Impairments of Memory and Learning in Older Adults Exposed to Polychlorinated Biphenyls Via Consumption of Great Lakes Fish

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An association between *in utero* polychlorinated biphenyl (PCB) exposure and impaired childhood intellectual functioning has been reported, but the potential impact of PCB exposure during adulthood on intellectual functioning has received little attention. We assessed the impact of PCBs and other fish-borne contaminants on intellectual functioning in older adults. The subjects were 49- to 86-year-old Michigan residents recruited from an existing cohort. Fish eaters ate > 24 lb of sport-caught Lake Michigan fish per year and non-fish eaters ate < 6 lb of Lake Michigan fish per year. A battery of cognitive tests including tests of memory and learning, executive function, and visual–spatial function was administered to 180 subjects (101 fish eaters and 79 non-fish eaters). Blood samples were analyzed for PCBs and 10 other contaminants. We evaluated cognitive outcomes using multiple regression. PCBs and dichlorodiphenyl dichloroethene (DDE) were markedly elevated in fish eaters. After controlling for potential confounders PCB, but not DDE, exposure was associated with lower scores on several measures of memory and learning. These included the Weschler Memory Scale verbal delayed recall (p = 0.001), the semantic cluster ratio (p = 0.006), and list A, trial 1 (p = 0.037), from the California Verbal Learning Test. In contrast, executive and visual–spatial function were not impaired by exposure to either PCBs or DDE. In conclusion, PCB exposure during adulthood was associated with impairments in memory and learning, whereas executive and visual–spatial function were unaffected. These results are consistent with previous research showing an association between *in utero* PCB exposure and impairments of memory during infancy and childhood. *Key words*: DDE, dichlorodiphenyl dichloroethene, executive function, Great Lakes fish, learning, memory, older adults, polychlorinated biphenyls, PCBs, visual–spatial function. *Environ Health Perspect* 109:605–611 (2001). [Online 5 June 2001]
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Great Lakes fish are contaminated with a host of pollutants including chlorinated organic compounds such as polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE), pesticides such as mirex and dieldrin, and trace amounts of metals such as lead and mercury. Although commercial fishing on the Great Lakes is subject to federal regulation, sport fishing is not regulated. Advisories have been developed to inform the public about which fish are safe to eat, but the impact of these advisories on fish consumption is unknown.

The health impacts of regular consumption of sport-caught Great Lakes fish are not clear. However, previous studies have reported an association between *in utero* exposure to PCBs via maternal consumption of Great Lakes fish and impaired intellectual functioning in infancy (*1*) and childhood (*2–4*). In these children, the clearest and most consistent negative association between PCB exposure and intellectual function was seen on tests involving verbal competence and short-term memory processing. Recently another team of investigators has reported a similar association between PCB exposure from Great Lakes fish and short-term memory processing in infancy (*5*). Deficits in intellectual function have also been reported in children whose mothers were exposed to PCBs and related compounds from non-fish sources in the Netherlands (*6*) and in Taiwan (*7*). In contrast, no relationship between PCB exposure and childhood intellectual functioning was observed in a cohort of children in North Carolina (*8*).

The potential impact of PCBs and other fish-borne contaminants on the intellectual functioning of adults has received very little attention. Older adults may be at increased risk from exposure to fish-borne contaminants such as PCBs and DDE because body burdens of these lipophilic compounds increase with age (*9*). At the same time, many aspects of neurological function decline with advancing age (*10*). We conducted the present study to determine if exposure to PCBs and other fish-borne contaminants negatively impacts neurocognitive functioning in older adults.

Methods

Sample

The subjects were selected from an existing cohort of people who consumed large amounts of Great Lakes fish (n = 572) or little or no Great Lakes fish (n = 419). The cohort was originally established in 1980–1982, and its characteristics have been described previously (*9,11*). The heavy fish eaters regularly consumed greater than 24 lb of sport-caught Lake Michigan fish per year, with consumption ranging from 24 to 270 lb/year (median = 38.5 lb/year). Subjects were recruited through visits to marinas, bait shops, and fishing clubs, and by referrals from other participants. The comparison group of people who consumed little or no Great Lakes fish was recruited through random-digit dialing in the communities where the fish eaters were recruited. They reported eating less than 6 lb of sport-caught fish per year.

The current study was restricted to individuals ≥ 49 years of age in 1992 (n = 549). Subjects were randomly selected from 12 cells defined by age (49–59, 60–69, ≥ 70), sex, and fish-eating status, with the goal of recruiting a total of 150–200 people. The details of subject recruitment and the demographic characteristics of participants and refusers have been published previously (*12,13*). Of those who were contacted, 104 of 158 fish eaters and 84 of 188 non-fish eaters were enrolled in the study (n = 188). Fish eaters who were enrolled had demographic and lifestyle characteristics similar to those of fish eaters who did not enroll, with the exception that fish eaters who participated were more likely to be employed (44% vs. 23%). This difference did not appear to be related to health status, as neither self-ratings of health nor number of hospitalizations within the previous 5 years differed by participant status. Among the non-fish eaters,

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there were no significant differences between participants and those who did not enroll.

The 188 subjects who agreed to participate were contacted by phone to arrange an in-home visit. A single examiner who was unaware of their exposure history administered a battery of cognitive and motor tests. Table 1 shows the order in which the tests were administered. The findings of the motor function tests have been reported elsewhere (*13*). All procedures involving human subjects were in accordance with national and institutional guidelines and were approved by the institutional review boards at three cooperating institutions: The University of Illinois at Urbana-Champaign, Michigan State University, and the Michigan Department of Community Health. All subjects provided written informed consent.

Main Outcome Measures

Memory and learning. Wechsler Memory Scale. We administered two subtests of the Wechsler Memory Scale Form I (WMS) (*14*) using Russell's revised procedures (*15*). The Logical Memory subtest consists of two paragraph-length passages. Each is read aloud by the examiner, followed by an immediate recall trial. After 30 min of unrelated testing, a delayed recall trial is administered without warning. Responses were scored according to the criteria of Power et al. (*16*). Scores from the two stories were summed, for a total of 46 points possible.

The Visual Reproduction subtest assesses recall of visually presented material. The test stimuli consist of four abstract geometrical designs printed on three 6 in × 4 in cards (the third card contains two figures). The cards are presented for 10 sec; after each is removed, the subject is asked to draw the design(s) from memory. As with LM, recall is assessed again after a 30-min delay. The drawings were scored according to Wechsler's (*14*) criteria and summed, for a total of 14 possible points.

California Verbal Learning Test. The California Verbal Learning Test (CVLT) (*20*) is a repeated-trials learning test comprising two fictional shopping lists (A and B). Each 16-item list of common household items contains four items from each of four general semantic categories (e.g., fruits). The examiner reads the lists aloud to the subject for recall. List A is presented five times, with immediate recall trials following each. List B is presented once, followed by free and category-cued recall of List A (short delay). After 20 min (long delay), memory for List A is assessed once more by free recall, cued recall, and recognition.

The CVLT was computer-administered using Fridlund and Delis's program (*21*), which scores the test according to the criteria of Delis et al. (*20*). The program yields 27 scores, quantifying different aspects of learning such as recall, recognition, use of strategies, and interference. Nine scores were selected *a priori* for analysis: List A Trials 1–5 total, List A short delay free recall, List A long delay free recall, Learning Slope, Perseverations, Semantic cluster ratio, Discriminability, Proactive interference (List B adjusted for List A Trial 1), and Recognition versus long delay free recall.

Executive function. Wisconsin Card Sorting Test. The Wisconsin Card Sorting Test (*18*) assesses abstract reasoning, concept formation, and shift of set strategies. Four "key cards" with geometric designs are placed before the subject. These cards differ along three dimensions: the shape, color, and number of the designs on the card (e.g., one red triangle, two green stars, etc.). The test stimuli are 128 similar cards, each containing random combinations of shape, color, and number. The subject is instructed to match each of the cards in the decks to one of the key cards, but not by which dimension the cards should be matched (initially color). The subject must deduce the correct sorting principle from examiner feedback as to whether each placement is "right" or "wrong." After 10 consecutive cards are correctly placed, the sorting principle is changed without warning. The test continues until six categories are completed or the cards are exhausted.

The test was scored according to Heaton's criteria (*18*), using the Psychological Assessment Resources' computer program (*19*). Four of the 12 scores computed by the program were selected *a priori* for analysis: total categories completed (0–6), failure to maintain set, perseverative responses, and percent perseverative errors (*18*).

Trail-Making Test Parts A and B. The Trail-Making Test (*22*) assesses complex visual scanning and attention under time pressure. Part A requires the subject to draw a line to connect 25 numbered circles in consecutive order. Part B also consists of 25 labeled circles, but the task is to connect the circles by alternating numbers with letters (i.e., 1-A-2-B-3-C, etc.). The score for each is the time to completion.

Short Category Test, Booklet Format. The Short Category Test (*25*) assesses abstract reasoning ability, concept formation, and hypothesis testing. The Short Category Test consists of five booklets, each containing 20 cards depicting various geometric shapes, lines, colors, and figures. All of the cards within a booklet are organized according to a single principle or concept. The subject is not told what the principle is, but must deduce it from examiner feedback

Table 1. Order of administration of neuropsychological test battery and interview.[a]

Test	References	No.[b]
Wechsler Memory Scale (immediate recall)	(*14–16*)	
Logical Memory		179
Visual Reproduction		178[c]
WAIS-R vocabulary subtest	(*17*)	179
Grooved Pegboard Test[d]		
Dominant hand		164
Non-dominant hand		161
Static Motor Steadiness Test[d]		
Dominant hand		165
Non-dominant hand		163
Wechsler Memory Scale (delayed recall)		
Logical memory		179
Visual reproduction		178[c]
Wisconsin Card Sorting Test	(*18,19*)	178[c]
California Verbal Learning Test (immediate and short delay recall)	(*20,21*)	177[e]
Trail-Making Test	(*22*)	
Trail A		178[c]
Trail B		177[c,f]
WAIS-R Digit Symbol	(*17*)	178[c]
Stroop color–word test	(*23*)	177[c,g]
California Verbal Learning Test (20 min delayed recall and recognition)		177[e]
Hooper Visual Organization Test	(*24*)	178[c]
Short Category Test	(*25*)	178[c]
Demographic/health interview		179
State-Trait Anxiety Inventory	(*26*)	179
Beck Depression Inventory	(*27*)	179

WAIS-R, Wechsler Adult Intelligence Scale-Revised.
[a]A self-administered questionnaire covering fish consumption and occupational history was mailed to participants in advance and collected on the day of testing. [b]Based on a potential maximum of 179, 8 participants refused to provide blood and 1 other participant was eliminated from analysis due to marked cognitive problems resulting from surgery to his carotid artery. [c]One subject had severe macular degeneration; all vision-dependent tests were removed from analysis. [d]Tests obtained from Lafayette Instruments, Lafayette, IN; for results of the motor tests, refer to Schantz et al. (*13*). [e]One subject refused the CVLT, and another was eliminated from analysis because the standardized instructions were misunderstood. [f]One subject refused to complete Trail B. [g]One color blind subject was unable to complete the Stroop color–word test.

and use it to provide the correct response to the remaining cards. The score is the total number of incorrect responses out of 100.

Stroop color–word test. The Stroop test (*23*) measures attention and selective concentration. It consists of three cards, each containing 100 stimulus items. The items on the cards are, respectively, color names printed in black (word), "X's" printed in colored ink (color), and color names printed in incongruous-colored ink (color–word; e.g. "blue" printed in red ink). The task for the first card is to read the words; the task for the second and third cards is to name the color of the ink the items are printed in. The subject is instructed to read/name the items on each card as quickly as possible for 45 sec.

The Stroop test was administered and scored according to the protocol of Golden (*23*), except that new cards were printed using a larger, bolder font. These cards preserved the order of items and the hue of the colors used in the originals, but made it easier for elderly subjects to discriminate the test items.

Visual–spatial function. Digit Symbol Substitution. The Digit Symbol Subtest from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (*17*) is a coding task assessing attention, visual scanning, visuomotor speed, and incidental memory. A key at the top of the page pairs nine nonsense symbols with the numbers 1–9. There are 93 divided boxes. The top sections of the boxes contain the numbers 1–9 in random order; the bottom sections are blank. The task is to draw the correct symbol below each number by referring to the key at the top of the page. The score is the number of squares the subject is able to complete in 90 sec.

Hooper Visual Organization Test. The Hooper Visual Organization Test (*24*) is a mental assembly task consisting of 30 simple line drawings of common objects, each of which has been cut into pieces and placed randomly on a card. The score is the number of correctly identified objects out of 30.

Confounding Variables

Through a careful review of the literature, we identified a large number of demographic, lifestyle, psychological, and health-related variables as potential confounders. These are listed in Table 2 and were described in detail in a previous publication (*13*). A comparison of the demographic, lifestyle, and psychological characteristics of the fish eaters and non-fish eaters has also been published previously (*12*). Fish eaters and non-fish eaters had very similar demographic characteristics, reported similar patterns of smoking and alcohol consumption, and had comparable scores on measures of intellectual functioning and affect. The only medical condition that differed between fish eaters and non-fish eaters was arthritis, which was reported more frequently in male fish eaters. Although PCB and DDE levels are correlated with fish-eating status, we hypothesized that any effects observed on the outcome measures would be due to contaminant exposure rather than fish consumption per se. Therefore, fish eaters and non-fish eaters were combined and analyses were performed using regression procedures.

Measures of Exposure

Several weeks after completion of the neuropsychological assessment battery, we collected a blood sample from 96% ($n = 180$) of the participants for residue analysis. One sample was not obtained because of a collapsed vein, one subject died before a sample could be collected, and six subjects refused the blood draw. The samples were analyzed for PCBs and 10 other contaminants including DDE, polybrominated biphenyls, hexachlorobenzene, oxychlordane, dieldrin, mirex, mercury, and lead (*11,28*). We analyzed PCBs, DDE, and other organochlorines in serum by gas chromatography. Lead and mercury were analyzed in whole blood by atomic absorption spectrophotometry. Serum or blood concentrations of the contaminants have been reported previously (*12,28*). Four chemicals, PCBs, DDE, lead, and mercury were higher in the heavy fish eaters than in those who ate little or no fish, but PCBs and DDE clearly emerged as the primary contaminants of concern and are, therefore, the focus of this report. The mean levels of each of the four contaminants in each of the 12 enrollment cells defined by age, sex, and fish-eating status are shown in Table 3. The levels of PCBs and DDE were markedly elevated in heavy fish eaters, both relative to age- and sex-matched non-fish eaters and relative to levels typically observed in the population at large (*29*). Non-fish eaters, while also exposed to PCBs and DDE, had much lower levels of both chemicals. Only 15 participants (8.4%) had serum PCB levels below the detection limit of 3.0 ng/g, and only 6 (3.4%) had DDE levels below the detection limit of 1.0 ng/g.

On average, males had higher PCB levels than females (mean: males 15.2 vs. females 9.2; $p = 0.01$), and PCB levels were also associated with increasing age (chi-square test, $p = 0.04$). For DDE however, the mean levels did not differ by sex ($p = 0.11$), but they did differ by age (chi-square test, $p < 0.001$). Lead and mercury were slightly elevated in fish eaters relative to non-fish eaters, but the levels were near background in all but a few subjects. Over one-half (54%) of participants had mercury levels below the detection limit of 2.0 ng/g. Polybrominated biphenyls, a contaminant unique to the state of Michigan, were detected in a subset of the subjects, but the levels did not differ between fish eaters and non-fish eaters. None of the other chemicals were detected in any of the subjects.

Statistical Analyses

We used SAS software, version 7 (SAS Institute Inc., Cary, NC) to perform all statistical analyses. We used regression analyses to assess the relationship between performance on each outcome measure and exposure to PCBs and DDE, while simultaneously controlling for potential confounders. Multiple linear regression was used for normally distributed continuous outcomes. Outcomes with distributions exhibiting appreciable skewness were dichotomized and analyzed by logistic regression.

We developed regression models for each of four classes of control variables (Table 2), starting with all correlates of the outcome variable identified through univariate analyses as being significant at $p < 0.20$. The preliminary multivariable model for each class of control variables retained all variables significant at $p < 0.10$. The final regression model

Table 2. Summary of covariates by category.[a]

Demographic	Lifestyle	Psychological functioning	Health
Age	Activity level	Overall intellectual function	Self-rating of overall health
Sex	Leisure/sports	WAIS-R Vocabulary subtest	General health (e.g., body mass index, hearing loss, visual impairment)
Education	Occupational	Emotion/stress	Physical symptoms (e.g., fatigue, dizziness, minor colds)
Income	Household	Beck Depression Inventory	Medical conditions (e.g., arthritis, thyroid disease, hypertension)
Employment status	Stair climbing	State-Trait Anxiety Inventory	Prescription and nonprescription drug use, categorized by class (e.g. antibiotics, diuretics, acetaminophen)
Marital status	Tobacco use		
Social support	Alcohol consumption		History of psychiatric illness, head injury, stroke
Household size	Caffeine consumption		
Dominant hand			

[a]For a complete list, see Schantz et al. (*13*).

combined the four separate models and the exposure variables for PCBs and DDE. We entered the exposure variables on the logarithmic scale and replaced nondetectable values with one-half the limit of detection. We explored alternate methods for handling participants with PCB and/or DDE levels below the detection limit (including removing them from the analyses altogether, but the final models for the outcome measures under discussion were essentially unchanged. PCBs and DDE were retained throughout the analyses irrespective of their statistical significance. All other variables were retained in the final model if they remained significant at $p < 0.10$. Variants of this approach have been applied in other settings when a large number of potential confounding variables need to be considered (*30,31*). Variables discarded previously because of their lack of significance were added back into the final model if they significantly improved its predictive power. We based formal checks for outliers and influential observations on leverage statistics and standardized residuals (*32*). Collinearity was assessed by variance inflation factors and condition numbers (*32*); no adjustments were needed. Prespecified interactions between PCB, DDE, and specific control variables (age and sex) were also tested for significance. Predicted scores on the cognitive tests were obtained from the final regression model.

Because serum lead and mercury concentrations were slightly elevated in fish eaters, we also evaluated the effects of these two contaminants on the various cognitive outcomes. As with PCB and DDE, lead and mercury were entered on the log scale and nondetectable values were replaced with one-half the detection limit. However, unlike the primary exposure variables, lead and mercury were retained in the final model only if they significantly ($p < 0.10$) added to its predictive power.

Results

Neuropsychological evaluations and blood samples were available from 180 subjects. However, one male non-fish eater who reported recent carotid artery surgery and had severely impaired cognitive performance was excluded *a priori* from all statistical analyses, leaving a final sample size of 179 (101 fish eaters and 78 non-fish eaters). All participants were white, lived independently, and were in good general health. The median age was 64.3 years (range 49–86 years), 42.5% were male, and 48% had a high school education or less. Approximately 57% of the sample had an annual income of < $40,000.

In the final sample of 179 people, total serum PCBs ranged from below the detection limit to 75 ng/g, with a median of 7.9 ng/g. DDE values ranged from nondetectable to 145 ng/g, with a median of 8.1 ng/g.

Measures of Memory and Learning

After controlling for potential confounders, higher PCB exposure was associated with lower scores on the verbal delayed recall (logical memory) portion of the WMS (Table 4). PCB was significant in the initial bivariate analysis ($p = 0.009$) and remained significant in the final multivariate regression model ($p = 0.001$). The negative beta coefficient for PCB (on the log scale) indicates an inverse relationship between PCB exposure and verbal delayed recall. DDE was not significant in the initial bivariate analysis ($p = 0.312$), but became significant in the presence of PCB, age, and the Wechsler Adult Intelligence Scale vocabulary score ($p = 0.016$). The beta coefficient for DDE was positive, indicating that higher DDE exposure was associated with higher scores on verbal delayed recall. Lead and mercury exposure did not significantly impact verbal delayed recall and were not retained in the final model.

To further illustrate the negative impact of PCB exposure on verbal delayed recall, we divided the sample into quartiles based on PCB exposure and calculated observed and predicted recall scores (Table 5). All but 5 of the 45 subjects in the highest PCB exposure quartile were fish eaters. A clear downward trend in verbal recall scores was seen with increasing PCB exposure.

Higher PCB exposure was also related to lower scores on two outcomes from the CVLT, the semantic cluster ratio ($p = 0.006$), and List A, Trial 1 ($p = 0.037$). DDE, lead, and mercury exposure were not related to these outcomes. The observed and predicted scores for the Semantic Cluster Ratio and List A, Trial 1, by PCB exposure quartile are shown in Table 5. For both tests, we observed a clear downward trend in scores with increasing PCB exposure.

Table 3. Summary statistics for PCB, DDE, lead, and mercury by sex, age, and fish-eating status.

			Fish eaters				Non-fish eaters			
Sex	Age (years)	Exposure	No.	Mean ± SD	Median	Min–Max	No.	Mean ± SD	Median	Min–Max
Male	< 60	PCB[a]	16	15.88 ± 14.8	10.60	ND–65.20	11	6.11 ± 4.2	5.00	ND–15.30
		DDE[b]		12.26 ± 9.2	9.60	1.80–36.70		7.12 ± 5.9	4.80	ND–17.40
		Lead[c]		4.40 ± 1.5	5.00	2.00–7.00		3.45 ± 1.6	3.00	ND–6.00
		Mercury[d]		3.18 ± 4.8	2.40	ND–20.50		2.05 ± 1.9	2.10	ND–5.00
	60–69	PCB	16	23.03 ± 19.1	17.25	ND–65.20	12	6.82 ± 3.5	5.95	3.40–15.50
		DDE		18.12 ± 17.7	8.70	ND–52.70		9.99 ± 8.0	7.95	1.80–31.50
		Lead		5.13 ± 1.8	5.00	3.00–9.00		5.08 ± 4.1	4.00	ND–15.00
		Mercury		3.96 ± 2.7	3.75	ND–9.80		ND	ND	ND–4.00
	≥ 70	PCB	14	24.69 ± 19.3	19.95	ND–75.00	7	5.66 ± 2.0	4.90	4.00–10.00
		DDE		28.09 ± 37.4	13.05	5.40–145.00		8.03 ± 6.4	6.90	3.00–21.40
		Lead		4.38 ± 1.7	4.00	2.00–7.00		3.67 ± 1.6	3.50	2.00–6.00
		Mercury		3.06 ± 2.9	2.85	ND–7.40		ND	ND	ND–3.50
Female	< 60	PCB[a]	21	8.67 ± 4.6	7.60	ND–23.00	19	4.64 ± 2.2	ND	ND–9.20
		DDE[b]		7.09 ± 4.6	6.20	ND–15.90		4.94 ± 4.3	4.50	ND–19.60
		Lead[c]		2.45 ± 1.5	2.00	ND–7.00		2.47 ± 2.2	2.00	ND–9.00
		Mercury[d]		ND	ND	ND–3.00		ND	ND	ND–4.10
	60–69	PCB	17	14.04 ± 6.8	12.40	4.00–26.30	16	8.71 ± 8.5	6.10	ND–25.90
		DDE		11.50 ± 6.3	10.00	2.90–26.40		8.46 ± 7.9	6.10	1.60–32.50
		Lead		3.29 ± 1.3	3.00	ND–6.00		2.75 ± 1.3	2.00	2.00–6.00
		Mercury		ND	2.00	ND–6.00		ND	ND	ND–3.30
	≥ 70	PCB	17	13.52 ± 10.8	12.10	ND–49.00	13	5.05 ± 3.8	4.70	ND–11.00
		DDE		22.63 ± 16.1	16.20	7.00–62.60		7.22 ± 6.1	5.80	ND–20.90
		Lead		3.38 ± 1.9	3.00	ND–7.00		3.54 ± 1.4	3.00	2.00–6.00
		Mercury		ND	ND	ND–8.00		ND	ND	ND–3.00

Abbreviations: Max, Maximum; Min, minimum; ND, below the limit of detection.
[a]Detection limit = 3.0 ng/g. [b]Detection limit = 1.0 ng/g. [c]Detection limit = 2.0 µg/dL. [d]Detection limit = 2.0 ng/g.

Measures of Executive and Visual–Spatial Function

In contrast to the measures of memory and learning, PCB, DDE, lead, and mercury exposure were not associated with poorer scores on any of the tests of executive or visual–spatial function. The final models including covariates, beta coefficients, and *p*-values for each outcome variable are shown in Table 4.

Age and Sex Interactions

PCB and DDE body burdens increase with age (*9*), and animal studies suggest that certain PCB-related cognitive deficits may be sex-specific (*33*). Therefore, we also tested age

Table 4. Covariates, β-coefficients, and significance levels of neuropsychological outcome measures.

Outcome measure	Covariates included in final model	No.	LogPCB β[a]	LogPCB *p*-Value	LogDDE β[a]	LogDDE *p*-Value
Memory and Learning						
Wechsler Memory Scale						
Logical memory						
Immediate	Education, income, vocabulary, blurred vision, peptic ulcer, NSAIDS	166[b]	–0.33	0.44	0.42	0.24
Delayed	Age, vocabulary, smoking status, blurred vision, antibiotics, NSAIDS	179	–1.33	0.001	0.85	0.02
Visual reproduction (referent > 10.0)						
Immediate[c]	Age, vocabulary, health self-rating, kidney disease, acetaminophen	178	0.07	0.82	–0.07	0.79
Delayed	Age, vocabulary, nonleisure activity level, arthritis, hardening of the arteries, bladder problems, acetaminophen, vitamin use	174[d]	–0.23	0.39	0.01	1.0
California Verbal Learning Test						
List A, Trial 1	Age, sex, vocabulary, leisure activity level, allergies, hardening of the arteries, kidney disease, “other” motor conditions (e.g., carpal tunnel syndrome), calcium channel blockers, diabetes medications, sex hormone replacement therapy, antidepressants	175[e]	–0.42	0.04	0.06	0.71
List A, Trials 1–5 Total	Age, sex, vocabulary, Beck depression score, leisure activity level, allergies, diabetes, “other” motor conditions	176[f]	–1.33	0.16	0.39	0.63
List A, short delay free recall	Age, sex, income, vocabulary, asthma, numbness/tingling in extremities	164[b]	0.05	0.86	–0.11	0.68
List A, long delay free recall	Age, sex, marital status, vocabulary, hypoglycemia, numbness/tingling in extremities, kidney disease	177	–0.43	0.17	0.44	0.11
Learning slope	Education, asthma, chronic bronchitis, hypertension, history of near-drowning incident, calcium channel blockers, antidepressants, diabetes medication	177	–0.01	0.95	0.04	0.44
List B, adjusted for List A Trial 1	List A trial 1, age, sex, vocabulary, bladder trouble, anemia, diuretics, narcotics/psychotropic medication	177	0.26	0.15	–0.06	0.70
Perseverations[c] (referent > 0)	Employment status, vocabulary, emphysema, “other” motor conditions, fatigue, diuretics, sex hormone replacement therapy, “other” medications (e.g., digestive aids, laxatives)	177	–0.21	0.43	–0.17	0.47
Semantic Cluster Ratio	Vocabulary, smoking status, blurred vision, NSAIDS, sex hormone replacement therapy, potassium replacement	174[g]	–0.24	0.006	0.05	0.51
Discriminability[c] (referent > 94%)	Age, sex, vocabulary, state anxiety, acetaminophen, vitamin use	177	0.44	0.12	–0.24	0.34
Recognition hits vs. long delay free recall[c] (referent < 36.3)	Sex, vocabulary, employment status, smoking status, hardening of the arteries, numbness/tingling in extremities, diabetes medication, sex hormone replacement therapy	177	0.03	0.91	0.41	0.12
Executive function						
Stroop color–word test						
Interference score[h]	Income, state anxiety, hypoglycemia	164[b]	0.13	0.88	–0.35	0.63
Wisconsin Card Sorting Test						
Number of categories completed[c] (referent = 6)	Age, vocabulary, arthritis, “other” motor condition, diabetes medication	178	–0.33	0.24	–0.21	0.40
Failure to maintain set[c] (referent >0)	Age, state anxiety, “other” motor condition, blurred vision, ACE inhibitors, steroidal hormones	178	–0.15	0.57	0.27	0.24
Perseverative responses[c] (referent < 22)	Age, education, frequent headaches	178	–0.28	0.28	–0.08	0.74
Percent perseverative errors[c] (referent < 16.05)	Age, vocabulary, history of near-drowning incident, frequent headaches, antidepressants, beta blockers	178	–0.42	0.13	–0.08	0.73
Trail-Making Test						
Trail A[i]	Age, vocabulary, smoking status, emphysema, balance trouble, diabetes medication, sex hormone replacement therapy	178	0.01	0.67	–0.01	0.73
Trail B[i]	Age, education, vocabulary, state anxiety, cancer (current), hardening of the arteries, beta blockers	177	–0.01	0.90	0.04	0.16
Short Category Test						
Total errors	Age, vocabulary, kidney disease, anti-arrhythmatics, acetaminophen, antidepressants, vitamin use	178	–0.15	0.91	–0.57	0.63
Visual–spatial function						
Hooper Visual Organization Test[c]						
Total correct (referent >25)	Age, sex, vocabulary, ACE inhibitors	178	–0.24	0.37	0.32	0.18
WAIS-R						
Digit Symbol raw score	Age, sex, vocabulary, education, stiff muscles, headache, diuretics, acetaminophen	176[e]	1.29	0.14	–1.44	0.06

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDS, nonsteroidal anti-inflammatory drugs
[a]Regression coefficient from multiple regression analysis. [b]Thirteen participants with missing values for income were eliminated from the final model. [c]Based on logistic regression; variables dichotomized based on median value for entire sample, except where noted. [d]Four participants with missing values for nonleisure activity level were eliminated. [e]Two influential observations removed. [f]One influential observation removed. [g]Three influential observations removed. [h]Color–word card raw score, adjusted for color card raw score. [i]Time in seconds, log transformed.

Table 5. Memory and learning test scores by PCB exposure quartile.

PCB Level (ng/mL)	WMS logical memory, delayed recall No.	Observed (mean ± SD)	Predicted mean	CVLT Semantic Cluster Ratio No.	Observed (mean ± SD)	Predicted mean	CVLT List A, Trial 1 No.	Observed (mean ± SD)	Predicted mean
ND[a]–4.6	44	9.67 ± 3.4	9.72	43	2.41 ± 0.9	2.31	44	7.64 ± 2.1	7.53
4.7–7.8	45	9.09 ± 5.2	9.26	44	2.20 ± 0.9	2.29	45	7.31 ± 2.3	7.26
7.9–13.8	45	8.39 ± 4.2	8.28	45	2.13 ± 0.8	2.12	45	6.91 ± 2.0	7.10
13.9–75.0	45	7.66 ± 3.9	7.54	43	1.88 ± 0.7	1.89	43	6.14 ± 1.5	6.11

[a]Below the detection limit of 3.0 ng/mL.

by exposure and sex by exposure interaction terms for statistical significance. However, none of the PCB or DDE by age or sex interactions was significant.

Discussion and Conclusions

This study suggests, for the first time, that PCB exposure during adulthood may be associated with impairments in certain aspects of memory and learning. Older adults exposed to PCBs through consumption of sport-caught Great Lakes fish had lower scores on the verbal delayed recall portion of the WMS as well as on two measures of the CVLT. In contrast, visual memory and other aspects of cognition including executive and visual–spatial function appeared to be unaffected by PCB exposure. Other contaminants in the fish, including DDE, mercury, and lead, did not appear to have any negative impact on cognitive function. Earlier we reported that fine motor function also seemed to be unimpaired by PCB or DDE exposure (*13*).

Wechsler Memory Scale Logical Memory

Perhaps the most striking effect of PCB exposure was the relationship between higher PCB exposure and delayed recall on the logical memory portion of the WMS. This test assesses the individual's memory for two paragraph-length passages (stories) 30 min after they are read aloud by the examiner. Participants with serum PCB concentrations in the upper quartile ($\geq$ 13.9 ng/g) scored, on average, about 2 points lower than those in the lowest quartile (9.67 vs. 7.66). Furthermore, 17 of the 45 people (38%) in the highest PCB exposure quartile had scores that were below the 25th percentile of the distribution (< 6), whereas only 4 of 44 individuals (9%) in the lowest quartile had scores below the 25th percentile. Overall, the performance on WMS logical memory delayed recall differed by PCB exposure (Cochran-Mantel-Haenszel test, 3 degrees of freedom; $p = 0.03$). In contrast to this clear effect of PCB exposure on verbal delayed recall on the WMS, there was not a significant effect of PCB exposure on verbal delayed recall as measured by the CVLT. Evidence for a negative impact on verbal delayed recall would be stronger if both these measures were affected. However, the two tests differ in several important ways, and these may make the WMS a more sensitive measure of deficits in delayed recall than the CVLT. The WMS logical memory test uses coherent stories, whereas the CVLT uses a list of objects presented in a standardized order. Also, the stories are presented only once and immediate recall is assessed only once. In contrast, the word list is presented five times for immediate recall, then both free and cued recall are assessed after a short delay. Finally, both tests include a surprise delayed recall, but the WMS uses a 30-min delay, whereas the CVLT uses a shorter 20-min delay.

The positive association between DDE exposure and verbal delayed recall on the WMS is very puzzling. DDE was significant only when in the presence of PCB and two other variables, age and vocabulary score, which suggests a complex higher order interaction between these variables. There was no indication of a similar relationship on any of the other cognitive outcome measures.

California Verbal Learning Test

The strongest negative effect of PCB exposure among the CVLT variables was seen on semantic clustering. The word lists for this test consist of 16 words, four in each of four categories (e.g., tools, fruits). Semantic clustering refers to the extent to which the subject groups the words by category during recall. Use of semantic clustering requires the subject to actively organize the words by their meaning. This results in more efficient encoding to long-term memory than do other strategies such as serial order clustering (*34*). Immediate recall uses working memory, a transient form of memory that keeps information "online" for a short period of time while it is being actively manipulated (*35*), but delayed recall, which occurs after 20–30 min of unrelated testing, must rely on long-term memory (*36*). Thus, it is not surprising that impairments were seen on both semantic clustering and verbal delayed recall. It is unclear why PCB exposure was related to poorer verbal delayed recall on the WMS logical memory test, but not on the CVLT, but it is possible that efficient semantic clustering is more critical for memory of a coherent story than for a random list of words.

Statistical Issues

In this study multiple statistical tests were performed on multiple cognitive outcomes, and only a few significant effects of contaminant exposure were observed. This raises the possibility that the significant findings were spurious associations. We believe that this is unlikely because four chemicals, PCBs, DDE, mercury, and lead, were evaluated as exposure variables, but all of the significant negative associations were related to PCB exposure. Also, several aspects of cognitive functioning including memory and learning, executive function, and visual–spatial function were assessed, but all of the negative effects were seen on the tests of verbal memory and learning. Children exposed to PCBs *in utero* via maternal consumption of Great Lakes fish also showed impairments, primarily on tests involving verbal and memory function (*1–4*). Despite these consistencies, it would be prudent to interpret the findings with caution until they have been replicated in an independent exposure cohort.

Conclusions

This study is the first to find that adults exposed to elevated levels of PCBs may be at risk of neuropsychological impairment. The results should be important in the risk assessment arena because current fish consumption advisories focus heavily on protecting the pregnant woman and fetus. As with children exposed *in utero*, certain aspects of verbal memory and learning seem to be the primary targets for PCB-related impairments in older adults. Executive, visual–spatial, and motor (*13*) function did not appear to be affected. Furthermore, other neurotoxic contaminants in the fish including DDE, mercury, and lead did not have any negative impact on cognitive or motor function. It is possible, however, that subtle changes in other outcomes or those related to other contaminants were missed because the modest sample size restricted statistical power. It is also possible that greater exposure to PCBs and/or these other contaminants would result in additional impairments. For example, workers exposed to PCBs in capacitor manufacturing plants have been reported to have serum PCB levels 10- to 100-fold higher than the levels that are typical in Great Lakes fish eaters (*37*). These workers may be at considerably greater risk of neuropsychological impairments than are Great Lakes fish eaters, and are a group that warrants further study.

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