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Polychlorinated Biphenyls and Risk of Testicular Germ Cell Tumors

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Abstract

Exposure to endocrine-disrupting chemicals, such as polychlorinated biphenyls (PCB), may alter hormonal balance and thereby increase risk of testicular germ cell tumors (TGCT). To study the relationship of PCBs to TGCT, prediagnostic serum samples from 736 cases and 913 controls in the Servicemen's Testicular Tumor Environmental and Endocrine Determinants study were analyzed. Adjusted odds ratios and 95% confidence intervals were estimated using logistic regression. PCB levels were examined in association with all TGCT and, separately, with each histologic type (seminoma and nonseminoma). Risks associated with seven functional groupings of PCBs, as well as sum of PCBs, were also examined. There were significantly decreased risks of TGCT in association with eight PCBs (PCB-118, PCB-138, PCB-153, PCB-156, PCB-163, PCB-170, PCB-180, and PCB-187) and no association with the remaining three (PCB-99, PCB-101, and PCB-183). The same eight congeners were significantly associated with decreased risk of nonseminoma, whereas five (PCB-138, PCB-153, PCB-156, PCB-163, and PCB-170) were associated with decreased risk of seminoma. All functional groupings of PCBs were also associated with decreased risk of TGCT and of nonseminoma, whereas six of the seven functional groups were associated with decreased risk of seminoma. Sum of PCBs was significantly associated with decreased risk of TGCT (P_{trend} = 0.006), nonseminoma (P_{trend} = 0.007), and seminoma (P_{trend} = 0.05). Overall, these data do not support the hypothesis that PCB exposure increases the risk of TGCT. [Cancer Res 2009;69(5):1901–9]

Introduction

The incidence of testicular germ cell tumors (TGCT) has been increasing in the United States and in other developed countries for at least 5 decades (1). Reasons for the increase are not clear, as the etiology of TGCT is poorly understood. The only well-described risk factors are cryptorchism, prior history of TGCT, family history of TGCT, and increased adult stature (2). The association of TGCT with a congenital anomaly regulated by androgen levels, as well as the similarity between testicular carcinoma *in situ* and primordial germ cells, has suggested that TGCT risk may be determined very early in life and may be affected by hormone levels (3–7). The ability of exogenous exposures, such as synthetic hormonal drugs, phytoestrogens, and persistent organochlorine compounds, to mimic the effects of endogenous hormones has led to speculation that these exposures might also be related to the development of TGCT and the other male reproductive disorders (cryptorchism, hypospadias, and impaired spermatogenesis) collectively known as the testicular dysgenesis syndrome (8, 9).

Recently, we reported that *p,p′*-dichlorodiphenyldichloroethylene (*p,p′*-DDE), the most persistent metabolite of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; dichlorodiphenyltrichloroethane, was significantly associated with increased risk of TGCT (10). Like *p,p′*-DDE, other organochlorine compounds share the ability to act as endocrine disruptors. Whereas *p,p′*-DDE has been shown to have antiandrogenic properties (11), various polychlorinated biphenyl (PCB) congeners are known to have estrogenic, antiestrogenic, androgenic, and antiandrogenic properties (12). The effect of PCBs on TGCT risk could then be similar to that of *p,p′*-DDE or could be dissimilar depending on the mix of PCB congeners present. One prior TCGT case-control study, conducted in Sweden, found no association between TGCT and total PCB level (13). The study, however, did find that mothers of the case men had significantly higher total PCB levels than did mothers of the control men (13). To pursue this lead and to examine the relationship between TGCT and specific PCBs, a study was conducted among members of the U.S. Armed Forces.

Materials and Methods

Study population. The source population for the current study is >4 million U.S. military personnel whose blood samples are stored at −30°C in the Department of Defense Serum Repository (DoDSR) in Silver Spring, Maryland (14). In the late 1980s, the DoDSR began storing surplus sera from HIV testing of military personnel. The Repository now includes >40 million samples from active-duty and reserve personnel, with ~2.3 million samples added each year. Blood samples are drawn at the time of service entry and, on average, are collected every 2 y thereafter. The earliest blood sample available from each individual was selected for the current study. The blood samples included in the current study were donated between 1987 and 2002.

Case identification was accomplished by linking the DoDSR computerized database, using a person-specific ID, to the Defense Medical Surveillance System to determine which of the serum donors had developed testicular cancer after donation. The histology of all reported testicular cancers was determined by examination of the original pathology reports or by review (6.5%) of the pathology slides. As the study was focused on TGCTs, the histologies were limited to classic seminoma or nonseminoma (embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratoma, and mixed germ cell tumor). The database linkage identified 961 case men who seemed to meet the study criteria. Of these men, 76 could not be traced, 27 had died, 3 were deployed, and 2 were deemed ineligible, leaving 853 possible participants. Of these men, 22 were in the process of being

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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contacted when the study closed. Thus, of the 831 men contacted, 754 (91%) agreed to participate. In the instances where the potential case participant was deceased (n = 27), the study attempted to obtain proxy information from the man's mother. Thirteen proxy questionnaires were completed. The TGCT cases were diagnosed between 1988 and 2003.

Men with a sample in the DoDSR who had not subsequently developed testicular cancer were eligible to participate as controls. The study was designed as a pair-matched case-control study, although additional controls were initially identified due to the transient nature of the military population. From the list of all possible controls for each case, four individuals who matched on birth date (within 1 y), race/ethnicity (white, black, and other), and date of available serum sample (within 30 d) were chosen at random as the control set. Among the controls, 2,579 were evaluated for inclusion. Of these men, 385 could not be traced, 18 had died, 64 were deployed, 2 were deemed ineligible, and 928 could not be contacted within 30 d. Of the remaining 1,182 men, 32 were in the process of being contacted when the study closed. Thus, of the 1,150 men contacted, 928 (81%) agreed to participate. Among the 754 cases and 928 controls enrolled, 720 were matched case-control pairs. The volume of serum in the samples of 18 cases and 15 controls was insufficient to conduct PCB analysis; thus, the final analysis set included 736 cases and 913 controls.

Study participation included completion of the study questionnaire, donation of a buccal cell mouthwash sample, permission to use a DoDSR serum specimen, and written informed consent to participate. In addition, each participant was asked for permission to contact his mother to enroll her in the study. For 30 d, every attempt was made to enroll the first control man in the set via tracing attempts, multiple letters, and telephone calls. If the potential control could not be contacted, the enrollment process began anew with the next man in the set. All participants were enrolled between April 2002 and January 2005. The study was approved by Institutional Review Boards of the National Cancer Institute (Bethesda, MD) and the Walter Reed Army Institute for Research (Silver Spring, MD).

Questionnaire data. Each participant was administered a computer-assisted telephone interview composed of nine modules. Cases were asked questions in reference to a date 1 y before their TGCT diagnosis (referred to as the "reference date"). Control participants were assigned the same reference date as their matched case. For the current analysis, participants were asked to report whether they had a personal history of cryptorchism, a family history of testicular cancer in first and second relatives, and their height and weight as of the reference date.

Laboratory methods. Levels of 15 PCB congeners were analyzed by the Human Toxicology Laboratory of the Institut National de Sante Publique du

Table 1. Selected characteristics of cases and controls in the STEED study

	Controls (n = 913)	All TGCT (n = 736)		Seminoma (n = 313)		Nonseminoma (n = 422)	
	n (%)	n (%)	P*	n (%)	P*	n (%)	P*
Reference age (y)			0.94		<0.0001		<0.0001
18–20	67 (7.3)	64 (8.7)		12 (3.8)		52 (12.3)	
21–25	306 (33.5)	238 (32.3)		57 (18.2)		180 (42.7)	
26–30	260 (28.5)	205 (27.9)		106 (33.9)		99 (23.5)	
31–35	159 (17.4)	132 (17.9)		74 (23.6)		58 (13.7)	
36–40	95 (10.4)	75 (10.2)		49 (15.7)		26 (6.2)	
41–45	26 (2.8)	22 (3.0)		15 (4.8)		7 (1.7)	
Race/ethnicity			0.47		0.10		0.37
White	780 (85.4)	623 (84.6)		253 (80.8)		370 (87.7)	
Black	34 (3.7)	22 (3.0)		12 (3.8)		10 (2.4)	
Other	99 (10.8)	91 (12.4)		48 (15.3)		42 (10.0)	
History of cryptorchism			<0.0001		0.07		<0.0001
No	897 (98.2)	697 (94.7)		302 (96.5)		394 (93.4)	
Yes	16 (1.8)	39 (5.3)		11 (3.5)		28 (6.6)	
Family history of testicular cancer †			0.0009		0.0004		0.02
No	899 (98.5)	705 (95.8)		297 (94.9)		407 (96.4)	
Yes	14 (1.5)	31 (4.2)		16 (5.1)		15 (3.6)	
BMI ‡			0.86		0.24		0.93
<18.5	11 (1.2)	9 (1.2)		4 (1.3)		4 (0.9)	
18.5–24.9	404 (44.2)	321 (43.6)		136 (43.5)		185 (43.8)	
25.0–29.9	451 (49.4)	359 (48.8)		147 (47.0)		212 (50.2)	
≥30.0	47 (5.1)	45 (6.1)		26 (8.3)		19 (4.5)	
Adult height (in)			0.0009		0.01		0.02
<68	257 (28.09)	151 (20.43)		60 (19.17)		91 (21.41)	
68–70	253 (27.65)	217 (29.36)		96 (30.67)		121 (28.47)	
71–72	237 (25.90)	193 (26.12)		84 (26.84)		109 (25.65)	
≥73	168 (18.36)	178 (24.09)		73 (23.32)		104 (24.47)	
DDE (ng/g lipid)			0.005		<0.0001		0.33
Q1 (≤157)	238 (26.10)	186 (25.31)		59 (18.91)		127 (30.09)	
Q2 (158–250)	230 (25.22)	167 (22.72)		68 (21.79)		98 (23.22)	
Q3 (251–390)	220 (24.12)	146 (19.86)		57 (18.27)		89 (21.09)	
Q4 (>390)	224 (24.56)	236 (32.11)		128 (41.03)		108 (25.59)	

*P value of χ^2 test.
†Family history in first- and second-degree relatives.
‡BMI = height/weight^2 (kg/m^2).

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Table 2. Pearson correlation coefficients of PCBs among controls in the STEED study

	PCB											Wolff groups				Inducers		
	101	118	138	153	156	163	170	180	183	187	Sum	1B	2A	2B	3	CYP	PB	MFO
PCB-99	0.26	0.71	0.73	0.63	0.59	0.59	0.38	0.34	0.48	0.41	0.67	0.45	0.70	0.58	0.70	0.69	0.69	0.66
PCB-101		0.45	0.23	0.24	0.15	0.21	0.18	0.21	0.23	0.20	0.34	0.67	0.32	0.21	0.27	0.38	0.39	0.27
PCB-118			0.81	0.77	0.70	0.75	0.57	0.54	0.62	0.56	0.82	0.66	0.92	0.73	0.76	0.83	0.80	0.85
PCB-138				0.96	0.90	0.91	0.78	0.74	0.82	0.75	0.95	0.69	0.93	0.94	0.93	0.94	0.93	0.96
PCB-153					0.91	0.96	0.87	0.86	0.88	0.85	0.98	0.77	0.91	0.97	0.97	0.97	0.97	0.97
PCB-156						0.95	0.83	0.78	0.72	0.71	0.90	0.62	0.92	0.92	0.86	0.88	0.87	0.95
PCB-163							0.87	0.84	0.80	0.82	0.95	0.73	0.92	0.94	0.92	0.94	0.94	0.96
PCB-170								0.96	0.81	0.86	0.88	0.75	0.76	0.94	0.87	0.87	0.87	0.88
PCB-180									0.84	0.91	0.87	0.80	0.72	0.90	0.88	0.87	0.87	0.83
PCB-183										0.85	0.86	0.77	0.72	0.87	0.92	0.89	0.90	0.82
PCB-187											0.86	0.86	0.69	0.86	0.87	0.87	0.86	0.80
Sum of PCBs												0.83	0.93	0.98	0.98	1.00	0.99	0.98
Wolff 1B													0.69	0.76	0.80	0.86	0.86	0.75
Wolff 2A														0.89	0.88	0.93	0.91	0.97
Wolff 2B															0.96	0.96	0.95	0.97
Wolff 3																0.98	0.99	0.94
CYP inducers																	1.00	0.97
Phenobarbital inducers																		0.96
Mixed function oxidase inducers																		

Quebec. The PCBs examined, by IUPAC number, were PCB-28, PCB-52, PCB-99, PCB-101, PCB-105, PCB-118, PCB-128, PCB-138, PCB-153, PCB-156, PCB-163, PCB-170, PCB-180, PCB-183, and PCB-187. The plasma samples, enriched with isotopically labeled internal standards, were denatured using formic acid. Analytes were then automatically extracted from the matrix by solid-phase extraction. Extracts were automatically cleaned on a florisil column and analyzed by gas chromatography-mass spectrometry. Detection of ions generated from negative chemical isolation was accomplished in the selected ion monitoring mode. Evaluation of concentrations was done by considering recoveries of the labeled internal standards. Linear calibrations extended up to 10 μg/L for most analytes. Higher concentrations were determined after appropriate dilutions. The mean detection limits approximated to 0.005 μg/L. All control samples were run in the same batch, on the same day, as their matched case sample. Average within-day variability ranged from 2% to 5%. Average recoveries were 80%. The PCB limits of detection, median levels, and coefficients of variation, which include both within- and between-batch variability determined from replicate QC samples, are shown in Supplementary Table S1. Accuracy of results was validated through successful participation in two external quality assessment schemes: the German External Quality Assurance Scheme (Erlangen University) and the AMAP Ring Test (Quebec).

To adjust all measurements for lipid levels, samples were analyzed for triglycerides, free and total cholesterol, and phospholipids. The measurements were made with enzyme bioassays using kits produced by Randox Laboratories. Measurements of PCBs and lipid levels were obtained for 739 cases and 915 controls.

In addition to analyzing each congener separately, the relationships of TGCT to previously suggested groupings of congeners were examined. The groupings used were as follows: Wolff groupings (15): Wolff group 1B (PCB-101 and PCB-187), Wolff group 2A (PCB-118 and PCB-156), Wolff group 2B (PCB-138 and PCB-170), and Wolff group 3 (PCB-99, PCB-153, PCB-180, and PCB-183); phenobarbitol inducers (PCB-99, PCB-101, PCB-153, PCB-163, PCB-180, and PCB-183; ref. 16); mixed function oxidase inducers (PCB-118, PCB-138, PCB-156, and PCB-170; ref. 16); and UDP-GT, CYP1A, and CYP2B inducers (PCB-99, PCB-101, PCB-118, PCB-153, PCB-156, PCB-180, PCB-183, and PCB-187; ref. 17). The PCBs in each of the groupings were calculated by summing over the individual results.

Statistical analysis. To conduct logistic regression analyses, lipid-adjusted PCB levels were categorized into quartiles based on the levels in controls. PCB levels that fell below or were equal to the limit of detection were imputed as the midpoint of the limit and were included in the first quartile for regression analysis. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to estimate the association of each PCB with risk of TGCT and separately with risk of seminoma and nonseminoma. One case was excluded from histology-specific analyses because tumor histology was unavailable.

Given the matched case-control design, risk estimates adjusting for confounders were first generated using conditional logistic regression, restricting the analysis to only the matched sets. Modeling using unconditional logistic regression was subsequently performed using the data from all participants. As the latter involved breaking the match, risk estimates derived from the unconditional logistic regression models were adjusted for the three matching factors: age at reference date, race/ethnicity, and date of serum sample collection. Both logistic regression models were adjusted for cryptorchism, family history of testicular cancer, age at serum draw, adult stature, and body mass index (BMI), as BMI is associated with plasma PCB levels (18). As previous research in the STEED population had identified *p,p′*-DDE as a risk factor, serum *p,p′*-DDE level was also included in the models (10). Tests for trend in risk were computed using scored variables for PCB levels, based on the median levels of each quartile, to evaluate possible dose-response relationships. As results using conditional and unconditional logistic regression were similar, only those using the latter approach are presented.

All tests were two sided, with $P < 0.05$ defined as the level of statistical significance.

Statistical analyses were conducted using Statistical Analysis System Release 9.1 (SAS Institute, Inc.).

Results

As shown in Table 1, 913 controls and 736 cases (313 seminoma, 422 nonseminoma, and 1 histology unavailable) were included in the analysis. Cases and controls were matched on age and ethnicity, resulting in no significant differences in the distributions of these variables. The seminoma cases were somewhat older than the controls, whereas the nonseminoma cases were somewhat younger. The cases, particularly the nonseminoma cases,

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Table 3. Adjusted relative risk of TGCTs by quartile of lipid-adjusted levels of serum organochlorines in the STEED study

	ng/g lipid	Controls	All TGCT		Seminoma		Nonseminoma	
		n	*n*	OR* (95% CI)	*n*	OR* (95% CI)	*n*	OR* (95% CI)
PCB-99								
Q1	<9.9	590	496	1.00	199	1.00	297	1.00
Q2	9.9–12.5	109	68	0.72 (0.52–1.02)	33	0.78 (0.50–1.22)	35	0.68 (0.44–1.04)
Q3	12.6–18.3	106	90	0.89 (0.64–1.24)	40	0.86 (0.56–1.34)	49	0.91 (0.61–1.35)
Q4	>18.3	107	81	0.80 (0.57–1.13)	41	0.80 (0.51–1.25)	40	0.76 (0.50–1.17)
P_{trend}				0.14		0.26		0.16
PCB-101								
Q1	<4.7	570	469	1.00	200	1.00	268	1.00
Q2	4.7–6.1	114	82	0.93 (0.67–1.27)	33	0.82 (0.53–1.27)	49	0.99 (0.68–1.45)
Q3	6.2–8.9	114	93	1.06 (0.78–1.44)	39	1.06 (0.70–1.61)	54	1.12 (0.77–1.62)
Q4	>8.9	114	90	1.01 (0.74–1.38)	40	1.12 (0.74–1.70)	50	0.91 (0.62–1.33)
P_{trend}				0.92		0.64		0.80
PCB-118								
Q1	<7.2	265	266	1.00	82	1.00	184	1.00
Q2	7.2–10.5	216	171	0.71 (0.53–0.94)	80	0.97 (0.66–1.44)	91	0.59 (0.42–0.82)
Q3	10.6–15.6	216	151	0.60 (0.45–0.81)	76	0.86 (0.57–1.28)	74	0.47 (0.33–0.68)
Q4	>15.6	216	148	0.55 (0.40–0.76)	75	0.72 (0.47–1.12)	73	0.45 (0.31–0.66)
P_{trend}				0.0007		0.10		0.0001
PCB-138								
Q1	<15.6	236	242	1.00	73	1.00	169	1.00
Q2	15.6–24.5	227	168	0.65 (0.48–0.88)	68	0.78 (0.51–1.20)	100	0.61 (0.43–0.86)
Q3	24.6–37.7	225	162	0.54 (0.39–0.75)	88	0.78 (0.50–1.22)	74	0.41 (0.28–0.61)
Q4	>37.7	225	164	0.46 (0.32–0.66)	84	0.52 (0.31–0.86)	79	0.42 (0.27–0.65)
P_{trend}				0.0001		0.01		0.0002
PCB-153								
Q1	<23.4	231	243	1.00	74	1.00	169	1.00
Q2	23.4–37.2	227	158	0.61 (0.45–0.82)	61	0.71 (0.46–1.09)	97	0.58 (0.41–0.82)
Q3	37.3–56.3	229	166	0.53 (0.38–0.73)	85	0.69 (0.44–1.09)	81	0.44 (0.30–0.65)
Q4	>56.3	226	169	0.45 (0.31–0.66)	93	0.52 (0.31–0.87)	75	0.40 (0.26–0.63)
P_{trend}				0.0003		0.02		0.0002
PCB-156								
Q1	<5.3	477	422	1.00	148	1.00	274	1.00
Q2	5.3–6.9	145	98	0.66 (0.48–0.90)	44	0.68 (0.45–1.05)	54	0.63 (0.43–0.92)
Q3	7.0–10.0	149	120	0.77 (0.56–1.06)	69	0.93 (0.62–1.40)	50	0.63 (0.42–0.93)
Q4	>10.0	142	96	0.57 (0.40–0.81)	52	0.54 (0.34–0.86)	44	0.58 (0.37–0.91)
P_{trend}				0.002		0.02		0.006
PCB-163								
Q1	<5.9	397	367	1.00	126	1.00	241	1.00
Q2	5.9–8.1	172	128	0.70 (0.52–0.93)	56	0.73 (0.48–1.09)	72	0.69 (0.49–0.98)
Q3	8.2–11.5	172	110	0.55 (0.40–0.76)	59	0.64 (0.42–0.98)	50	0.46 (0.31–0.69)
Q4	>11.5	172	131	0.59 (0.42–0.83)	72	0.58 (0.37–0.92)	59	0.57 (0.37–0.86)
P_{trend}				0.001		0.02		0.002
PCB-170								
Q1	<6.5	335	311	1.00	101	1.00	210	1.00
Q2	6.5–9.7	192	145	0.73 (0.55–0.98)	61	0.74 (0.49–1.12)	84	0.74 (0.53–1.05)
Q3	9.8–14.5	193	136	0.61 (0.44–0.84)	71	0.68 (0.44–1.04)	65	0.56 (0.38–0.82)
Q4	>14.5	193	144	0.56 (0.39–0.80)	80	0.56 (0.35–0.91)	63	0.55 (0.36–0.85)
P_{trend}				0.002		0.03		0.005
PCB-180								
Q1	<15.8	234	222	1.00	65	1.00	157	1.00
Q2	15.8–25.9	227	177	0.83 (0.62–1.12)	65	0.97 (0.63–1.48)	112	0.80 (0.57–1.12)
Q3	26.0–41.8	226	176	0.68 (0.49–0.95)	90	0.86 (0.55–1.37)	85	0.59 (0.40–0.87)
Q4	>41.8	226	161	0.56 (0.38–0.82)	93	0.67 (0.39–1.13)	68	0.51 (0.32–0.81)
P_{trend}				0.003		0.08		0.004

(*Continued on the following page*)

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Table 3. Adjusted relative risk of TGCTs by quartile of lipid-adjusted levels of serum organochlorines in the STEED study (Cont'd)

	ng/g lipid	Controls	All TGCT		Seminoma		Nonseminoma	
		n	*n*	OR* (95% CI)	*n*	OR* (95% CI)	*n*	OR* (95% CI)
PCB-183								
Q1	<4.2	689	573	1.00	219	1.00	353	1.00
Q2	4.2–5.1	74	44	0.62 (0.41–0.93)	24	0.65 (0.38–1.09)	20	0.56 (0.32–0.96)
Q3	5.2–6.6	75	54	0.75 (0.50–1.12)	36	0.91 (0.56–1.47)	18	0.55 (0.31–0.97)
Q4	>6.6	75	65	0.86 (0.58–1.29)	34	0.77 (0.46–1.29)	31	0.92 (0.56–1.52)
P_{trend}				0.13		0.25		0.14
PCB-187								
Q1	<5.8	386	350	1.00	111	1.00	239	1.00
Q2	5.8–8.0	177	133	0.70 (0.52–0.94)	59	0.81 (0.54–1.21)	74	0.65 (0.45–0.92)
Q3	8.1–11.6	175	120	0.58 (0.42–0.81)	62	0.71 (0.46–1.10)	57	0.49 (0.33–0.73)
Q4	>11.6	175	133	0.60 (0.42–0.86)	81	0.75 (0.47–1.20)	52	0.48 (0.31–0.75)
P_{trend}				0.004		0.27		0.0004

*Adjusted for matching variables, serum DDE level, age at serum draw, BMI, and height.

were significantly more likely than the controls to have a history of cryptorchism (OR, 3.3; 95% CI, 1.8–5.9; $P < 0.0001$). The cases were also significantly more likely to have a family history of testicular cancer (OR, 2.9; 95% CI, 1.5–5.5; $P = 0.0009$), to be taller ($P = 0.0009$), and to have higher serum levels of *p,p′*-DDE ($P = 0.005$) than the controls. No difference ($P = 0.86$) in BMI was evident, however.

Before examining the relationship between PCBs and TGCT, two preliminary analyses were conducted: an examination of the length of the interval between serum collection and diagnosis, and a comparison of mean total lipid levels among cases and controls. The mean and median intervals between serum collection and diagnosis/reference date were 3.9 and 3.3 years, respectively. A comparison of the intervals between the cases and controls found no significant difference ($P = 0.89$). Similarly, a comparison of the mean lipid levels between the cases and controls found no significant difference ($P = 0.11$; data not shown). As persons were exposed to mixtures of PCBs, rather than to single PCB congeners, the correlations between the congeners and the groupings are shown in Table 2. As anticipated, the PCB groupings were highly correlated with each other and with the more highly chlorinated congeners.

Of the 15 congeners analyzed, four (PCB-28, PCB-52, PCB-105, and PCB-128) were excluded from data analysis as fewer than 35% of the study samples had values above the limit of detection (Supplementary Table S1). The results of the adjusted analyses of the other PCBs are displayed in Table 3. There were significant inverse associations between TGCT risk and 8 of the 11 PCBs analyzed: PCB-118 (Q4 OR, 0.55; 95% CI, 0.40–0.76; $P_{trend} = 0.0007$), PCB-138 (Q4 OR, 0.46; 95% CI, 0.32–0.66; $P_{trend} = 0.0001$), PCB-153 (Q4 OR, 0.45; 95% CI, 0.31–0.66; $P_{trend} = 0.0003$), PCB-156 (Q4 OR, 0.57; 95% CI, 0.40–0.81; $P_{trend} = 0.002$), PCB-163 (Q4 OR, 0.59; 95% CI, 0.42–0.83; $P_{trend} = 0.001$), PCB-170 (Q4 OR, 0.56; 95% CI, 0.39–0.80; $P_{trend} = 0.002$), PCB-180 (Q4 OR, 0.56; 95% CI, 0.38–0.82; $P_{trend} = 0.003$), and PCB-187 (Q4 OR, 0.004; 95% CI, 0.42–0.86; $P_{trend} = 0.004$). When the analysis was restricted to the nonseminoma cases, the same eight congeners were significantly inversely associated with risk. Among the seminoma cases, five of the congeners were statistically significantly inversely associated with risk, although the gradient of the trends tended to be less steep than the gradient of the nonseminoma relationships.

The analyses of PCBs by functional groups are shown in Table 4. Total TGCT was significantly inversely associated with all PCB groupings examined: Wolff group 1B ($P_{trend} = 0.02$); Wolff group 2A ($P_{trend} < 0.0001$); Wolff group 2B ($P_{trend} = 0.0002$); Wolff group 3 ($P_{trend} = 0.002$); the inducers of UDP-GT, CYP1A, and CYP2B ($P_{trend} = 0.0005$); the phenobarbital inducers ($P_{trend} = 0.0003$); the mixed function oxidase inducers ($P_{trend} < 0.0001$); and the sum of PCBs ($P_{trend} = 0.0004$). Similarly, nonseminoma was significantly inversely associated with all groupings, whereas seminoma was associated with all groups except Wolff group 1B ($P_{trend} = 0.33$).

As DDE had previously been shown to be related to increased risk of TGCT in the STEED population, an examination of sum of PCBs, stratified by DDE, was undertaken.

As shown in Table 5, none of the trends in total PCB exposure was significant in the strata of individuals with low DDE levels. Among the individuals with high DDE levels, however, PCB levels were significantly inversely related to risk of all TGCT ($P_{trend} = 0.03$) and to nonseminoma ($P_{trend} = 0.04$). The interaction analyses, however, did not find, however, that the relationship between PCBs and TGCT differed significantly by DDE stratum.

To determine whether the congener-specific or the PCB grouping analyses were affected by the inclusion of persons whose interval between serum collection and diagnosis was <1 year, subgroup analyses that eliminated the data from those individuals were performed. The subgroup analyses resulted in no differences in results (data not shown).

Discussion

The incidence of TGCT has been increasing in the United States since before World War II (19). Although few risk factors have been identified, several studies have reported that there is a pronounced birth cohort effect on risk, suggesting that changes in exogenous exposures may be related to the trend (20). One exogenous exposure, endocrine-disrupting chemicals, including PCBs, has been the subject of much speculation, as animal data suggested

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Table 4. Adjusted relative risk of TGCTs by quartile of PCB groupings in the STEED study

	Controls	All TGCT		Seminoma		Nonseminoma	
	n	*n*	OR* (95% CI)	*n*	OR* (95% CI)	*n*	OR* (95% CI)
Wolff group 1B (101, 187)							
(potentially estrogenic, weak phenobarbital inducers)							
Q1	227	214	1.00	64	1.00	150	1.00
Q2	229	193	0.88 (0.66–1.18)	77	0.97 (0.64–1.48)	116	0.83 (0.59–1.16)
Q3	228	156	0.64 (0.46–0.89)	76	0.77 (0.49–1.22)	79	0.56 (0.38–0.83)
Q4	228	171	0.65 (0.46–0.93)	95	0.80 (0.49–1.29)	76	0.55 (0.36–0.84)
P_{trend}			0.02		0.33		0.004
Wolff group 2A (118, 156)							
(potentially antiestrogenic, immunotoxic, dioxin-like, non-*ortho* and mono-*ortho* substituted)							
Q1	229	244	1.00	75	1.00	169	1.00
Q2	227	156	0.59 (0.44–0.79)	61	0.64 (0.42–0.99)	95	0.56 (0.40–0.79)
Q3	228	189	0.62 (0.45–0.85)	102	0.83 (0.54–1.28)	87	0.50 (0.34–0.72)
Q4	229	147	0.42 (0.29–0.59)	75	0.44 (0.27–0.72)	71	0.38 (0.25–0.58)
P_{trend}			<0.0001		0.002		<0.0001
Wolff group 2B (138, 170)							
(potentially antiestrogenic, immunotoxic, limited dioxin activity, di-*ortho* substituted)							
Q1	228	231	1.00	71	1.00	160	1.00
Q2	228	164	0.66 (0.49–0.90)	60	0.70 (0.45–1.08)	104	0.68 (0.48–0.95)
Q3	228	176	0.58 (0.42–0.81)	92	0.75 (0.48–1.17)	84	0.49 (0.33–0.73)
Q4	229	165	0.46 (0.31–0.67)	90	0.49 (0.29–0.83)	74	0.43 (0.27–0.68)
P_{trend}			0.0002		0.01		0.0004
Wolff group 3 (99, 153, 180, 183)							
(phenobarbital, CYP1A, and CYP2B inducers)							
Q1	228	233	1.00	75	1.00	158	1.00
Q2	228	161	0.63 (0.47–0.85)	60	0.63 (0.41–0.97)	101	0.64 (0.46–0.91)
Q3	228	171	0.57 (0.41–0.80)	86	0.64 (0.40–1.00)	84	0.53 (0.36–0.78)
Q4	228	170	0.49 (0.34–0.70)	892	0.49 (0.29–0.81)	78	0.46 (0.29–0.71)
P_{trend}			0.002		0.02		0.003
UDP-GT, CYP1A, and CYP2B inducers (99, 101, 118, 153, 156, 180, 183, 187)							
Q1	228	236	1.00	75	1.00	161	1.00
Q2	228	166	0.64 (0.48–0.87)	62	0.67 (0.44–1.02)	104	0.65 (0.46–0.91)
Q3	228	166	0.55 (0.39–0.76)	85	0.64 (0.41–1.00)	80	0.47 (0.32–0.70)
Q4	228	166	0.47 (0.33–0.68)	90	0.50 (0.30–0.83)	76	0.44 (0.28–0.68)
P_{trend}			0.0005		0.003		0.03
Phenobarbitol inducers (99, 101, 153, 163, 180, 183)							
Q1	228	234	1.00	74	1.00	160	1.00
Q2	228	166	0.65 (0.48–0.87)	68	0.74 (0.49–1.12)	98	0.61 (0.43–0.86)
Q3	228	172	0.58 (0.42–0.81)	82	0.62 (0.39–0.97)	89	0.55 (0.38–0.81)
Q4	228	162	0.46 (0.32–0.66)	88	0.47 (0.29–0.79)	74	0.43 (0.28–0.67)
P_{trend}			0.0003		0.006		0.0009
Mixed function oxidase inducers (118, 138, 156, 170)							
Q1	222	233	1.00	73	1.00	160	1.00
Q2	234	173	0.63 (0.46–0.84)	66	0.64 (0.42–0.99)	107	0.65 (0.46–0.91)
Q3	228	175	0.54 (0.39–0.75)	90	0.66 (0.42–1.03)	85	0.47 (0.32–0.69)
Q4	229	155	0.41 (0.38–0.60)	84	0.42 (0.25–0.71)	70	0.39 (0.25–0.61)
P_{trend}			<0.0001		0.003		<0.0001
Total PCBs (99, 101, 118, 138, 153, 156, 163, 170, 180, 183, 187)							
Q1	228	235	1.00	75	1.00	160	1.00
Q2	228	163	0.62 (0.46–0.83)	58	0.58 (0.38–0.90)	105	0.65 (0.46–0.92)
Q3	228	169	0.55 (0.40–0.77)	92	0.67 (0.42–1.05)	77	0.46 (0.31–0.69)
Q4	228	167	0.46 (0.32–0.67)	87	0.45 (0.27–0.76)	79	0.45 (0.29–0.71)
P_{trend}			0.0004		0.01		0.001

(*Continued on the following page*)

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Table 4. Adjusted relative risk of TGCTs by quartile of PCB groupings in the STEED study (Cont'd)

	Controls	All TGCT		Seminoma		Nonseminoma	
	n	*n*	OR* (95% CI)	*n*	OR* (95% CI)	*n*	OR* (95% CI)
Total PCB exposure †							
Q1	228	224	1.00	74	1.00	150	1.00
Q2	227	171	0.88 (0.67–1.16)	60	0.90 (0.60–1.35)	111	0.84 (0.61–1.15)
Q3	227	175	0.73 (0.54–0.98)	91	0.89 (0.59–1.34)	84	0.62 (0.43–0.88)
Q4	228	162	0.61 (0.43–0.86)	88	0.64 (0.41–1.02)	73	0.55 (0.37–0.83)
P_{trend}			0.006		0.05		0.007

*Adjusted for matching variables, serum DDE level, age at serum draw, BMI, and height.
†Total PCB exposure is sum of all PCB observations above the limit of detection for all PCBs assayed: 28, 52, 99, 101, 118, 128, 138, 153, 156, 163, 170, 180, 183, and 187.

that they might be related to a variety of male reproductive disorders in humans (8, 20). The results of the current study, however, that PCBs are inversely related to risk of TGCT do not support the hypothesis. In that the inverse association seemed more pronounced, although nonsignificantly so, among persons with high serum levels of *p,p′*-DDE, it is possible that the effect of PCBs will depend on the mix of other endocrine disruptors also present. Even at lower serum *p,p′*-DDE levels, however, there was no indication that PCBs served to increase risk.

PCBs are a group of related compounds composed of two carbon-linked benzene rings to which are attached between 1 and 10 chlorine atoms. Between 1929 and 1977, PCBs were manufactured and used in the United States as insulators and coolants in electrical equipment, and in the production of numerous household products. Concerns about possible long-term health effects first surfaced in the 1960s when PCBs were reported to be prevalent in wildlife and persistent in the environment (21). Subsequent animal studies reported that PCB exposure resulted in several outcomes, including neurobehavioral changes, hypothyroidism, reproductive disorders, and tumors. Among humans, mass PCB food poisonings in Japan (1968) and Taiwan (1979) resulted in chloracne, menstrual irregularities, altered immune responsiveness, and general fatigue. In 1977, the sole manufacturer of PCBs in the United States, the Monsanto Company, ceased production 2 years before the formal ban by U.S. Environmental Protection Agency. Based on the animal data and on occupational studies in humans, IARC has classified PCBs as being a probable carcinogen in humans (22).

In humans, PCBs are stored in adipose tissue and levels tend to increase with age (12). Thus, it is difficult to determine in the present study when the study participants were exposed. PCBs, however, can cross the placental barrier and are present in breast milk; thus, some of the exposure may have occurred *in utero* and/or via breast-feeding. If significant exposure occurred *in utero*, PCBs may also affect the risk of the male reproductive congenital anomalies that are associated with TGCT. To date, very few studies of either cryptorchism or hypospadias have examined PCB levels, however. Two studies of cryptorchism and PCBs have been reported and neither has found a relationship (23, 24). In contrast, a study of the prevalence of hypospadias in Greenland found an unexpectedly low rate despite high levels of PCBs in the population (25), suggesting that PCBs might be inversely associated with risk of hypospadias.

Among the testicular dysgenesis syndrome disorders (9) that become evident in adulthood (impaired spermatogenesis and TGCT), more studies have examined the relationship of PCBs with the former than the latter. In general, the results of the PCB-fertility studies are somewhat equivocal. Several studies have found statistically significant associations with impaired sperm variables (26–28), whereas others have found associations only in subsets of their populations (29–31) or not all (32). In contrast, several studies have reported direct associations between PCB levels and fertility (33, 34). The summary of the international INUENDO study of PCBs and fertility in four populations, however, concluded that a representative congener, PCB-153, did not seem to affect fertility or to have direct hormone-like activity (35).

Only one prior study of TGCT and PCBs has been reported to date (13). A case-control study of Swedish men found no association of TGCT with sum of PCBs, estrogenic PCBs, or enzyme-inducing PCBs. An examination of PCB levels in the mothers of the men, however, found that mothers of the cases had significantly higher levels of 21 of the 37 congeners tested. When the PCBs were examined by functional group, the analysis found that the case mothers had significantly higher levels of sum of PCBs and enzyme-inducing PCBs. Interpretation of the mothers' results is rather difficult, however, as the mothers' blood samples were obtained ~30 years after their sons were born. Body burdens of PCBs in women are affected by weight changes, child bearing, and lactation over time, so it is unclear to what extent the mothers' PCB levels were representative of their levels during pregnancy with their sons. It is uncertain why the sons' results differed from the results of the current study, but the discrepancy may be related to the small size of the Swedish study (n = 58 cases, 61 controls), differences in the PCB mixtures used in each country, and timing of the collection of blood samples, as population PCB levels have declined since they were banned. The blood samples in the Swedish study were drawn at a later time (1997–2000) than the samples in the current study, suggesting that the PCB levels might be lower in the Swedish study. A comparison of median levels of estrogenic PCBs and enzyme-inducing PCBs, however, only partially supports this conjecture. The median level of estrogenic PCBs among the Swedish control men was 25 ng/g lipid in contrast with the median control level in the current study of 69.7 ng/g lipid. The median level of the enzyme-inducing PCBs, however, was 174 ng/g lipid among Swedish controls and 73.9 ng/g lipid among

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Table 5. Risk of TGCT by DDE and PCB levels in the STEED study

	All TGCT	Seminoma	Nonseminoma
	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
Low DDE (<147 ng/g lipid)			
Cases/controls (*n*)	343/455	123/455	219/455
Sum of PCBs Q1	1.00	1.00	1.00
Sum of PCBs Q2	0.59 (0.41–0.85)	0.70 (0.41–1.19)	0.56 (0.37–0.85)
Sum of PCBs Q3	0.67 (0.42–1.06)	0.72 (0.37–1.41)	0.62 (0.36–1.07)
Sum of PCBs Q4	0.75 (0.40–1.41)	1.05 (0.45–2.44)	0.59 (0.27–1.28)
P_{trend}	0.36	0.93	0.15
High DDE (≥147 μg/g lipid)			
Cases/controls (*n*)	390/457	189/457	201/457
Sum of PCBs Q1	1.00	1.00	1.00
Sum of PCBs Q2	0.41 (0.20–0.85)	0.33 (0.13–0.87)	0.45 (0.20–1.00)
Sum of PCBs Q3	0.27 (0.13–0.56)	0.35 (0.14–0.91)	0.21 (0.09–0.48)
Sum of PCBs Q4	0.28 (0.13–0.60)	0.27 (0.10–0.74)	0.28 (0.12–0.66)
P_{trend}	0.03	0.11	0.04
$P_{interaction}$	0.48	0.29	0.72

*Adjusted for reference age, race, serum date, family history of TGCT, cryptorchism, age at serum draw, BMI, and height.

U.S. controls. It is also possible that the level of risk or protection of PCBs is determined by the mixtures of congeners present in any location or the presence of other compounds with endocrine-disrupting properties. For example, *p,p′*-DDE was not related to TGCT in the Swedish study but was related to risk in the STEED population (10). This difference may be explained by the lower general level of *p,p′*-DDE in Sweden than in the United States (36).

Why PCBs would be inversely associated with TGCT remains to be determined. *p,p′*-DDE, which has shown antiandrogenic properties, was associated with increased risk in the same population. PCBs have a range of estrogenic, antiestrogenic, androgenic, and antiandrogenic effects (12). Examining the effect by the Wolff groupings (15), only two (PCB-101 and PCB-187) of the PCBs in Wolff group 1 (potentially estrogenic) were examined in the current study. Whereas PCB-101 had no relationship with risk, PCB-187 was inversely associated with both TGCT and nonseminoma. All of the Wolff group 2 (potentially antiestrogenic, dioxin like) PCBs examined (PCB-118, PCB-156, PCB-138, and PCB-170) were significantly inversely related to TGCT risk. Two of the four Wolff group 3 (phenobarbitol, CYP1A, and CYP2B inducers) PCBs were significantly inversely related to risk (PCB-153 and PCB-180), whereas there was no relationship with PCB-99 or PCB-183. Given that there were inverse relations in all the groups, it is not clear what effect is most important in determining risk. In light of the DDE relationship, however, it seems unlikely that an antiandrogenic effect of PCBs would be inversely related to risk. An antiestrogenic effect, however, might be related, especially as the ratio of androgenic to estrogenic exposures has been postulated to be important in TGCT development. Although there was no statistically significant difference in the relationship of PCB levels to TGCT in low and high DDE strata, significant trends only in the high DDE strata may indicate that the presence of other endocrine disruptors is critical to determining the effect of PCBs.

A major advantage of the current study was that prediagnostic serum samples were analyzed. Other advantages were that participants were drawn from a well-defined population, the tumors were histologically confirmed, and the participants were likely to be representative of a wide spectrum of the underlying population. Study limitations include that some potential participants could not be contacted due to deployment, the analysis adjusted for self-reported body size rather than measured body size, and the study could not determine when and how the participants were exposed to PCBs. Inability to contact men due to deployment presents a potential bias in that deployed men might be different in some way that nondeployed men. As most young men in military service are healthy and fit, however, it would seem unlikely that that deployment would confer substantial bias.

In conclusion, the current study suggests that PCBs are inversely associated with the risk of TGCT, particularly with nonseminoma. The results argue for further examination of PCBs and TGCT in other populations, as PCBs are detectable in a large proportion of the world's population. It will be particularly instructive to examine PCB levels in concert with other endocrine disruptor levels to determine whether the inverse association detected in the current study is a result of exposure to other environmental chemicals.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Bray F, Ferlay J, Devesa SS, McGlynn KA, Moller H. Interpreting the international trends in testicular seminoma and nonseminoma incidence. Nat Clin Pract Urol 2006;3:532–43.
2. McGlynn KA. Environmental and host factors in testicular germ cell tumors. Cancer Invest 2001;19:842–53.
3. Dieckmann KP, Pichlmeier U. Clinical epidemiology of testicular germ cell tumors. World J Urol 2004;22:2–14.
4. Skakkebaek NE, Berthelsen JG, Giwercman A, Muller J. Carcinoma-*in-situ* of the testis: possible origin from gonocytes and precursor of all types of germ cell tumours except spermatocytoma. Int J Androl 1987;10:19–28.
5. Toppari J, Kaleva M. Maldescendus testis. Horm Res 1999;51:261–9.
6. Rajpert-De Meyts E, Bartkova J, Samson M, et al. The emerging phenotype of the testicular carcinoma *in situ* germ cell. APMIS 2003;111:267–78.
7. Toppari J, Virtanen H, Skakkebaek NE, Main KM. Environmental effects on hormonal regulation of testicular descent. J Steroid Biochem Mol Biol 2006;102:184–6.
8. Toppari J, Larsen JC, Christiansen P, et al. Male reproductive health and environmental xenoestrogens. Environ Health Perspect 1996;104 Suppl 4:741–803.
9. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod 2001;16:972–8.
10. McGlynn KA, Quraishi SM, Graubard BI, Weber JP, Rubertone MV, Erickson RL. Persistent organochlorine pesticides and risk of testicular germ cell tumors. J Natl Cancer Inst 2008;100:663–71.
11. Kelce WR, Stone CR, Laws SC, Gray LE, Kemppainen JA, Wilson EM. Persistent DDT metabolite p,p′-DDE is a potent androgen receptor antagonist. Nature 1995;375:581–5.
12. Ulbrich B, Stahlmann R. Developmental toxicity of polychlorinated biphenyls (PCBs): a systematic review of experimental data. Arch Toxicol 2004;78:252–68.
13. Hardell L, van Bavel B, Lindstrom G, et al. Increased concentrations of polychlorinated biphenyls, hexachlorobenzene, and chlordanes in mothers of men with testicular cancer. Environ Health Perspect 2003;111:930–4.
14. Rubertone MV, Brundage JF. The Defense Medical Surveillance System and the Department of Defense serum repository: glimpses of the future of public health surveillance. Am J Public Health 2002;92:1900–4.
15. Wolff MS, Camann D, Gammon M, Stellman SD. Proposed PCB congener groupings for epidemiological studies. Environ Health Perspect 1997;105:13–4.
16. McFarland VA, Clarke JU. Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis. Environ Health Perspect 1989;81:225–39.
17. Chevrier J, Eskenazi B, Bradman A, Fenster L, Barr DB. Associations between prenatal exposure to polychlorinated biphenyls and neonatal thyroid-stimulating hormone levels in a Mexican-American population, Salinas Valley, California. Environ Health Perspect 2007;115:1490–6.
18. Wolff MS, Britton JA, Teitelbaum SL, et al. Improving organochlorine biomarker models for cancer research. Cancer Epidemiol Biomarkers Prev 2005;14:2224–36.
19. Zheng T, Holford TR, Ma Z, Ward BA, Flannery J, Boyle P. Continuing increase in incidence of germ-cell testis cancer in young adults: experience from Connecticut, USA, 1935-1992. Int J Cancer 1996;65:723–9.
20. McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L, Tarone RE. Trends in the incidence of testicular germ cell tumors in the United States. Cancer 2003;97:63–70.
21. Jensen S, Johnels AG, Olsson M, Otterlind G. DDT and PCB in marine animals from Swedish waters. Nature 1969;224:247–50.
22. World Health Organization; International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, genetic and related effects: an updating of selected IARC monographs from volumes 1 to 42. Lyon (France): IARC; 1987.
23. Hosie S, Loff S, Witt K, Niessen K, Waag KL. Is there a correlation between organochlorine compounds and undescended testes? Eur J Pediatr Surg 2000;10:304–9.
24. Mol NM, Sorensen N, Weihe P, et al. Spermaturia and serum hormone concentrations at the age of puberty in boys prenatally exposed to polychlorinated biphenyls. Eur J Endocrinol 2002;146:357–63.
25. Giwercman YL, Kleist KE, Giwercman A, et al. Remarkably low incidence of hypospadias in Greenland despite high exposure to endocrine disrupters; possible protective effect of androgen receptor genotype. Pharmacogenet Genomics 2006;16:375–7.
26. Rozati R, Reddy PP, Reddanna P, Mujtaba R. Role of environmental estrogens in the deterioration of male factor fertility. Fertil Steril 2002;78:1187–94.
27. Hauser R, Chen Z, Pothier L, Ryan L, Altshul L. The relationship between human semen parameters and environmental exposure to polychlorinated biphenyls and p,p′-DDE. Environ Health Perspect 2003;111:1505–11.
28. Richthoff J, Rylander L, Jonsson BA, et al. Serum levels of 2,2′,4,4′,5,5′-hexachlorobiphenyl (CB-153) in relation to markers of reproductive function in young males from the general Swedish population. Environ Health Perspect 2003;111:409–13.
29. Bush B, Bennett AH, Snow JT. Polychlorobiphenyl congeners, p,p′-DDE, and sperm function in humans. Arch Environ Contam Toxicol 1986;15:333–41.
30. Dallinga JW, Moonen EJ, Dumoulin JC, Evers JL, Geraedts JP, Kleinjans JC. Decreased human semen quality and organochlorine compounds in blood. Hum Reprod 2002;17:1973–9.
31. Rignell-Hydbom A, Rylander L, Giwercman A, Jonsson BA, Nilsson-Ehle P, Hagmar L. Exposure to CB-153 and p,p′-DDE and male reproductive function. Hum Reprod 2004;19:2066–75.
32. Weiss JM, Bauer O, Bluthgen A, et al. Distribution of persistent organochlorine contaminants in infertile patients from Tanzania and Germany. J Assist Reprod Genet 2006;23:393–9.
33. Cok I, Donmez MK, Satiroglu MH, et al. Concentrations of polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like PCBs in adipose tissue of infertile men. Arch Environ Contam Toxicol 2008;55:143–52.
34. Ensslen SC, Riedel HH, Bluthgen H, Heeschen W. [Chlorinated hydrocarbons in seminal plasma and male fertility]. Zentralbl Gynakol 1990;112:817–21.
35. Bonde JP, Toft G, Rylander L, et al. Fertility and markers of male reproductive function in Inuit and European populations spanning large contrasts in blood levels of persistent organochlorines. Environ Health Perspect 2008;116:269–77.
36. National Resources Defense Council. Healthy milk, healthy baby. 2007 [cited 2008 January 16]. Available from: http://www.nrdc.org/breastmilk.

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