are for the dataset after gross outliers were removed (see below) and ranged from 0.24 (CB 32 + 16 and CB 201) to 0.89 (CB 90 + 101). This overall goodness-of-fit was lower than that typically observed for PVA models of PCBs in environmental media such as sediment and water (Johnson et al., 2000). The lower goodness-of-fit observed for certain analytes suggested that more than five end-members might be required to account for the overall variance in the Mohawk serum PCB dataset (i.e., there were additional sources of systematic variance present). However, while goodness-of-fit improved as additional PCs were retained (as it must, by definition),

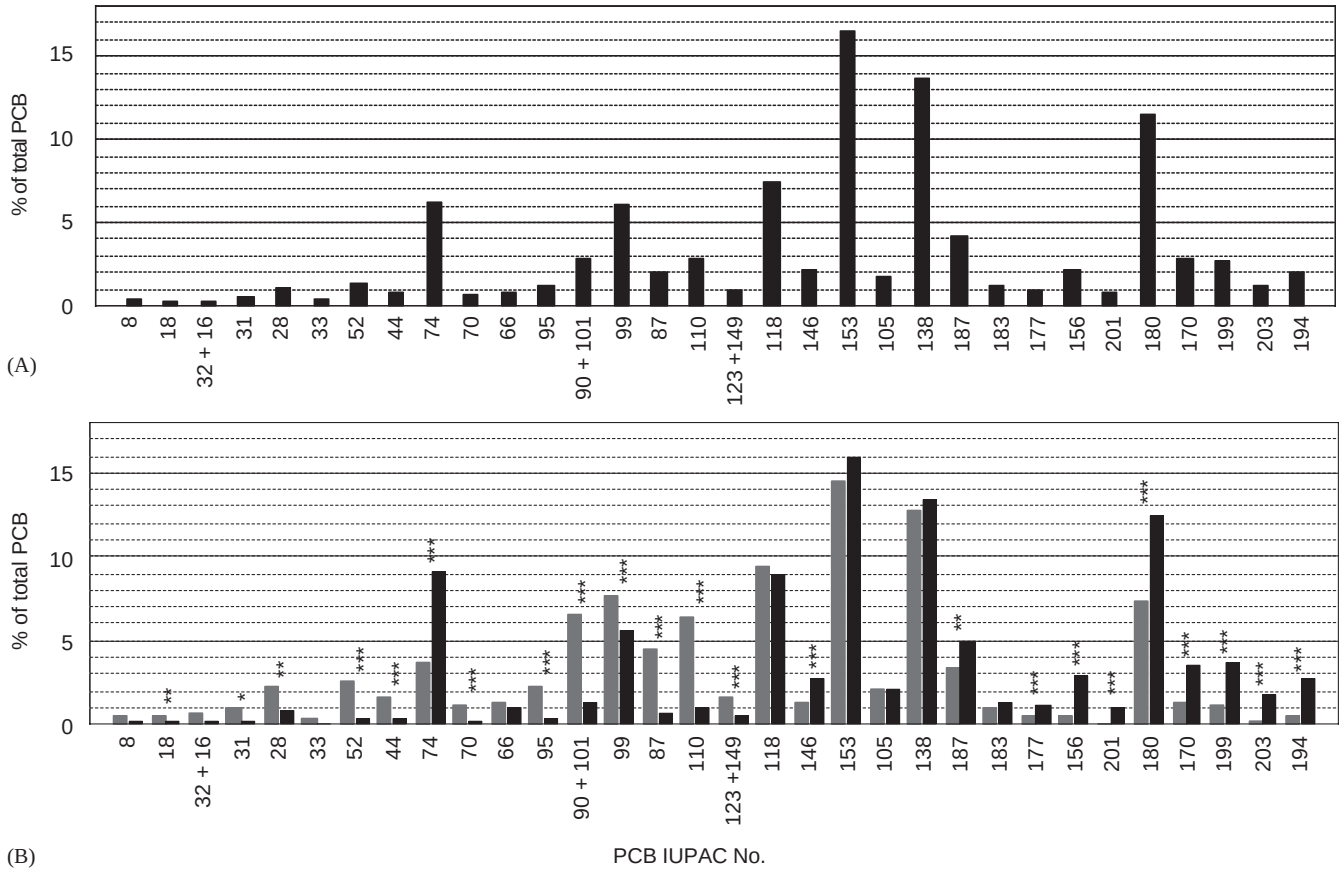

Fig. 1. (A) Mean serum PCB congener profile for 753 adult Akwesasne Mohawks, (B) Mean serum PCB congener profiles for the youngest 5% (gray bars) and oldest 5% (black bars) adult Akwesasne Mohawks. Data for individual CB analytes are normalized to the percentage of total PCB. The congeners shown are those selected for PVA. Statistically significant differences (by ANOVA and the Newman–Keuls test) between the youngest and oldest subject data are indicated (*$P<0.05$; **$P<0.01$; ***$P<0.001$).

there was no clear threshold number of end-members that resulted in a dramatic improvement in the fit of many congeners, i.e., the improvement in fit was very gradual. In addition, as six, seven, eight, and higher-numbered end-member models were resolved and evaluated, the new end-member patterns differed in degree rather than in kind, i.e., the new patterns appeared to be intermediate variants of existing end-members. Consequently, the results presented below were derived from the five end-member PVA model, which described the major patterns observed in this dataset.

Miesch CD scatter plots were also used to identify individual subject data with poor fit to the model (outliers), as indicated by substantially higher or lower experimentally measured levels compared to calculated values for one or more specific analytes. In the present study, outliers generally exhibited a higher measured than predicted level, an observation not uncommon with PVA of PCB data (Johnson et al., 2000, 2002). These outliers are of interest for future study, since they may identify subjects with unique or anomalous serum PCB congener patterns. However, they were removed from the present PVA model, which sought to identify PCB patterns for the dataset as a whole.

3.3. PCB composition and age dependence of individual end-member patterns

Discussion of the results of a PVA model applied to environmental media typically includes detailed description of the chemical compositions of derived end-members, the relative contribution of the end-member patterns in specific media, and their potential interpretation in the context of known chemical sources and alteration mechanisms (Johnson et al., 2000). A similar approach was employed in the present study, for which visual and statistical (cosine θ metric) comparisons were made between the major serum end-member patterns and other potentially relevant PCB compositional profiles determined in this laboratory and from other published sources.

Given the marginal fit for some analytes in the PVA model and the novelty of its application to human data, it was also crucial to evaluate whether derived end-member patterns were characteristic of actual individual

Table 2
Total serum PCB levels and PVA mixing proportions for individual Mohawk subjects exhibiting the highest proportional content of each end-member pattern

Subject	ΣPCB[a]	Mixing proportions (%)[b]				
		EM-1	EM-2	EM-3	EM-4	EM-5
1	4.20	**46.2**	30.3	5.2	11.7	6.6
2	1.83	7.0	**74.2**	−1.8	10.4	10.2
3	1.99	−4.5	6.9	**70.1**	30.8	−3.3
4	0.41	−5.9	18.7	−10.2	**83.6**	13.8
5	19.21	0.9	−4.1	18.8	39.3	**45.1**
All[c]	4.39	4.8	14.3	27.4	**41.5**	12.0

[a]Mean total serum PCB (ng/g; zero substituted for nondetected congeners).

[b]Proportion (%) of subjects' overall serum PCB congener profile accounted for by each PVA end-member pattern. Value in bold is the proportion of the major contributing end-member pattern for each subject (see also Figs. 2–6 for end-member patterns and individual subject serum profiles). Negative values are due to the maximum negativity tolerance of −12% allowed in the PVA model (see text). By definition, the mixing proportions for all five end-members must sum to 100% for each subject.

[c]Mean proportion of each end-member pattern present in the averaged serum PCB profile for the full PVA dataset of 702 subjects.

serum profiles evident in the cohort. Therefore, the composition of each derived end-member was also compared with the congener pattern of the subject exhibiting the highest proportion of that end-member pattern contributing to his or her overall serum PCB profile. The relative proportions of each end-member pattern in the serum PCB profile, in addition to total serum PCB data for each of these five subjects, are summarized in Table 2. As discussed above, the mixing proportions for all end-members must sum to 100% for each subject. Table 2 also presents the relative contribution of each end-member pattern to the mean serum congener profile (i.e., Fig. 1A) for the full Mohawk cohort. Throughout this report, end-member patterns are presented with individual analyte data normalized to the percentage of the total composition for the subset of 32 analytes (total of 37 congeners) selected for PVA as described previously.

The composition of the first end-member pattern (EM-1; Fig. 2A) consisted primarily of di- to penta-substituted CBs, with tri- and tetra-CBs dominating, along with low proportions of several hepta-CBs. Most of these congeners are thought to be readily metabolized (labile) in mammalian tissue, although CB 28, the highest contributing congener in EM-1, is more persistent than other EM-1 congeners due to its *p*,*p*′-chlorine-substitution pattern (Brown, 1994). Fig. 2D shows the serum congener profile for the subject with the highest proportion of EM-1. This subject's serum congener profile contained a 46% contribution from this end-member pattern (Table 2, subject 1; Fig. 3A, circled symbol), an observation consistent with the presence of lower CBs in a pattern analogous to that of EM-1. This serum profile (Fig. 2D) also clearly differed from the mean PCB profile of the Mohawk cohort (Fig. 1A) in its complement of low-chlorinated congeners. Fig. 3A illustrates the relationship between age and the relative proportion (i.e., "fractional contribution") of the EM-1 congener pattern present in the serum PCB profile for each Mohawk adult. Most subjects exhibited low proportions of this pattern, as reflected by the large grouping of data points around zero in Fig. 3A and by the 4.6% contribution of EM-1 to the averaged serum PCB profile for the full cohort (Fig. 1A; Table 2). However, Fig. 3A also indicates that approximately 5% of subjects displayed EM-1 proportions of 20% or greater. Although no clear age dependence was apparent for EM-1, when this end-member pattern accounted for >20% of the total serum PCB profile, it was generally in Mohawks younger than 40 years of age.

Among potentially relevant source patterns, quantitative comparison of the EM-1 composition revealed the highest similarity (cosine $\theta = 0.91$) with a profile (Fig. 2B) previously reported in air samples taken near a heavily PCB-contaminated water body on the Akwesasne Reserve (i.e., "Contaminant Cove") located just east of the General Motors landfill (Chiarenzelli et al., 2000) and another derived in laboratory studies (Chiarenzelli et al., 1997) of volatilized A1248 (not shown). In contrast, the EM-1 pattern was less consistent with that of native commercial A1248 liquid (Fig. 2C), the major source of Aroclor in the St. Lawrence River near Akwesasne (Sokol et al., 1994). For example, the major congeners 74, 99, 87, 110, and 118 present in the native commercial mixture were missing from EM-1, while hepta-CBs are not present at significant levels in A1248.

Fig. 4A shows the composition of EM-2, a pattern dominated by penta- and hexa-CBs. CB 153 was the major persistent congener present in EM-2, along with CBs 138 + 163 + 164 and 180. In addition, major congeners in this pattern included labile CBs such as 95, 90 + 101, 87, 110, and 123 + 149. Fig. 4C shows the serum congener profile for a subject with a 74% contribution (Table 2, subject 2) from the EM-2 pattern. The major EM-2 congeners are clearly apparent in this subject's profile. However, the presence of CBs 74, 66, 146, and 187 in this profile, which are absent from EM-2, is consistent with contributions from other end-member patterns (Table 2). Fig. 3B shows the relationship between the relative proportion of EM-2 and subject age for the Mohawk cohort. Although considerable scatter was apparent, there was a significant ($r^2 = 0.31$; $P < 0.05$) negative correlation with age for all subjects. Several individuals younger than 30 years of age exhibited very high (>60%) contributions from the EM-2 pattern in their serum congener profiles.

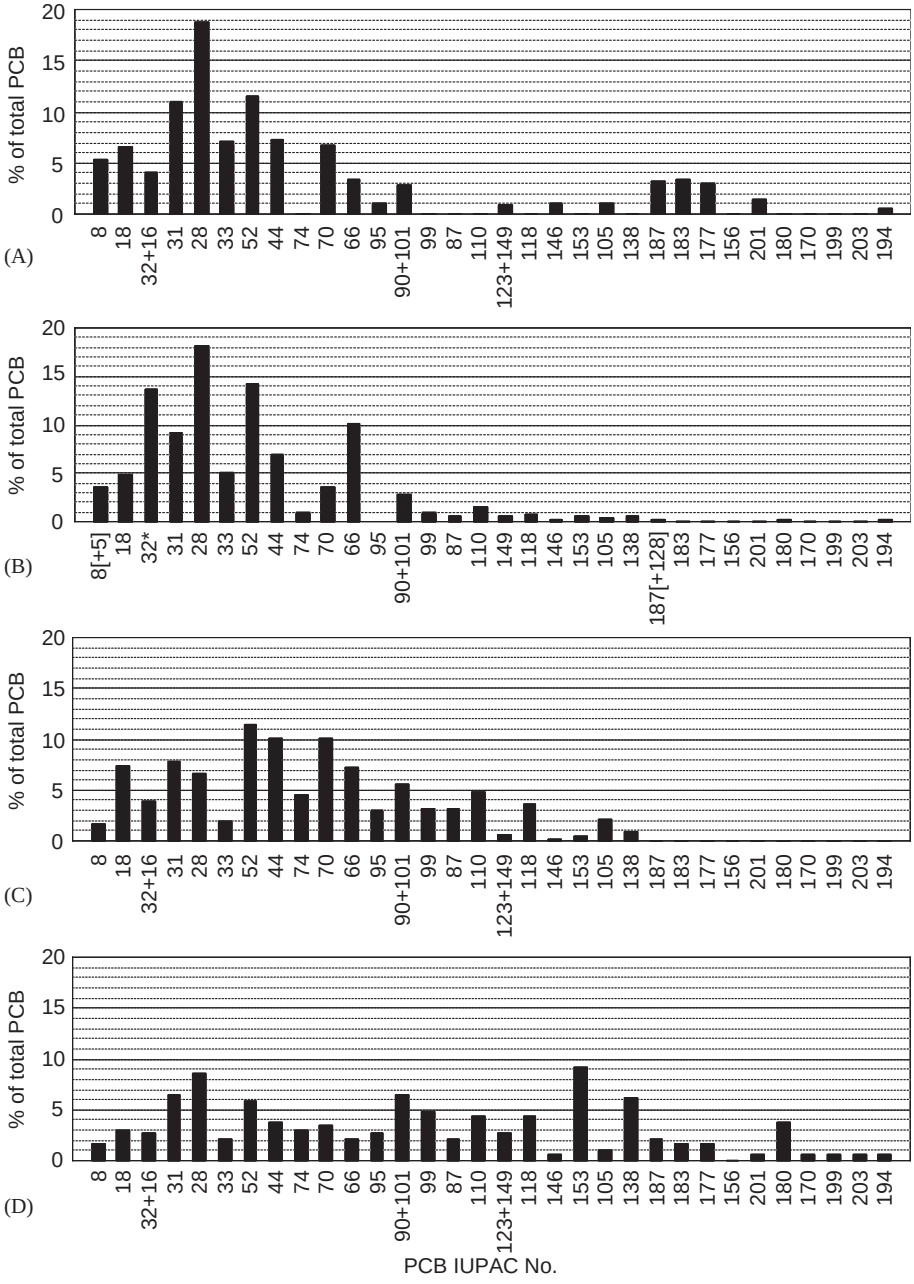

Fig. 2. Congener compositions of (A) EM-1 as determined by PVA of serum PCB congener data for 702 adult Mohawks, (B) air sampled above "Contaminant Cove" at the western boundary of Akwesasne in summer 1993 (Chiarenzelli et al., 2000), (C) native commercial A1248 liquid, and (D) serum from the subject with the highest proportion (46.2%) of EM-1 (see also Table 2 and Fig. 3A). For profiles not generated in the authors' laboratory (i.e., B), the same congener elution order as that in the other samples is presented to facilitate comparisons. Differences in congener coelutions between samples are indicated by brackets; congeners analyzed in the authors' laboratory but not by others are shown in italics. For brevity, CB 138 is listed alone although it coelutes with CBs 163 and 164 for all samples. In addition, CB 32 coelutes with CBs 11, 12, and 13 for the sample shown in (B).

Of the potential source profiles examined, the EM-2 pattern was most similar to (cosine $\theta = 0.91$) that of native commercial A1254 (Fig. 4B). In particular, labile CBs 70, 95, and 110, which are prominent in A1254, were also present in the EM-2 pattern. While high, the match with A1254 was not exact, as the EM-2 pattern did contain slightly lower proportions of CBs 52, 118, and 138 and higher levels of CBs 87, 110, 153, and 180.

The composition of EM-3 (Fig. 5A) was dominated by persistent hexa- and higher chlorinated congeners, in particular CB180. In contrast, labile congeners were essentially absent from this end-member pattern. The serum profile for a subject with a 70% contribution from EM-3 (Table 2, subject 3) is shown in Fig. 5C. The patterns are quantitatively very similar (cosine $\theta = 0.92$), with the major difference being higher

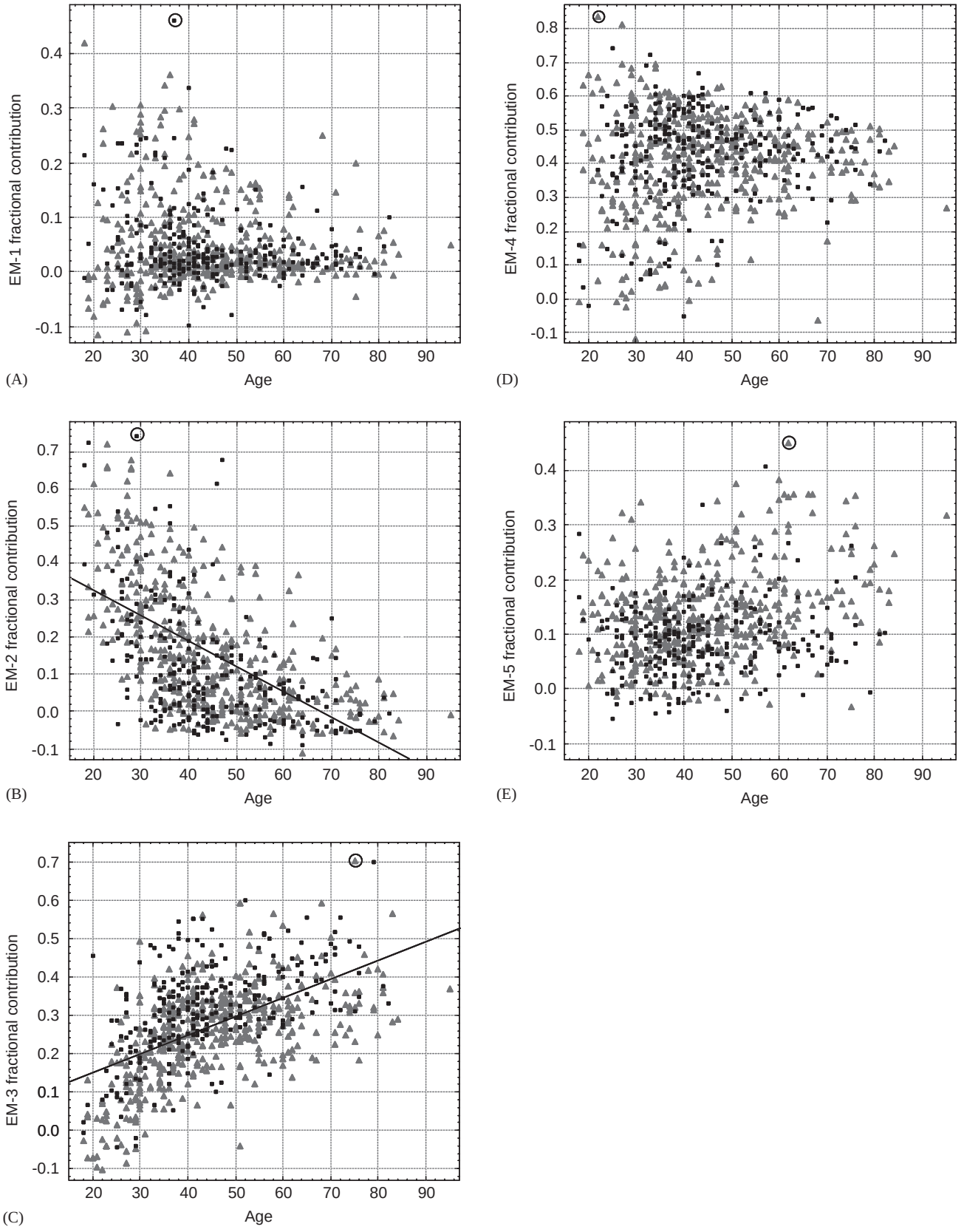

Fig. 3. Age and gender dependence of the fractional contribution (i.e., the relative proportion of each end-member pattern that contributes to the overall serum profile) for (A) EM-1, (B) EM-2, (C) EM-3, (D) EM-4, and (E) EM-5 for individual Mohawk men (black squares) and women (gray triangles). Lines in (B) and (C) represent best-fit linear regression of data for all subjects. Circled symbols represent the subjects with the highest proportional contribution from each respective end-member pattern (see also Table 2 for details).

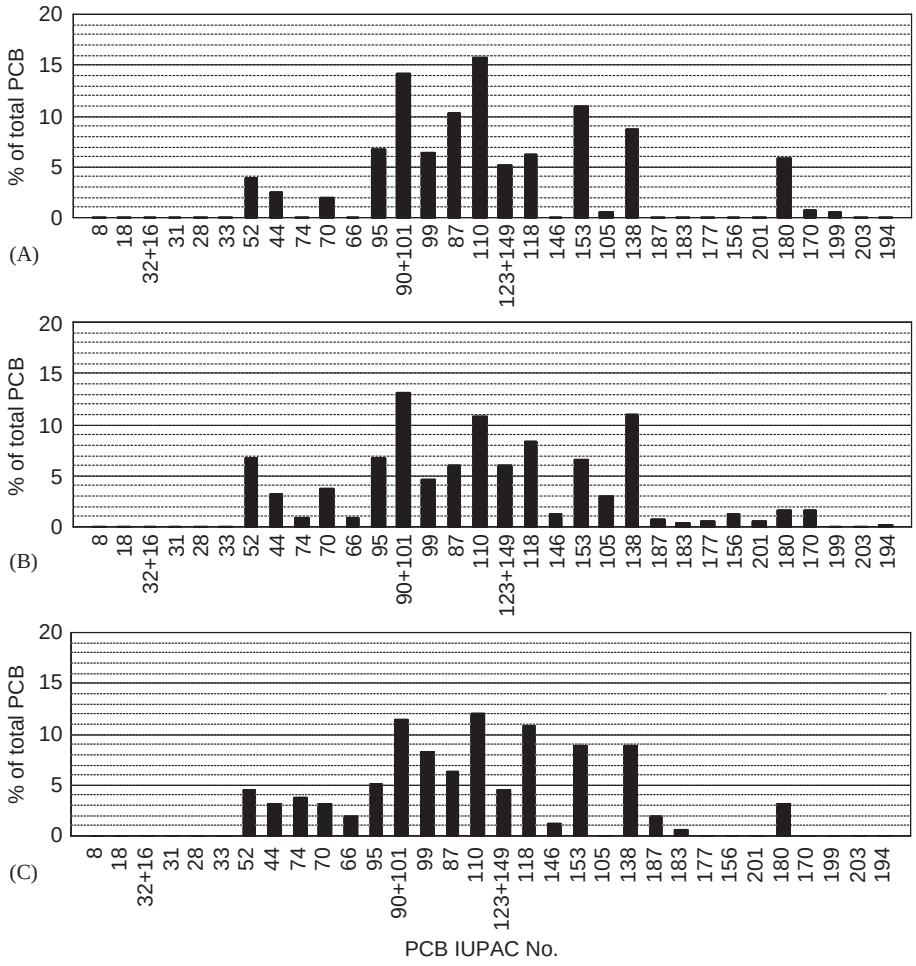

Fig. 4. Congener compositions of (A) EM-2, (B) native commercial A1254 liquid, and (C) serum from the subject with the highest proportion (74.2%) of EM-2 (see also Table 2 and Fig. 3B).

proportions of CBs 138 + 163 + 164 and 153 in this subject's profile, a shift consistent with the 32% contribution from EM-4 (Table 2). A positive ($r^2 = 0.29$; $P < 0.05$) age-dependent trend was noted for EM-3 (Fig. 3C). The EM-3 pattern closely matched (cosine $\theta = 0.90$) that of native commercial A1262 (Fig. 5B), especially in the proportions of persistent hepta- and octa-CBs. However, labile congeners, including CBs 95, 90 + 101, 110, and 123 + 149, which are present at significant levels in A1262 (Frame, 1997), were absent from this end-member pattern. In addition, proportions of CBs 74, 146, and 156 were higher in EM-3 than in A1262.

The congener composition of EM-4 is shown in Fig. 6A. This pattern was dominated by four analytes, the common and persistent di-*ortho*-substituted CBs 99, 138 + 163 + 164, 153, and 180. These CBs are typically reported as major serum congeners in virtually all published human studies (Hansen, 1998; National Center for Environmental Health, 2003). In contrast, one other common persistent congener, CB 118, was represented at much lower proportions in the EM-4 pattern. In addition, labile congeners were virtually absent from the composition of this end-member. The EM-4 pattern was a major contributor to the serum profiles of most Mohawk subjects (Fig. 3D; Table 2), although no clear relationship with subject age was noted. A close match (cosine $\theta = 0.91$) between the EM-4 composition (Fig. 6A) and the serum PCB profile (Fig. 6B) of the subject exhibiting the highest contribution from this end-member (84%, Table 2) was determined. The EM-4 congener profile was not analogous to that of any commercial Aroclor or any other potential source pattern examined.

EM-5 exhibited an unusual composition with very high proportions of the persistent mono-*ortho*-substituted CBs 74 and 118 and lesser amounts of CBs 66, 99, 105, and 138 (Fig. 6C). All of these congeners are generally prevalent in serum from the Mohawk participants (Table 1). However, two other common and persistent congeners, CBs 153 and 180, were only minimally represented in the EM-5 pattern. As with EM-4, labile congeners were also absent from the composition of this end-member. Most Mohawk subject

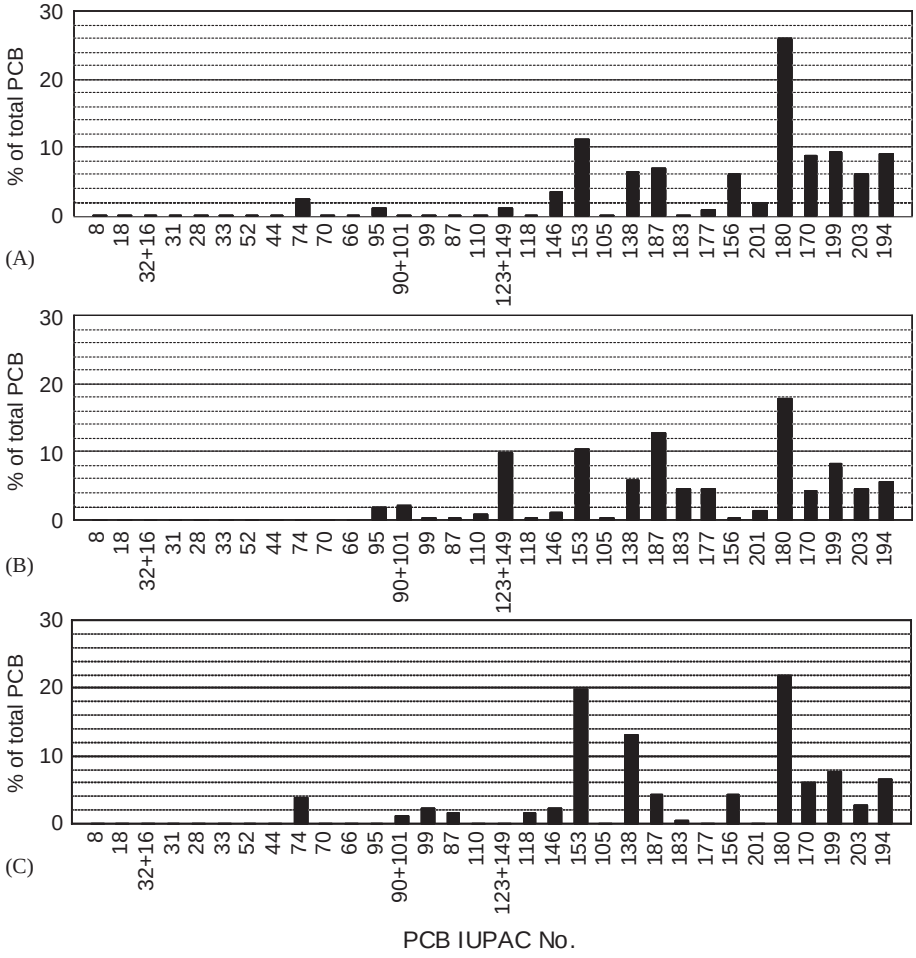

Fig. 5. Congener compositions of (A) EM-3, (B) commercial A1262 liquid, and (C) serum from the subject with the highest proportion (70.1%) of EM-3 (see also Table 2 and Fig. 3C).

serum profiles contained EM-5 proportions of 30% or less (Fig. 3E). The serum PCB profile of the subject with a 45% contribution from EM-5 (Table 2, subject 5) is shown in Fig. 6D. While the EM-5 congener pattern is clearly apparent in this subject's profile, other inputs (i.e., from EM-3 and -4) are also evident. No significant age dependence was noted with EM-5 for either gender. As was noted for EM-4, the EM-5 congener pattern was not analogous to that of any commercial Aroclor or to any other potentially relevant source pattern.

4. Discussion

Human PCB body burden, as reflected by serum lipid congener profile, is an integrated function of external and internal factors, including source, route, and timing of exposure and individual determinants of uptake, metabolism, and clearance (toxicokinetics) (Hansen, 1998; Karmaus et al., 2001; James et al., 2002; Gladen et al., 2003; Wicklund-Glynn et al., 2003). In the present study, the mean serum PCB profile observed for the adult Mohawk cohort was consistent with a combination of an age-dependent accumulation of persistent congeners and of ongoing background ambient environmental and/or dietary exposure. This averaged profile did not resemble unaltered A1248, the major PCB mixture contaminating the Akwesasne environment, suggesting that the majority of adult Akwesasne Mohawks were not experiencing direct high-level exposure to this contaminant at the time of blood sampling. While the mean total serum PCB level observed for the Mohawks is consistent with general US population exposure (ATSDR, 2000; National Center for Environmental Health, 2003), other data suggest increased exposure for specific individuals and/or subsets of the population. For example, a small number of Mohawks exhibited total serum PCB concentrations of >20 ppb, a level considered to be substantially elevated by current measures (ATSDR, 2000; Orloff et al., 2003). In addition, although the mean serum congener profile for this population suggests homogeneity of exposure, data for individual subjects revealed the considerable diversity of serum PCB

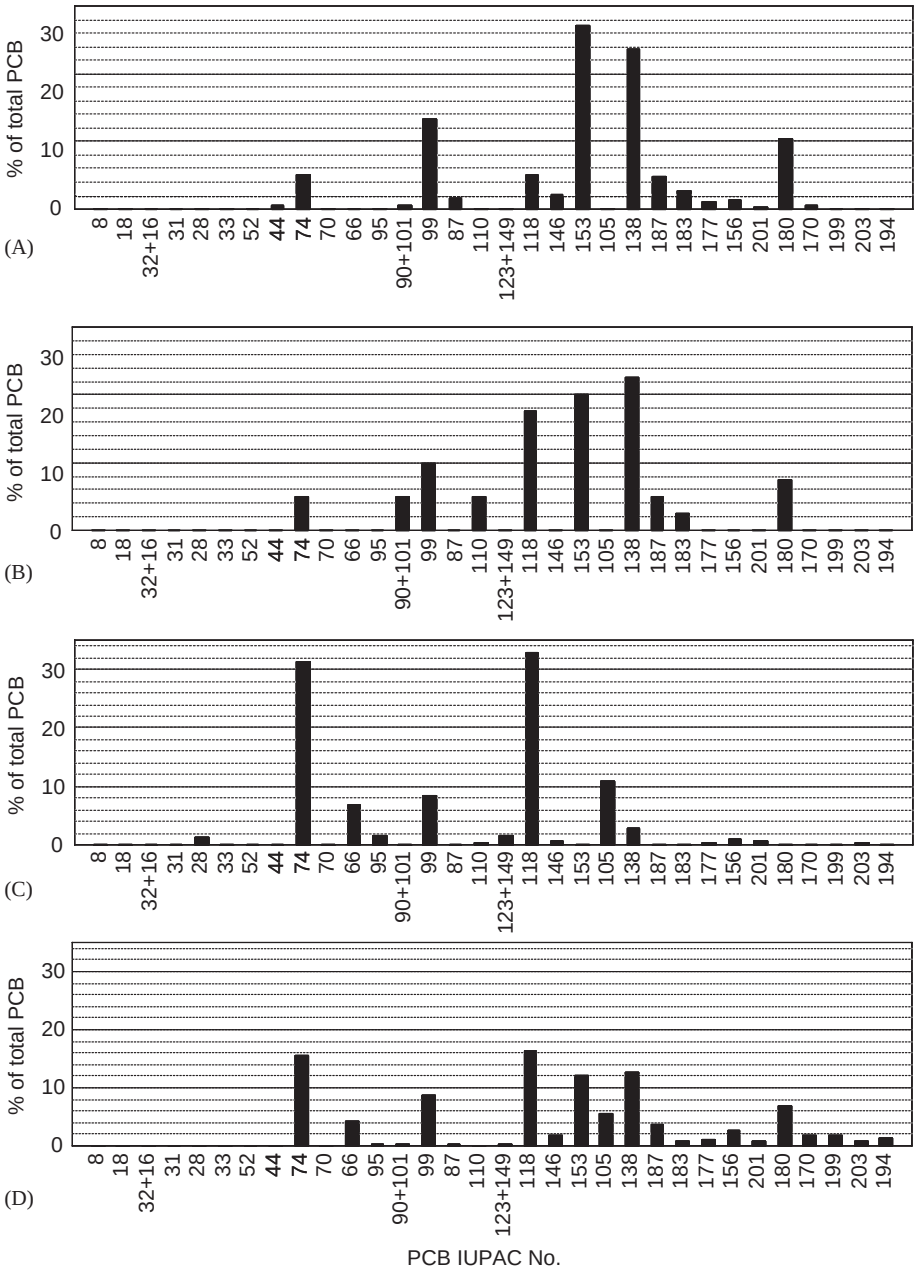

Fig. 6. Congener compositions of (A) EM-4, (B) serum from the subject with the highest proportion (83.6%) of EM-4 (see also Table 2 and Fig. 3D), (C) EM-5, and (D) serum from the subject with the highest proportion (45.1%) of EM-5 (see also Table 2 and Fig. 3E).

congener profiles that may be encountered in a human population, even one from a relatively small geographic area. Anomalous congener-specific serum PCB profiles, which have been reported in the past on a limited basis (Burse et al., 1991; Korrick and Altshul, 1998; Hansen et al., 2003), may be evidence for unusual exposure patterns.

While congener-specific data are clearly superior to total serum PCB values for assessing PCB exposure (Luotamo et al., 1991; Hansen, 1998), the examination of averaged serum profiles for a population provides only a limited understanding of major contributing PCB sources and individual modifying factors. To date, attempts to correlate mean congener profiles with specific external exposure sources have met with modest success (Anderson et al., 1998; Gerstenberger et al., 2000; Hansen et al., 2003). A different approach to this challenge is to utilize EDA techniques, where the objectives are to find patterns, correlations, and relationships in the dataset itself with few a priori assumptions or hypotheses, i.e., to characterize and explore a dataset prior to attempting conventional statistical hypothesis testing. Rigorous probabilistic methods generally require a set of narrow assumptions

regarding the structure of the data, and such an approach is not appropriate if those critical assumptions cannot be safely assumed. Moreover, in the case of an emergent and complex area such as PCB source/exposure/toxicokinetics assessment, information sufficient to know what hypotheses to test is often lacking.

Several multivariate EDA techniques, including PCA and hierarchical cluster analysis (HCA), have been employed to discern patterns of PCBs and related compounds in environmental media and biota (Echarri et al., 1998; Ashley and Baker, 1999; Heemken et al., 2000; Serrano et al., 2000). In addition, attempts have been made to associate environmental PCB source profiles with human body burden using multivariate EDA approaches (Burse et al., 1994; Duarte-Davidson et al., 1994a, b; Angulo et al., 1999; Löffler and Van Bavel, 2000; Wingfors et al., 2000; Hwang et al., 2001). These reports support the general applicability of EDA to both environmental and biological PCB datasets. However, PCA and HCA still have significant drawbacks when used as stand-alone tools for determining contributing PCB profiles (Johnson et al., 2002). In contrast, self-training receptor models (also called mixing models) are EDA methods that allow contributing chemical fingerprints to be resolved in complex environmental systems without a priori assumption of contributing patterns and without the use of training datasets (Tukey, 1977; Ehrlich et al., 1994; Salau et al., 1997; Johnson et al., 2000). As stated earlier, PVA, one of several such methods, is used to determine three parameters of interest in an environmental/biological system: (1) the number of component mixtures (end-members in PVA terminology) contributing to the system, (2) the chemical composition of each mixture, and (3) the relative contribution of each mixture in each sample (Full et al., 1981, 1982; Johnson et al., 2002). For example, in a recent study PVA was used to resolve five distinct PCB end-member patterns and their relative contributions to the total congener profile in suspended particulate matter from San Francisco Bay (Johnson et al., 2000). This report suggested that the application of PVA to serum PCB data could provide insight into major exposure sources that other approaches cannot, since PVA-derived end-member patterns could be associated with the route or timing of exposure or with specific toxicokinetic factors. Despite this promise, there have been no reports on the use of self-training receptor models such as PVA for the analysis and interpretation of human PCB congener data.

PVA applied to Mohawk serum PCB profiles indicated that such datasets are considerably noisier than those typically obtained with environmental media. This observation supports the idea that, in humans, nonlinear processes (e.g., metabolism) will modify external exposure patterns in all but the youngest and/or recently exposed individuals. The influence of microbial dechlorination, one such nonlinear process, on the application of linear mixing models to PCB data has been discussed elsewhere in the literature (Johnson and Quensen, 2000). In those studies, the results noted for dechlorinated systems included a generally poorer fit than was obtained with a system of pure linear source pattern mixing and the detection of higher-order end-member patterns representing intermediates between earlier resolved, lower-order patterns. For the Mohawk dataset, numerous outliers (subjects) were also identified and removed. These anomalous samples, which are currently under investigation, may reflect unique sources or subject characteristics, measurement/analytical error, or some other as yet unidentified factor. Finally, a large number of congeners were removed from the model due to a low detection rate and/or a very poor fit to the model. Despite these complications, PVA identified five distinct end-member patterns, each of which was clearly evident in the raw serum PCB data for individual subjects. This result indicates that the patterns are not mathematical artifacts but instead reflect the wide range of congener patterns actually present within the dataset.

The primary goal of PVA, and of EDA in general, is to provide testable hypotheses regarding the underlying chemical and biological reality of the model-generated results. As discussed below in this context, the identified end-member patterns are interpretable with respect to known or suspected PCB sources at Akwesasne and/or individual subject-dependent factors. For example, it is well accepted that toxicokinetic processes will preferentially alter PCB patterns in biota toward a profile dominated by persistent congeners (particularly CBs 153, 138, and 180), regardless of the original PCB exposure source(s) (Safe, 1994; Hansen, 1998; Gladen et al., 2003). Some results of the present study are consistent with the appearance of such a "terminal" profile. For example, the A1262-like pattern (EM-3) derived by PVA contained highly chlorinated, persistent congeners and was positively correlated with subject age. However, more labile congeners present at high levels in commercial A1262 (such as CB 149) (Frame, 1997) were only minimally represented in this pattern. In addition, CB 74, another highly persistent congener, was present in EM-3 but is virtually absent from A1262. These findings suggest that EM-3 is not directly associated with ongoing exposure to A1262 or any other commercial Aroclor mixture, a conclusion consistent with the lack of known or suspected input of this Aroclor to the Akwesasne environment. Instead, a reasonable hypothesis is that EM-3 represents a contributing pattern associated with a lifetime accumulation of persistent CBs.

As discussed previously, the reporting of averaged congener profiles in human PCB exposure studies has contributed to the widely held belief that PCB patterns in biota are largely invariant and do not reflect original

sources in any predictable way. In the present study, the mean Mohawk serum PCB congener profile did not closely correspond to that of unaltered A1248, the primary PCB source contaminant at Akwesasne. This finding is consistent with the tenet expressed above and supports minimal current exposure to this mixture among the Mohawks in general. However, other findings suggest that this conclusion may not be true for all subjects under all exposure scenarios and that PCB patterns present at the time of exposure may indeed be evident in individual serum profiles. For example, one identified pattern (EM-2) did bear considerable similarity to unaltered A1254, including its complement of relatively labile CBs. The presence of low-persistence congeners in EM-2 would support a continuing (or recent episodic) as opposed to distant-past exposure to this Aroclor. The pattern was most apparent in younger individuals and was negatively correlated with age. One reasonable hypothesis based on these data is that EM-2 reflects continuing exposure to an "A1254-like" source across all age groups in the Mohawk cohort combined with age-dependent dilution of the pattern by the accumulation of more persistent congeners. While the EM-2 pattern is reasonably consistent with A1254 exposure, the precise identity of a relevant source and route for Mohawk subjects cannot be directly determined from the data and awaits further investigation. However, since this Aroclor was widely used in electrical transformers and capacitors and other industrial equipment, potential sources could include manufacturing plants or hydroelectric power-generating facilities located upstream from Akwesasne on the St. Lawrence River.

A high correspondence of EM-1 to patterns reported for locally contaminated air (Chiarenzelli et al., 2000) and for vapor derived from A1248 liquid (Chiarenzelli et al., 1997) was noted in the present study. This finding suggests that the EM-1 pattern could represent a volatile PCB profile and supports the hypothesis that higher proportions of the EM-1 pattern in selected individuals may be due to concurrent inhalation exposure to PCBs at the time of blood sampling. Volatilized congeners could be derived from major known point source locations at Akwesasne, such as Contaminant Cove or the many tons of PCBs present in soil repositories at various sites near the Reserve (Sokol et al., 1994). Outdoor PCB air levels of up to 1400 ng/m^3 (prior to capping of the General Motors landfill in 1987) and up to 20 ng/m^3 (in 1993) have been reported near these contamination sources at Akwesasne (ATSDR, 1999; Chiarenzelli et al., 2000). Contemporaneous remediation efforts have also been suggested to result in inhalation exposure "pulses", as buried material is excavated or dredged and exposed to air (Hansen 1998, 2001; Chiarenzelli et al., 1998). While most Mohawk subjects exhibited low contributions from EM-1 to their overall congener profile, the data do provide evidence that inhalation may be a quantifiable exposure pathway for at least a subset of Akwesasne residents. Research is currently underway to examine correlations between residential proximity to possible local sources of airborne PCBs at Akwesasne and the proportions of the EM-1 pattern present in individual subjects.

Finally, the EM-4 and EM-5 patterns are unique in that their compositions are restricted to a small number of persistent congeners (CBs 99, 138, 153, and 180 in EM-4 and CBs 74, 105, and 118 in EM-5). The characteristic pattern of EM-4 is generally consistent with the persistent PCB component of the mean serum congener profile of Mohawk adults as determined in the present study and as commonly reported for other human cohorts. For example, recent blood data (National Center for Environmental Health, 2003) for a limited number of congeners analyzed in more than 1000 subjects indicate that the EM-4 congeners are those generally detected at the highest levels in subjects with ambient (i.e., no known elevated environmental or dietary) exposure. Consequently, one plausible hypothesis is that EM-4 represents the persistent component of contributions to body burden from continuous low-level PCB exposure from a variety of general (i.e., ambient and dietary) exposure sources.

The EM-4 and -5 congeners are the major persistent CBs present in Aroclors 1254 and 1248, respectively. It is also noteworthy that these congeners (i.e., persistent di-*ortho* CBs for EM-4 and mono-*ortho* CBs for EM-5) are preferentially biotransformed by the CYP2B and CYP1A isozymes, respectively (Brown, 1994; Wolff et al., 1997; Hansen, 1998). An alternative hypothesis is therefore that these two end-member patterns represent intermediate bioaccumulation profiles, i.e., those that follow a loss of labile congeners after exposure to these native PCB mixtures but that appear prior to the "terminal" cumulative pattern (EM-3). In this model, differences among subjects in the relative proportions of these patterns could reflect the source or duration/timing (window) of external exposure and/or interindividual variability in the metabolic processing of specific congeners. Other workers have described associations among sets of persistent congeners similar to our PVA results. For example, studies in human cohorts have reported at least moderate statistical correlations between CBs 74, 99, 105, and 118 in one group and CBs 138 and 153 in another (Devoto et al., 1997; Gladen et al., 1999a, b, 2003; Longnecker et al., 2000). Given our present data, we cannot make inferences about the time frame that might be necessary to alter the pattern in blood from one that reflects the original source pattern to one that has higher proportions of recalcitrant, highly chlorinated congeners such as CB 180. Currently planned serial blood sampling of selected Mohawk subjects will be valuable in this regard.

The present study is the first reported application of a multivariate statistical mixing model to human PCB congener data. The PVA method clearly adds a useful new dimension to the analysis and interpretation of congener-specific PCB data and further justifies efforts to collect such data in environmental epidemiologic studies. As discussed here and elsewhere, the primary result of any PVA effort is a set of hypotheses (many of which may not have been obvious a priori) regarding the nature of the identified contributing patterns and their possible relationship with exposure and internal subject variables. Confirmatory modeling and/or hypothesis testing must then be conducted to verify and extend the PVA results. Our findings support the utility of this approach for the analysis of serum PCB congener profiles and provide a number of important hypotheses regarding the existence and nature of source- and subject-dependent factors that can modify PCB body burden. These hypotheses can be tested in a number of ways. For example, the detected end-member patterns can be correlated, in either retrospective or prospective studies, with specific exposure and demographic variables, including diet, breastfeeding history, occupational exposure, and residential proximity to PCB point sources, that are potentially relevant to this or other populations. Prospective studies can also provide valuable data on how end-member patterns and proportions change over time in an exposed population and how these changes may relate to external and internal determinants of PCB body burden in individual subjects. Finally, the ready availability of appropriate software and documentation for the PVA method should encourage its utilization for the analysis of human congener-specific PCB datasets by other investigators.

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