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ANALYSIS OF PCB CONGENERS RELATED TO COGNITIVE FUNCTIONING IN ADOLESCENTS

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Abstract

To investigate the characteristics of PCBs that are linked to cognitive functioning, those congeners that were concurrently found in 271 Mohawk adolescents were grouped according to structure (dioxin-like or non-dioxin-like) and persistence (persistent or low-persistent). After the effects of the congener groups were orthogonalized, regression analyses (controlling for a number of variables found to be related to the cognitive outcomes) examined the relationship of each congener group to scores on three cognitive tests (the non-verbal Ravens Progressive Matrices, the Test of Memory and Learning, and the Woodcock Johnson – Revised). Five subtests from these cognitive tests were found to be associated with one or more PCB congener groups, most often at a moderate level. Two measures of long term memory (Delayed Recall and Long Term Retrieval) were associated with all four congener groups. Nevertheless, examination of the role of individual congeners in the significantly related congener groups revealed that almost all congeners associated with cognitive outcomes were non-dioxin-like and *ortho*-substituted. A notable exception was the Ravens test where scores were associated only with dioxin-like congeners. This finding adds to the limited evidence of neurotoxic effects of dioxin-like congeners. Auditory Processing was related only to the persistent congener group. The association of the non-persistent congener group with three cognitive test scores (Delayed Recall, Long Term Retrieval and Comprehension-knowledge) suggests that the Mohawk adolescents have experienced continuing or recent environmental exposure to PCBs that is sufficient to result in detectable cognitive decrements. Comparison of our findings with those of other human studies was limited by the

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relative lack of specificity of both PCB measures and cognitive outcome measures in much previous work.

Keywords

Polychlorinated biphenyls; congeners; cognition; memory; adolescents; Mohawk

Introduction

Numerous studies have reported negative effects associated with prenatal or perinatal exposure to polychlorinated biphenyls (PCBs) on aspects of cognitive functioning in children (Jacobson and Jacobson 1996; Patandin et al., 1999; Vreugdenhil et al., 2002; Vreugdenhil et al., 2004; Walkowiak et al., 2001). Concurrent PCB body burden has been negatively associated with memory in adolescents (Newman et al., 2006), memory and learning in older adults (Schantz et al., 2001), and attention performance in adults (Peper et al., 2005).

However there is considerable variation in findings of different studies that may have several sources. Variation could be due to the particular congeners comprising the different exposures in studies of PCBs and cognition. PCBs include 209 chemical species (congeners) that differ in the extent and pattern of chlorination of the biphenyl structure (Agency for Toxic Substances and Disease Registry 2000). At any single time point, PCB body burden is a function of: 1) the subject's past and recent exposure history, and 2) the subject's individual determinants of uptake, metabolism, and clearance, i.e., toxicokinetics (Frame 1997; Gladen et al., 2003; Glynn et al., 2003; Hansen 1998; James et al., 2002; Karmaus et al., 2001). Biological persistence of individual congeners and, consequently, their relative contribution to the body burden, varies with structure (Brown, Jr. 1994; Safe 1994). Higher chlorinated congeners (*i.e.*, those with six or more chlorines) and those with *para*- (*i.e.*, 4,4'-) chlorine ring substitution are, in general, metabolized slowly in humans and typically make up the bulk of body burden. However, recent PCB exposure will also result in the presence of less persistent congeners in tissue. Past exposure to labile congeners may also result in effects that continue to be demonstrated (Hansen 1998).

Typically in human studies, PCB congeners are grouped, either as total PCBs or the sum of several commonly found congeners, or are indexed by a single congener, usually PCB 153 (Longnecker et al., 2003). However, studies using a summative PCB measure do not reveal which types of congeners are influential, and what features of these congeners are linked to effects.

Despite the analytic capability of identifying particular PCB congeners, human studies have not studied groups of congeners defined by structure or toxicological action in part because the human neurotoxic mechanisms of PCB action are not well understood at this time. In one of the few studies to consider specific PCB congeners, no pattern could be detected in the congeners found to be related to neurological optimality deficits at 10 to 21 days in humans (Huisman et al., 1995). Unlike the predominant neurochemical findings (Seegal et al., 1990; Tilson and Kodavanti 1998; Wong et al., 2001) behavioral evidence in experimental animals has demonstrated physical and learning effects for both *ortho*-substituted and dioxin-like PCB congeners, with no clear pattern (Holene et al., 1998; Tilson et al., 1979). Studying the effects of specific PCB congeners of known structure or hypothesized toxicological effects would help clarify sources of inconsistency in the findings of the human studies. In some cohorts, negative associations have not been found (Daniels et al., 2003; Grandjean et al., 2001; Gray et al., 2005; Longnecker et al., 2004;

Vermeir et al., 2005; Vreugdenhil et al., 2002), and in others appear to be transient (Stewart et al., 2003; Winneke et al., 2005) or delayed (Walkowiak et al., 2001).

Further inconsistency between study findings may arise from differences in the cognitive outcome measures employed. Study results would vary not only according to the PCB congeners evident in the sample of participants, but also the particular neuropsychological processes involved in the outcome measures employed. Human studies have included various measures of developmental or psychological functioning, according to the age of the participants, the tests available in the years testing was conducted, and experimenter focus. While many of the tests provide a global measure such as IQ, the tests used are not functionally equivalent and do not comprise the same number, type or specificity of psychological processes. Moreover, the processes involved in psychological functioning may change with age and may be at risk of disruption by PCBs at different ages (Walkowiak et al., 2001).

For all of these reasons, researchers have called for more investigation of specific congener effects (Rice 2005; Schantz et al., 2003). Such congener specific analyses would not only increase understanding of relationships and the processes by which observed effects occur – they would inform recommendations of public health agencies concerning the targeting and urgency of remediation, according the known effects of the congeners prevalent in an area (Rice 2005).

In the present paper we reexamine the cognitive outcomes found to be associated with the summative measure of PCBs used in our earlier analysis (Newman et al., 2006). In that analysis we summed all 16 PCB congeners with a rate of detection in the adolescent sample of 50% or greater into a single measure, and found it to be related to two separate measures of long-term memory, as well as comprehension-knowledge. In the current paper we test hypotheses about the effects of congener characteristics on cognitive outcomes by grouping congeners for re-analysis according to their structural similarity (dioxin-like and non-dioxin-like), and their known persistence. Because of the high correlation between the congener groups created we transformed the grouped PCB variables to orthogonalize their effects. Many of the published findings (e.g. Vreugdenhil et al., 2004; Winneke et al., 2005) have included commonly found congeners known to be of high persistence (138, 153, 180 and sometimes 118). We also investigate the role of a subgroup of low-persistence, non-dioxin-like congeners, to determine if either recent episodic or chronic continuing exposure negatively impacts cognitive functioning in the adolescents (Brown, Jr. 1994; Hansen 1998). If these congener groups show associations with cognitive outcomes, further analysis of the associations of specific congeners comprising the groups is warranted. The battery of tests employed provided more specificity about cognitive outcomes than do most other human studies, yet addresses cognitive domains that have been associated with exposure in these studies.

Methods

Sample and location

The Mohawk Adolescent Well-Being Study (MAWBs) was conducted in the years 1995–2000 in partnership with residents of the Akwesasne Mohawk Nation, a sovereign territory lying on both sides of the St. Lawrence River and spanning the boundaries of New York State, and Ontario and Quebec, Canada. Several industrial complexes are in close proximity to Akwesasne, including a National Priority Superfund Site (General Motors Central Foundry Division), and two New York State Superfund Sites (Reynolds Metal Company and Aluminum Company of America).

Study protocols and methods have previously been described in detail (Newman et al., 2006; Schell et al., 2003b), and are briefly reviewed here. All study protocols were approved by the Institutional Review Board at the University at Albany, State University of New York, and informed consent was obtained from all participants. Two hundred and seventy one mother-adolescent pairs, who met eligibility criteria, enrolled in and completed the study. To be eligible, the adolescent must have: 1) been 10 to 16 years 11 months old, 2) been a singleton birth, 3) never been hospitalized with a brain injury, 4) had no history of serious organic or psychological pathology as determined by a physician or psychologist, nor 5) a diagnosis of Fetal Alcohol Syndrome or Fetal Alcohol Effects. Forty-eight percent of the adolescents were male.

Procedures

Trained data collectors, who were members of the Akwesasne community and had no prior knowledge of participants' toxicant levels, conducted all data collection, including cognitive testing and blood draws, and maternal interviewing. Data collectors received extensive training at the University at Albany and on-site, both before the study began and regularly throughout the project. Videotapes of the cognitive testing were periodically reviewed in order to maintain standardized procedures.

Fasting blood draws (15 ml) were taken in the adolescent's home upon his/her first rising in the morning. Assessment of cholesterol and triglycerides was performed at the Clinical Chemistry and Hematology Laboratory, Wadsworth Center for Laboratories and Research, New York State Department of Health. The facility is CLIA-approved and a member of the CDC reference laboratory network for lipid measurements (Myers et al., 2000). Serum lipid concentrations were measured on a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN) using a cholesterol esterase and oxidase/peroxidase method for total cholesterol (Allain et al., 1974) and a glycerol kinase-based procedure that corrects for free glycerol in the specimen (Kohlmeier 1986) for triglycerides.

Toxicants

Analyses of PCBs and organochlorine pesticides (*p,p*'-DDE, HCB), and mirex were conducted at the University at Albany's Exposure Assessment Laboratory. High resolution, ultratrace, congener-specific analysis was performed by parallel dual-column (splitless injection) gas chromatography with electron capture detection (DeCaprio et al., 2000). This method quantitates up to 83 individual PCB congeners and 18 PCB congeners as pairs or triplets. Lead and mercury analyses were conducted by Le Centre de Toxicologie due Quebec in Sainte-Foy, Quebec Canada. Lead was analyzed by Zeeman-corrected graphite furnace atomic absorption spectrometry (Parsons and Slavin 1993), and mercury by cold-vapor atomic absorption spectrometry.

The method recommended by the U.S. Environmental Protection Agency (U.S.Environmental Protection Agency 1998) was used to impute values below the method detection limits (mdl) for all toxicants with rates of detection of 50% or greater (see Schell et al. (2003a)). The algorithm calculates a value depending on the mdl and the rate of detection of each toxicant (Cohen 1950; Gupta 1952). This method was also used for all imputations of non-detected lead, mercury, HCB, and mirex levels. It was not used for *p,p*'-DDE as all samples had detectable levels. For those congeners detected in less than 50% of the sample, the most common practice for imputation was applied by replacing any individual datum that was below the mdl with the midpoint value between zero and the mdl of each analyte or congener.

Congener groups

PCBs are indicated by IUPAC numbers throughout. Sixteen PCB congeners with rates of detection of 50% or greater are included in the present analysis (ΣPCBs50% = PCBs 118, 101[+90], 153, 110, 99, 87, 138 [+163+164], 180, 95, 52, 74, 105,149 [+123], 187, 70, 84). Specific congeners were also grouped according to structure: 1) PCB congeners are defined as dioxin-like or non-dioxin-like based upon the criteria used by the World Health Organization and other regulatory agencies; and 2) high and low-persistence groupings. This resulted in 1) dioxin-like (PCBs 105, 118, 149[+123]); 2) non-dioxin-like (PCBs 52, 70, 84, 74, 87, 95, 99, 101[+90], 110, 138[+163+164], 153, 180, 187); 3) a highly persistent grouping (PCBs 74, 99, 105, 118, 138[+163+164], 153, 180, 187); and 4) a low-persistence grouping which includes tetra- or penta-PCBs that are *ortho* substituted and that have at most one *para* chlorine (PCBs 52, 70, 84, 95, 110, 101[+90], 87). The group of dioxin-like congeners does not contain the more potent dioxin-like congeners (Van den Berg et al., 2006) as they were not measurable with the analytic method employed. The low-persistence grouping of congeners (all of which are non-dioxin-like) was found to include the most potent reducers of dopamine concentrations in cell cultures (Shain et al., 1991). The congeners within a specific group were combined quantitatively by a simple summation for this analysis. Similar groupings were created with PCB congeners detected in at least 10% of the sample, and these were also tested for any relationships with the outcomes of interest.

Cognitive tests

The Woodcock Johnson-Revised Tests of Cognitive Ability, Standard and Supplemental Batteries (Woodcock and Johnson 1990), or WJ-R, yields a measure of overall cognitive functioning (Broad Cognitive Ability Extended, BCAE), as well as seven cluster scores that provide information regarding an individual's abilities in specific domains of cognition. These domains are Long Term Retrieval (LTR), Short Term Memory (STM), Processing Speed (PSD), Auditory Processing (APG), Visual Processing (VPG), Comprehension-Knowledge (CKN), and Fluid Reasoning (FRG). The WJ -R has good psychometric properties, with a stated validity of 0.60 to 0.70, and reliability of 0.90. Adolescents were administered both the Standard and Supplementary Batteries, whereas mothers were administered only the Standard Battery.

The Ravens Progressive Matrices (RPM), Standard Form (Raven et al., 1992) is a measure of intellectual ability and reasoning skills. The Ravens assesses the individual's ability to discern patterns and derive meaning from complex data. The Ravens is thought to be culturally "fair" because it is a nonverbal measure, i.e. language is not utilized in the testing materials or administration. Furthermore, the Ravens has been normed on individuals of different cultural backgrounds.

The Test of Memory and Learning (TOMAL) (Reynolds and Bigler 1994) is a measure of general and specific memory functioning. The TOMAL yields a Verbal Memory Index (VMIS), Non-verbal Memory Index (NMIS), Delayed Recall Index (DRIS), and Composite Memory Index (CMIS).

Statistical Analysis

All substantive statistical analyses were performed using SPSS version 15.0.1 (SPSS 2001). For the multivariate analysis, a list of potential confounders was generated from measured factors that previous research suggests are likely to be related to cognitive functioning. These were sex, age (years), the adolescent's body mass index (BMI), cholesterol and triglyceride levels, total caloric, fat and protein intake, maternal BMI, maternal Broad Cognitive Ability, a weighted index of socioeconomic status (which includes maternal education, maternal employment (current, full/part time), maternal marital status, size and

condition of the house, number of motor vehicles and age of newest vehicle within the household), the number of social problems (i.e. health, relative, legal, marital, drinking, drug use, etc.) within the household, gravidity, number of cigarettes the mother smoked per day during pregnancy, duration of breastfeeding in weeks, and levels of other toxicants (HCB, DDE, mirex, blood lead, and mercury). Those selected from this list for inclusion in the multiple regression models were selected empirically, based on the inclusive decision rule of bivariate correlation of $p<0.2$ with one or more cognitive scores, as has previously been described (Newman et al., 2006).

Variables with skewed distributions were log transformed (lead, mercury, PCBs, *p,p*'-DDE, HCB, breastfeeding duration (weeks), and number of cigarettes mothers smoked per day during pregnancy). Mirex levels were categorized into three groups because of the high rate of nondetectable levels: non-detects (below the minimum detection limit of 0.02 ppb; 54.2%), low detects (0.02–0.03 ppb; 18.1% of the sample), and high detects (0.04–1.17 ppb; 27.7% of the sample).

Our objective of simultaneously assessing the effect of a dioxin-like congener group and a non-dioxin-like congener group, and a highly persistent grouping simultaneously with a low-persistence congener group, invokes the common but vexing data analytic condition of multicollinearity. The problems and treatments of multicollinearity have been investigated by many researchers and it is a standard topic in all introductions to multiple regression. Strong bivariate correlations between PCB groupings (shown in Table 3) and much weaker correlations between each cognitive score and PCB groupings (reported in Table 6) substantiate our concern and indicate all of the usual conditions associated with multicollinearity and partialling fallacy (Gordon, 1968).

Managing the intercorrelation of risk factors presents a formidable challenge because it is difficult to accurately disentangle and rank the contributions of individual factors deemed important to the subject of study. Our solution is to orthogonalize our congener groupings, creating new sets of orthogonal variables, using a modified Gram-Schmidt procedure (Golub & Van Loan, 1996) available as the *orthog* procedure in the Stata software package (StataCorp, 2007). Given that the order (that is, the conceptual priority) of the variables determines the orthogonalization, we generate four orthogonal transformations: one in which our dioxin-like congener group precedes our non-dioxin-like group, then vice versa; a third in which our highly persistent grouping precedes our low-persistence congener group, then vice versa.

Orthogonal variables produce numerical accuracy for highly collinear variables and they are easy to interpret. In essence, the transformations residualize the variables according to their specified order. With two variables, the first variable retains all of its variation (and therefore all of its covariation with the dependent variable), while the second variable retains only its residual variation that remains after removing its covariation with the first variable. The orthogonal variables are then scaled as standard normal variables with zero means and unit variances (and standard deviations) so that their metric in a substantive multiple regression is in standard deviation units.

Results

Table 1 provides a description of the participating adolescents, including cognitive test scores. Relevant maternal scores are also shown. Participating youth ranged in age from 10 through 16 years with a median of 13.2 years, and on average showed cognitive functioning similar to comparison adolescents on whom the WJ-R, TOMAL and Ravens were normed. Forty-eight percent were male.

Grouped PCB and specific congener levels are shown in Table 2. Akwesasne adolescents' PCB levels ranged between 0.05 and 3.32 ppb, dependent on the congener grouping. *p,p'*-DDE levels were found to be highest of the all the persistent organic pollutants, with a maximum level of 4.80 ppb. Heavy metal levels were consistently low, neither exceeding the CDC threshold. Correlation among the PCB groupings is shown in Table 3. All groupings are positively correlated at r = 0.6 or above.

Of the potential covariates examined for their relationship with the cognitive outcomes of interest, bivariate correlations (Table 4) determined that the following were related to at least one cognitive score at a $p<0.2$ level, and so were included in the final model: sex; age in years; adolescent and maternal BMI (kg / m ^{2}); adolescent triglyceride and cholesterol levels; maternal Broad Cognitive Ability Standard score; SES index; number of reported social problems; gravidity; cigarette use during pregnancy; breast feeding duration (in weeks); *p,p*'-DDE; HCB; blood lead; mercury; and mirex. Each congener group's converse (e.g. non-dioxin-like for dioxin-like; low-persistent for highly persistent) was also included as a covariate in the multivariate analysis.

Multivariate regression models predicting each cognitive domain were calculated for the four orthogonally transformed PCB congener groups made up of congeners found in more than 50% of the sample (Table 5). The sum of dioxin-like PCBs was a significant, inverse, predictor of Ravens scores. All congener groupings were consistently and negatively associated with both Long Term Retrieval and Delayed Recall. The sum of highly persistent PCBs was inversely and significantly associated with Auditory Processing. The sum of low-persistent PCBs was a significant, inverse predictor of Comprehension-Knowledge. Verbal Memory, Non-verbal Memory, Composite Memory, Broad Cognitive Ability Extended, Short Term Memory, Processing Speed, Visual Processing, and Fluid Reasoning were not significantly associated with any congener group. The reported results did not differ when calculations included those less prevalent congeners found in 10% of the sample or more.

The effect of an increase of one standard deviation in the PCB congener group may be expressed as a proportion of one standard deviation of the relevant cognitive test. Following Cohen's (1988) guidelines for effect sizes that may be considered small, moderate or large, we found that most of the significant relationships described above indicate moderate effects of 0.40 or greater. A one standard deviation increase in the dioxin-like congener group was associated with decreases in Ravens, Delayed Recall and Long Term Retrieval of 0.32, 0.33 and 0.35 standard deviation units respectively. A one standard deviation increase in the non-dioxin like congener group was associated with decreases of 0.41 and 0.52 standard deviation units in Delayed Recall and Long Term Retrieval respectively. A one standard deviation increase in the persistent congener group was associated with decreases in Delayed Recall, Long term Retrieval, and Auditory Processing of 0.48, 0.49, and 0.43 standard deviation units respectively. Finally, a one standard deviation increase in the low-persistent congener group was associated with decreases of 0.28, 0.41 and 0.27 standard deviation units of Delayed Recall, Long Term Retrieval and Comprehension-knowledge respectively.

Because the regression analyses showed that hypothesized congener groups were associated with some cognitive outcomes (Ravens, Long Term Retrieval, Delayed Recall, Auditory Processing, Comprehension-Knowledge), bivariate correlations between the individual PCB congeners comprising these groups and those five cognitive outcomes were examined also (Table 6). (Eight cognitive outcomes were not correlated significantly with any of the 16 congeners.) Long Term Retrieval was significantly correlated ($p<.05$) with seven PCB congeners, more than any other cognitive test. Six of these seven were non-dioxin-like (di-*ortho* substituted congeners PCBs 87, 99, 101[+90], 110, and 138[+163+164, and tri-*ortho*

substituted PCB 84). Delayed Recall, a similar measure to Long Term Retrieval, was significantly correlated with only two congeners (PCBs 153 and 187), both non-dioxin-like (di-*ortho* substituted). Auditory Processing was significantly correlated with the non-dioxin-like (di-*ortho* substituted) PCB 187. The Ravens test was significantly correlated with only the dioxin-like congener PCB 105.

Our multivariate analysis (Table 5) showed that the congeners grouped by persistence category were related to some cognitive outcomes also. Examination of the bivariate correlations of cognitive outcomes (Table 6) with congeners in the persistence groups found to be significant showed that for those congeners categorized as persistent, Delayed Recall was significantly correlated with PCBs 153 and 187, Long Term Retrieval was significantly correlated with PCBs 99 and 138[+163+164], and Auditory Processing with PCB 187. Several low-persistent congeners were also correlated with Long Term Retrieval (PCBs 101[+90], 110, 87, and 84).

Discussion

In this paper we tested whether congener structure (dioxin-like, and non-dioxin-like) and relative persistence of the congeners detected in concurrent body burden would be related to cognitive functioning in our adolescent participants. We found that, with very few exceptions, all relationships were negative. All four congener groups created for the analyses were significantly associated with some cognitive scores, in most cases to a moderate degree. Our statistical transformation of the PCB group variables allowed us to determine their separate effects. The battery of tests we used allowed for the investigation of specific cognitive functions and the scores on these specific functions revealed associations with PCB congener types. By contrast, the global scores of memory and cognition (respectively the Composite Memory score and the Broad Cognitive Ability Extended score) did not reveal these associations.

The two measures of long term memory (Long Term Retrieval and Delayed Recall) were associated with all four congener groupings, suggesting that this association is robust, and that the memory function is susceptible to toxic exposure at more than one developmental period and by more than one congener type. (The various measures of shorter term memory showed a different pattern, and in fact the Short Term Memory score showed only non-significant relationships with congener groups.) In contrast to the pervasive associations between long term memory and congener group, some of our observed cognitive outcomes were associated with only particular congener types. Ravens (a non-verbal problem solving test) was associated only with the dioxin-like congener group (and in fact only PCB 105), Auditory Processing was associated only with the persistent congener group (and in fact only PCB 187), and Comprehension-knowledge was associated only with the less-persistent congener group (and no individual PCB congeners).

The importance of congener type on neurobehavioral outcomes has not received much systematic attention in previous studies with human populations (Schantz et al., 2003). Lack of experimenter control of exposure, limited and idiosyncratic exposure patterns in various human environments, and correlation between exposure to various congeners, have hindered the conclusions about congener specific effects that can be drawn from human studies. Research carried out in the laboratory and with animals has led to the conclusion that *ortho*-substituted, non-planar PCBs with non-dioxin-like activity affect brain neurochemistry. Seegal, Bush and Shain (1990) conclude from their in vitro studies that such congeners reduce brain dopamine, but that planar, dioxin-like congeners do not alter dopamine. Tilson and Kodavanti (1998) conclude from review of the literature and their own work that non-dioxin-like *ortho*-substituted congeners are the most neurotoxic PCBs. They suggest that

PCB-induced changes in calcium dependent enzymes may have synaptic effects which could be related to the storage of information and hence memory functioning. This suggestion would be consistent with our own finding of the association of the non-dioxin-like congener group with our two measures of long term memory, and the fact that almost all of the individual congeners associated with the long term memory scores were *ortho*-substituted non-dioxin-like PCB congeners (but would not explain why Long Term Retrieval was also related to one dioxin-like congener).

Animal learning has been linked to non-dioxin-like PCB exposure. Holene (1998) reported that the non-dioxin-like di-*ortho*-substituted congener (PCB 153) had a negative effect on rats' learning (but so did co-planar PCB 126). Commenting on previous research in 1998, Hansen reported that researchers generally considered that *ortho*-substituted congeners were most potent, and that coplanar congeners were not potent. A review of animal studies by Shantz and Widholm (2001) also pointed to the role of *ortho*-substituted non-dioxin-like congeners in deficits in learning and memory.

Our results show that both non-dioxin-like and dioxin-like congener groups relate to long term memory functioning in adolescents. Nevertheless, almost all of the individual congeners associated with Long Term Retrieval were *ortho*-substituted non-dioxin-like, as were both of the congeners associated with Delayed Recall. Moreover, the non-dioxin-like congener group had moderate effect sizes on these two memory scores whereas the dioxin-like congener group had smaller effects.

The associations of the memory scores and non-dioxin-like congener group body burden are consistent with the laboratory and animal studies already mentioned. On the other hand, our finding about dioxin-like congeners is worthy of note, especially the finding that Ravens scores were negatively associated with the dioxin-like congeners only. Previous research has provided little evidence that dioxin-like congeners are neurotoxic. Patandin et al. (1999) found that in the breast fed members of their Dutch study, measures of dioxin exposure were not related to the intellectual or language performance of the children. Indeed, Shantz and Widholm (2001) report a positive association between dioxin exposure and some measures of spatial learning in animals. The Ravens is a problem solving task involving visual-perceptual reasoning and requiring no spoken language in either administration or response. This makes the test unique among those in the batteries administered to the children in the various human cohorts. The test author (Raven et al., 1992) reviews limited evidence that particular areas and types of brain activity are involved in the performance of the test; these may be different from those associated with the other cognitive subtests used in the current study and in previous cohorts, and so be affected by different PCB generated processes.

Thus our findings in regard to congener structure are in part consistent with previous reports of the effects of *ortho*-substituted non-dioxin-like congener structure on cognitive functioning, specifically long term memory scores. The findings, moreover, add to this literature in that they show that exposure to dioxin-like congeners is also associated with deficits in memory and non-verbal reasoning scores. However, it should be noted that the dioxin-like congener most strongly associated with this finding (along with other dioxin-like congeners measured in this study), has very low dioxin-like activity as compared to the highly potent congeners 126 and 169. This suggests that the neurobehavioral effects we observed may involve a mechanism other than Ah receptor activation (Van den Berg et al., 2006).

Differential persistence of PCB congeners will influence the degree to which their effects are evident in individuals of different ages. Developmental risk posed by exposure to PCB congeners is likely to vary according to the extent those congeners accumulate in the body

and thus have persistent influence (e.g. Brown, Jr. 1994). Because of chronic accumulation, PCB body burden increases with age (Brown, Jr. 1994; DeCaprio et al., 2005), but the burden of particular congeners will vary according to the rate they are metabolized and cleared from human tissue, as well as their ongoing existence in external exposure sources (Hansen 1998).

The participants in the current study were preadolescents and adolescents, unlike those in the other human cohort studies. Most studies of PCB effects on development have taken infant or early childhood endpoints. Any effects that are evident in adolescence may have resulted from episodic exposure that occurred prenatally, earlier in childhood and/or currently. Effects may also result from chronic exposure. Cognitive outcomes may also be affected by previous episodic exposure to labile congeners that are no longer detectable.

We related our participants' cognitive scores to their concurrent PCB body burdens, whereas other studies have employed measures of prenatal or perinatal PCB exposure. The effects of prenatal exposure are most established with humans (Schantz et al., 2004); animal studies (Holene et al., 1998; Rice and Hayward 1997; Schantz et al., 2003), and limited human research (Walkowiak et al., 2001) provide evidence of post-natal exposure effects also. As reported above, our results do show that that concurrently measured PCB levels are related to measures of cognitive functioning. We cannot specify the timing of the exposure that contributed to the current PCB body burden, but by comparing congeners of different degrees of known persistence, we can get some indication of the likely timing of exposure that resulted in cognitive deficits.

Exposure to low-persistent congeners could not have occurred prenatally or in early childhood; there must be a source of exposure that is more recent and within the physiological clearance time of the congener. The presence of low-persistent congeners in current body burden reflects recent episodic or ongoing exposure (Hansen 1998). Effects associated with these congeners must have occurred relatively recently. On the other hand, cognitive effects associated with persistent congeners could have occurred at any time from conception to the present. We found that the two long term memory outcomes (Delayed Recall and Long Term Retrieval) were related to both the persistent and the low-persistent congener groups, mostly to an extent that would be considered moderate. The implication of low-persistence congeners in these outcomes, as well as the Comprehension-knowledge outcome, indicates that there has been exposure to PCBs either in the recent past or at the time of testing for these adolescents which has affected their cognitive functioning although in most cases to a modest degree. In addition, exposure to persistent PCB congeners could have occurred early in the participant's life, but could also reflect ongoing exposure. As well as long term memory functioning, auditory functioning was associated moderately with evidence of exposure to persistent congeners. Taken together, these results provide concern that there could still be sufficient environmental exposure to PCBs for these Mohawk adolescents to result in decrements in their performance on several cognitive subtests.

We found that Auditory Processing scores were significantly and moderately associated with the persistent PCB congeners. Based on animal studies that show that hearing loss in animals may be associated with PCB exposure, Schantz, Widholm and Rice (2003) recommend investigation of auditory functioning in humans exposed to PCBs. Our results show that lower scores on the auditory processing subtest of the WJ-R were associated with only the congeners in the persistent group. Because persistent congeners are most indicative of PCBs operating early in the participant's life, this finding is consistent with the suggestion from animal studies (Crofton et al., 2000; Goldey and Crofton 1998), but not results of a study of children (Longnecker et al., 2004) that auditory mechanisms are particularly susceptible to PCB damage at a period in early development. Nevertheless, caution is

needed in drawing this conclusion because of our inability to know when persistent congeners had effects and also because of variations in the nature of auditory processing measured in different studies. In the animal studies, auditory acuity was measured, whereas in the current study more processing of the auditorily presented material was required.

Our analyses provide us with an opportunity to examine the association of congener PCB 153 which has been used as a marker of general PCB level in human studies (e.g. Longnecker et al., 2003). In our study this congener was classified in the non-dioxin-like and the persistent congener groups which were associated with Delayed Recall, Long Term Retrieval, and Auditory Processing. In multivariate and bivariate testing, PCB 153 was not associated with Long Term Retrieval or Auditory Processing, but was associated with Delayed Recall. Thus, relying on PCB 153 in analyses of specific cognitive dimensions may not detect all relevant effects.

The comparison of our findings with those of other published human studies is complicated because different studies use different measures of cognitive performance, and few allow satisfactory cognitive outcome specificity. There are multiple ways to characterize and measure cognitive functioning. The methods selected in studies depend on the age of the participants among other factors. Common methods are tests of general intelligence (such as the Stanford Binet, Wechsler or McCarthy tests), developmental status (such as the Bayley), psycho-neurological performance, habituation, reaction time, and various facets of memory. None-the-less, methods are not interchangeable, different cognitive processes are involved in each method, and the processes involved in psychological functioning may change with age and may be at risk to disruption by PCBs at different ages (Walkowiak et al., 2001).

In our research we used a battery of cognitive tests that provides more refined cognitive measures than most studies. Some, but not all, of these cognitive domains are represented in the outcome measures of other studies. For example, our battery provides a summary measure of intellectual functioning (the Broad Cognitive Ability Extended score of the WJ-R) comparable to the summary measures provided by general intelligence tests. The WJ-R also provides measures on seven cognitive dimensions that are not represented explicitly on the other intellectual tests. Our battery is unique in that it included a non-verbal intelligence test (the Ravens). We also include a memory test that provided separate measures of verbal, non-verbal, short term memory and long term memory. These memory domains are involved in the measures of some other studies, although not often explicitly. (An exception is Schantz et al., (2001), which uses the Wechsler Memory Scale.) In fact, most other studies lack the outcome specificity of our study and therefore do not allow direct outcome comparison.

In conclusion, in much of the published human literature, both the PCB exposure and the cognitive outcomes are incompletely analyzed and specified. As a result, sensitive linking of the two is not possible, and results have not been generated that can validate and extend our own. So, even though we have been able to determine some aspects of PCB congeners that are linked to specific cognitive outcomes, future studies are needed to test the effects of the congener groups we have used (using both the particular congeners and others of the same specified type), and use outcome measures that are more functionally specific.

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Table 1

Characteristics of the sample

Adolescents	**N**	**Mean**	**Median**	**SD**	**Minimum**	**Maximum**
Age (years)	271	13.2	13.2	1.96	10.0	17.0
BMI (kg/m^2)	269	24.1	23.1	5.29	13.6	43.5
Triglyceride level (mg/dL)	259	87.2	76	44.20	25	259
Cholesterol level (mg/dL)	259	159.5	156	28.93	100	251
Ravens (RPM)	268	54.2	57	26.48	1	99
TOMAL:						
Verbal Memory (VMIS)	269	99.2	100	11.56	66	138
Nonverbal Memory (NMIS)	269	101.0	101	12.05	62	133
Delayed Recall (DRIS)	269	99.7	100	8.36	72	120
Composite Memory (CMIS)	269	100.3	101	10.36	65	137
Woodcock Johnson - Revised (WJ-R)						
Broad Cognitive Ability Extended (BCAE)	236	100.7	100	12.41	66	135
Long Term Retrieval (LTR)	269	106.2	106	12.71	75	147
Short Term Memory (STM)	266	99.0	97	12.97	54	152
Processing Speed (PSD)	268	100.4	100	14.78	62	141
Auditory Processing (APG)	263	95.6	95	12.15	68	139
Visual Processing (VPG)	269	114.7	114	13.13	77	160
Comprehension-Knowledge (CKN)	250	95.3	94	12.02	67	135
Fluid Reasoning (FRG)	258	102.8	101	13.14	70	142
Mothers						
Maternal BMI (kg/m^2)	269	29.5	28.8	6.07	16.3	56.0
Maternal Broad Cognitive Ability Standard	249	95.3	95	10.74	70	126
Socioeconomic Status Index	271	24.5	25	5.61	9	37
Number of Social Problems Reported	269	0.4	0	0.80	0	4
Gravidity	269	2.2	2	1.39	1	8
Cigarette Use during Pregnancy (#/day)	269	2.7	0	6.55	0	40
Breastfeeding Duration (weeks)	269	6.4	0	12.77	0	51.2

Table 2

PCB and other toxicant levels among Akwesasne Mohawk youth*.

PCBs (ppb)	N	Structure	ROD	Dioxin-like (Y/N)	Persistence (H/M/L)	GM	Median	SD	Minimum	Maximum
ΣDioxin-like PCBs50%[a,c]	271	-	-	-	-	0.11	0.10	0.064	0.05	0.45
ΣDioxin-like PCBs10%[b,d]	271	-	-	-	-	0.13	0.12	0.073	0.06	0.50
ΣNondioxin-like PCBs50%[a,e]	271	-	-	-	-	0.55	0.52	0.319	0.24	2.52
ΣNondioxin-like PCBs10%[b,f]	271	-	-	-	-	1.03	0.95	0.504	0.57	3.32
ΣPersistent PCBs50%[a,g]	271	-	-	-	-	0.39	0.36	0.257	0.15	2.45
ΣPersistent PCBs10%[b,h]	271	-	-	-	-	0.61	0.57	0.346	0.31	3.16
ΣLow-persistent PCBs50%[a,i]	271	-	-	-	-	0.24	0.22	0.156	0.11	1.22
ΣLow-persistent PCBs10%[b,j]	271	-	-	-	-	0.51	0.45	0.263	0.31	1.72
PCBs >50% IUPAC#[a]										
118	271	2,3’,4,4’,5	99.6%	Y	H	0.06	0.06	0.041	0.02	0.28
101[+90][k]	271	2,2’,3,4’,5 + 2,2’4,5,5’	98.5%	N	L,M	0.05	0.04	0.040	0.02	0.30
153	271	2,2’,4,4’,5,5’	97.8%	N	H	0.09	0.08	0.087	0.02	0.98
110	271	2,3,3’,4’,6	95.2%	N	L	0.05	0.05	0.040	0.02	0.34
99	271	2,2’,4,4’,5	94.5%	N	H	0.04	0.05	0.029	0.02	0.21
87	271	2,2’,3,4,5’	91.5%	N	L	0.04	0.04	0.024	0.02	0.16
138[+163+164][k]	271	2,2’,3,4,4’,5’ + 2,3,3’,4’,5’,6 + 2,3,3’,4’,5,6	90.0%	N	H,M,L	0.07	0.07	0.055	0.02	0.47
180	271	2,2’,3,4,4’,5,5’	89.3%	N	H	0.04	0.04	0.052	0.01	0.39
95	271	2,2’,3,5’,6	79.3%	N	L	0.03	0.02	0.019	0.01	0.15
52	271	2,2’,5,5’	78.6%	N	L	0.03	0.02	0.027	0.01	0.16
74	271	2,4,4’,5	73.4%	N	M	0.02	0.02	0.037	0.01	0.53
105	271	2,3,3’,4,4’	63.5%	Y	H	0.02	0.02	0.016	0.01	0.13
149[+123][k]	271	2,2’,3,4’,5’,6 + 2,3’,4,4’,5’	59.0%	Y	L,H	0.02	0.02	0.018	0.01	0.12
187	271	2,2’,3,4’,5,5’,6	57.6%	N	M	0.02	0.02	0.017	0.01	0.15
70	271	2,3’,4’,5	55.4%	N	L	0.02	0.02	0.016	0.01	0.11
84	271	2,2’,3,3’,6	53.1%	N	L	0.02	0.02	0.009	0.01	0.08

PCBs (ppb)	N	Structure	ROD	Dioxin-like (Y/N)	Persistence (H/M/L)	GM	Median	SD	Minimum	Maximum
PCBs >10% <50% IUPAC#[b]										
170	271	2,2',3,3',4,4',5	45.0%	N	H	0.02	0.01	0.018	0.01	0.13
66	271	2,3',4,4'	37.6%	N	M	0.01	0.01	0.011	0.01	0.08
28	271	2,4,4'	33.6%	N	M	0.02	0.01	0.041	0.01	0.25
158	271	2,3,3',4,4',6	31.7%	N	M	0.01	0.01	0.005	0.01	0.05
31	271	2,4',5	31.7%	N	L	0.02	0.01	0.025	0.01	0.18
92	271	2,2',3,5,5'	27.3%	N	L	0.01	0.01	0.008	0.01	0.06
174	271	2,2',3,3',4,5,6'	26.9%	N	L	0.01	0.01	0.007	0.01	0.05
177	271	2,2',3,3',4,5',6'	25.5%	N	H	0.01	0.01	0.007	0.01	0.06
29	271	2,4,5	24.7%	N	L	0.01	0.01	0.008	0.01	0.06
97	271	2,2',3,4',5'	22.1%	N	L	0.01	0.01	0.008	0.01	0.07
71	271	2,3',4',6	16.6%	N	L	0.01	0.01	0.007	0.01	0.08
77	271	3,3',4,4'	14.8%	Y	M	0.01	0.01	0.013	0.01	0.09
156	271	2,3,3',4,4',5	14.4%	Y	H	0.01	0.01	0.012	0.01	0.14
15	271	4,4'	10.3%	N	M	0.02	0.02	0.013	0.02	0.13
Other Toxicants[a]										
HCB (ppb)	271		97.8%	-	-	0.03	0.03	0.019	0.02	0.19
p,p' -DDE (ppb)	271		100.0%	-	-	0.37	0.35	0.345	0.09	3.08
Mirex (ppb)	271		45.8%			0.02	0.01	0.092	0.01	1.17
Blood Lead (μg/dL)	265		70.9%	-	-	0.71	1.40	0.970	0.07	4.80
Total Mercury (μg/dL)	265		93.6%	-	-	0.09	0.09	0.097	0.02	0.58

[*] Only those congeners that were found to be significantly correlated with the outcome variables are shown in the detected in <50% or >10% group.

Abbreviations: PCB, polychlorinated biphenyls; PPB, parts per billion; IUPAC, International Union of Pure and Applied Chemistry; GM, geometric mean; SD, standard deviation; persistence: H, hi

[a] Values below the mdl were calculated following the EPA recommended method for estimating non-detected values as described in Schell et al., 2003.

[b] Values below the detection limit have been replaced by the value midway between the detection limit and zero.

[c] ΣDioxin-like congeners in >50% of the sample= IUPAC#s 105,118,149[+123].

[d] ΣDioxin-like congeners in >10% of the sample= IUPAC#s 77,105,118,149[+123],156.

[e] ΣNondioxin-like congeners in >50% of the sample = IUPAC#s 52,70,84,74,87,95,99,101[+90],110,138[+163+164],153,180,187.

[f] ΣNondioxin-like congeners in >10% of the sample = IUPAC#s 52,70,84,74,87,95,99,101[+90],110,138[+163+164],153,180,187,132,146,158,170,183,199,28,31,44,47[+59], 66,130,141,151,174,177,18,196,29,33,8,92,97,128,144,15,172,176,190,203,24[+2

[g] ΣPersistent PCBs detected in >50% of the sample = IUPAC#s 74,99,105,118,138[+163+164],153,180,187

[h] ΣPersistent PCBs detected in >10% of the sample = IUPAC#s 74,99,105,118,138[+163+164],153,180,187,47[+59],28,66,77,130,158,199,128,146,156,170,172,177,183,190,196,203.

[i] ΣLowPersistent PCBs detected in >50% of the sample = IUPAC#s 52,70,84,95,110,101[+90],87.

[j] ΣLowPersistent PCBs detected in >10% of the sample = IUPAC#s 52,70,84,95,110,101[+90],87,8,18,29,31,33,40,42,44,49,53,56,71,92,97,132,141,144,151,174,176,24[+27],15.

[k] Bracket indicates 'minor' congener based on aroclor concentration (Frame, 1997).

Table 3

Correlation between PCB groupings.

	ΣDioxin-like PCBs50%[a]	**ΣNondioxin-like PCBs50%[a]**	**ΣPersistent PCBs50%[a]**	**ΣLow-persistent PCBs50%[a]**
ΣDioxin-like PCBs50%[a]		0.73	0.72	0.74
ΣNondioxin-like PCBs50%[a]	0.73		0.93	0.79
ΣPersistent PCBs50%[a]	0.72	0.93		0.57
ΣLow-persistent PCBs50%[a]	0.74	0.79	0.57	

[a]Values below the mdl were calculated following the EPA recommended method for estimating non-detected values as described in Schell et al., 2003.

Table 4

Correlation of covariates with each cognitive domain.

	RPM (n=268)		VMIS (n=269)		NMIS (n=269)		DRIS (n=269)		CMIS (n=269)		BCAE (n=236)		LTR (n=269)		STM (n=266)		PSD (n=268)		APG (n=263)		VPG (n=269)		CKN (n=250)		FRG (n=258)	
	r	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***
Adolescent																										
Sex (M/F)	**0.11**	0.08	**0.18**	<0.01	**0.11**	0.06	**0.18**	<0.01	**0.17**	0.01	**0.17**	0.01	0.05	0.37	0.04	0.52	**0.40**	<0.01	0.05	0.44	**0.20**	<0.01	**−0.09**	0.18	**0.14**	0.02
Age (years)	0.00	1.00	0.00	0.96	0.03	0.65	−0.07	0.25	0.01	0.90	**0.13**	0.05	−0.04	0.48	0.07	0.25	**0.25**	<0.01	−0.03	0.66	**0.15**	0.02	0.03	0.69	**0.14**	0.03
BMI (kg/m^2)	−0.05	0.41	**0.09**	0.13	0.05	0.43	0.06	0.30	**0.08**	0.18	−0.02	0.81	0.05	0.37	−0.01	0.90	0.07	0.25	−0.03	0.58	0.04	0.52	−0.02	0.74	0.00	0.95
Triglyceride level (mg/dL)	−0.06	0.31	**0.09**	0.14	0.04	0.56	**0.09**	0.15	0.08	0.22	0.01	0.88	**0.08**	0.19	−0.01	0.84	0.05	0.43	0.04	0.52	−0.02	0.76	−0.05	0.40	−0.03	0.62
Cholesterol level (mg/dL)	0.06	0.33	**0.08**	0.19	0.03	0.61	0.03	0.66	0.06	0.30	**0.09**	0.16	**0.09**	0.13	0.08	0.22	0.04	0.49	0.03	0.63	−0.06	0.30	**0.08**	0.20	0.08	0.23
Maternal																										
Maternal BMI (kg/m^2)	**−0.09**	0.15	−0.05	0.45	−0.04	0.48	−0.01	0.88	−0.05	0.45	**−0.19**	<0.01	0.04	0.56	**−0.18**	<0.01	−0.03	0.63	**−0.12**	0.06	−0.05	0.44	**−0.18**	0.01	**−0.09**	0.14
Maternal Broad Cognitive Ability	**0.25**	<0.01	**0.21**	<0.01	**0.24**	<0.01	**0.12**	0.07	**0.27**	<0.01	**0.29**	<0.01	**0.21**	<0.01	**0.28**	<0.01	**0.21**	<0.01	**0.20**	<0.01	**0.14**	0.02	**0.16**	0.02	**0.24**	<0.01
Socioeconomic Status Index	0.06	0.32	**0.10**	0.12	**0.17**	0.01	**0.12**	0.05	**0.16**	0.01	**0.15**	0.03	0.03	0.63	**0.15**	0.01	**0.10**	0.10	**0.11**	0.07	0.11	0.07	0.07	0.24	**0.13**	0.04
Number of Social Problems Reported	**−0.13**	0.03	−0.07	0.26	**−0.17**	0.01	**−0.09**	0.13	**−0.15**	0.02	**−0.10**	0.13	−0.05	0.40	−0.04	0.58	**−0.12**	0.05	−0.07	0.25	−0.02	0.73	−0.05	0.47	**−0.10**	0.11
Pregnancy Order	**−0.11**	0.08	**−0.10**	0.09	−0.05	0.44	**−0.09**	0.14	**−0.09**	0.17	**−0.16**	0.01	−0.02	0.73	−0.06	0.31	**−0.11**	0.08	**−0.10**	0.10	−0.06	0.34	**−0.13**	0.04	**−0.10**	0.11
Cigarette Use during Pregnancy (#/day)	**−0.19**	<0.01	−0.05	0.43	**−0.12**	0.04	**−0.11**	0.06	**−0.10**	0.10	**−0.13**	0.05	0.01	0.82	0.00	0.95	**−0.09**	0.14	**−0.11**	0.08	**−0.15**	0.01	**−0.10**	0.12	**−0.12**	0.05
Breastfeeding Duration (weeks)	0.05	0.39	0.07	0.26	0.07	0.26	0.06	0.31	0.07	0.22	0.08	0.23	−0.02	0.74	0.07	0.28	−0.04	0.53	0.05	0.43	**0.13**	0.03	**0.12**	0.07	**0.10**	0.10
Other Toxicants																										
HCB (ppb)	0.02	0.80	−0.07	0.25	**−0.10**	0.12	**−0.11**	0.08	**−0.11**	0.07	0.04	0.53	**−0.09**	0.13	0.06	0.30	−0.06	0.36	**0.09**	0.15	−0.01	0.81	0.08	0.21	0.04	0.53
p,p'-DDE (ppb)	0.05	0.42	0.01	0.89	0.04	0.50	−0.04	0.50	0.03	0.66	**0.10**	0.13	−0.03	0.64	**0.11**	0.08	−0.03	0.64	0.05	0.41	0.02	0.79	**0.14**	0.03	**0.14**	0.03
Mirex (ppb)	**−0.08**	0.17	0.04	0.53	0.04	0.52	**0.08**	0.18	0.05	0.43	0.07	0.26	0.05	0.45	0.07	0.28	0.03	0.57	0.04	0.50	−0.05	0.39	0.08	0.21	0.02	0.74
Blood Lead (µg/dL)	−0.04	0.53	**−0.16**	0.01	**−0.09**	0.13	**−0.13**	0.03	**−0.14**	0.02	**−0.13**	0.04	−0.03	0.58	−0.08	0.22	**−0.13**	0.03	0.05	0.47	−0.06	0.37	−0.05	0.43	**−0.18**	<0.01
Total Mercury (µg/dL)	0.00	0.94	−0.04	0.56	0.04	0.55	**0.08**	0.20	−0.01	0.93	−0.03	0.64	0.01	0.90	−0.02	0.79	−0.06	0.32	**−0.09**	0.17	0.01	0.84	**−0.10**	0.11	−0.08	0.22

Abbreviations: RPM = Ravens Progressive Matrices; VMIS = TOMAL Verbal Memory Index; NMIS = TOMAL Non-verbal Memory Index; DRIS = TOMAL Delayed Recall Index; CMIS = TOMAL Composite Memory Index; BCAE = WJ-R Broad Cognitiv Ability Extended; LTR = WJ-R Long Term Retrieval; STM = WJ-R Short Term Memory; PSD = WJ-R Processing Speed; APG = WJ-R Auditory Processing; VPG = WJ-R Visual Processing; CKN = WJ-R Comprehension-knowledge; FRG = WJ-R Fluid Reasoning.

Bold denotes p<0.2.

Table 5

Results of multivariate analysis of the relationship of PCB groupings to cognitive outcomes (n = 203 – 230)*.

	ΣDioxin-like PCBs50%[a,b]			ΣNondioxin-like PCBs50%[a,b]			ΣPersistent PCBs50%[a,b]			ΣLow-persistent PCBs50%[a,b]		
	Std. β	***p***	**r^2**	**Std. β**	***p***	**r^2**	**Std. β**	***p***	**r^2**	**Std. β**	***p***	**r^2**
Ravens (RPM)	**−0.16**	0.04	17.5%	−0.08	0.30	17.4%	−0.14	0.14	16.3%	−0.06	0.40	16.3%
TOMAL:												
Verbal Memory (VMIS)	−0.02	0.77	11.0%	−0.10	0.22	11.0%	−0.15	0.13	11.1%	−0.05	0.45	11.1%
Nonverbal Memory (NMIS)	−0.05	0.57	11.3%	−0.07	0.41	11.3%	−0.08	0.38	11.3%	−0.05	0.50	11.3%
Delayed Recall (DRIS)	**−0.16**	0.04	12.5%	**−0.21**	0.01	12.5%	**−0.22**	0.02	12.6%	**−0.16**	0.02	12.6%
Composite Memory (CMIS)	−0.04	0.63	14.3%	−0.10	0.23	14.3%	−0.14	0.15	14.4%	−0.06	0.40	14.4%
Woodcock Johnson (WJ-R):												
Broad Cognitive Ability Extended (BCAE)	−0.08	0.34	17.9%	−0.11	0.20	17.9%	−0.14	0.14	18.2%	−0.08	0.30	18.2%
Long Term Retrieval (LTR)	**−0.16**	0.04	11.3%	**−0.25**	0.00	11.3%	**−0.20**	0.03	11.5%	**−0.22**	0.00	11.5%
Short Term Memory (STM)	0.06	0.43	13.1%	0.00	0.97	13.1%	−0.04	0.64	13.0%	0.04	0.62	13.0%
Processing Speed (PSD)	0.00	0.95	26.5%	−0.02	0.79	26.5%	−0.06	0.49	26.7%	0.00	1.00	26.7%
Auditory Processing (APG)	−0.14	0.09	11.0%	−0.13	0.13	11.1%	**−0.23**	0.02	12.2%	−0.08	0.27	12.2%
Visual Processing (VPG)	−0.07	0.41	11.7%	−0.09	0.25	11.7%	−0.04	0.69	12.3%	−0.11	0.13	12.3%
Comprehension-Knowledge (CKN)	−0.14	0.08	16.0%	−0.15	0.06	16.0%	−0.15	0.12	16.1%	**−0.15**	0.05	16.1%
Fluid Reasoning (FRG)	−0.05	0.52	17.8%	0.06	0.48	17.8%	−0.07	0.43	17.8%	−0.04	0.58	17.8%

*Covariates included in the analysis are: Sex; age (yrs);adolescent and maternal BMI (kg/m2); adolescent triglyceride and cholesterol levels; maternal Broad Cognitive Ability Standard score; SES index; # reported social problems; gravidity; cigarette use during pregnancy; breast feeding duration (wks); *p,p'* -DDE; HCB; Pb; Hg; mirex, and the converse PCB congener group.

[a]Values below the mdl were calculated following the EPA recommended method for estimating non-detected values as described in Schell et al., 2003.

[b]Orthogonal transformation was applied to all PCB grouping variables

Bold denotes p<0.05.

Table 6

Results of bivariate correlations between each cognitive score and PCB groupings and PCB congeners found in 50% or more of the sample.

	RPM (n=268)		VMIS (n=269)		NMIS (n=269)		DRIS (n=269)		CMIS (n=269)		BCAE (n=236)		LTR (n=269)		STM (n=266)		PSD (n=268)		APG (n=263)		VPG (n=269)		CKN (n=250)		FRG (n=258)	
PCBs (ppb)	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***
ΣDioxin-like PCBs50%[a,c]	−0.11	0.07	0.03	0.61	−0.01	0.85	−0.03	0.65	0.02	0.78	−0.01	0.93	−0.05	0.40	0.08	0.17	−0.04	0.50	−0.04	0.54	−0.04	0.49	−0.03	0.62	0.01	0.86
ΣDioxin-like PCBs10%[b,d]	**−0.13**	0.03	0.03	0.61	−0.03	0.57	−0.05	0.39	0.00	0.96	0.00	0.97	−0.07	0.23	0.10	0.10	−0.05	0.43	−0.03	0.63	−0.02	0.70	−0.01	0.93	0.01	0.92
ΣNondioxin-like PCBs50%[a,e]	−0.03	0.67	−0.02	0.70	−0.03	0.64	−0.11	0.08	−0.03	0.64	0.00	0.96	**−0.15**	0.02	0.08	0.19	−0.06	0.35	−0.03	0.61	−0.03	0.65	−0.01	0.92	0.03	0.60
ΣNondioxin-like PCBs10%[b,f]	−0.04	0.48	0.01	0.88	−0.04	0.52	−0.11	0.08	−0.02	0.80	0.02	0.72	−0.11	0.06	0.11	0.07	−0.01	0.83	−0.03	0.58	−0.02	0.77	0.00	0.96	0.03	0.60
ΣPersistent PCBs50%[a,g]	−0.04	0.56	−0.04	0.50	−0.03	0.63	−0.11	0.08	−0.04	0.51	0.00	0.99	−0.11	0.07	0.08	0.21	−0.08	0.18	−0.06	0.35	−0.01	0.86	0.02	0.74	0.04	0.48
ΣPersistent PCBs10%[b,h]	−0.05	0.39	−0.02	0.77	−0.04	0.50	−0.12	0.06	−0.03	0.59	0.02	0.80	−0.09	0.13	0.10	0.10	−0.05	0.42	−0.07	0.29	0.01	0.88	0.02	0.78	0.04	0.51
ΣLow-persistent PCBs50%[a,i]	−0.03	0.66	0.02	0.70	−0.02	0.79	−0.06	0.36	0.01	0.88	−0.01	0.88	**−0.14**	0.02	0.08	0.20	0.00	0.98	0.00	0.97	−0.06	0.37	−0.07	0.29	0.02	0.78
ΣLow-persistent PCBs10%[b,j]	−0.05	0.42	0.03	0.59	−0.05	0.44	−0.08	0.18	−0.01	0.93	0.01	0.83	−0.12	0.06	0.10	0.11	0.03	0.67	−0.01	0.87	−0.05	0.42	−0.04	0.52	0.02	0.80
PCB IUPAC#																										
118	−0.09	0.14	0.03	0.59	0.02	0.77	−0.01	0.88	0.04	0.57	0.01	0.91	−0.03	0.61	0.07	0.23	−0.04	0.54	−0.06	0.30	−0.04	0.56	−0.02	0.71	0.05	0.40
101[+90][k]	−0.04	0.55	0.00	0.97	0.00	0.94	−0.06	0.29	0.00	0.94	−0.02	0.78	**−0.13**	0.04	0.05	0.43	0.01	0.92	0.00	0.97	−0.05	0.46	−0.08	0.23	0.00	0.99
153	0.02	0.73	−0.05	0.39	−0.02	0.76	**−0.15**	0.01	−0.04	0.48	−0.03	0.65	−0.11	0.06	0.06	0.29	−0.08	0.21	−0.07	0.28	−0.03	0.61	−0.01	0.82	0.05	0.46
110	0.00	0.94	0.01	0.89	0.00	0.96	−0.04	0.55	0.01	0.88	−0.04	0.58	**−0.14**	0.02	0.04	0.47	−0.03	0.65	−0.03	0.66	−0.03	0.60	−0.07	0.29	0.00	0.94
99	0.04	0.48	−0.01	0.86	0.01	0.90	−0.04	0.51	0.00	1.00	−0.02	0.79	**−0.12**	0.04	0.00	0.96	−0.04	0.46	−0.05	0.43	0.02	0.80	−0.03	0.66	0.09	0.17
87	−0.01	0.81	0.05	0.46	0.01	0.85	−0.02	0.70	0.04	0.52	0.01	0.89	**−0.13**	0.04	0.12	0.05	−0.02	0.79	0.03	0.63	−0.07	0.22	−0.06	0.37	0.02	0.71
138[+163+164][k]	−0.02	0.76	−0.03	0.65	0.00	0.97	−0.04	0.52	−0.02	0.75	0.05	0.49	**−0.13**	0.03	0.10	0.11	−0.08	0.19	0.08	0.22	0.01	0.92	0.06	0.32	0.03	0.60
180	−0.03	0.68	−0.08	0.20	−0.07	0.26	−0.09	0.16	−0.08	0.17	0.02	0.77	−0.09	0.16	0.04	0.50	−0.09	0.14	−0.06	0.33	0.02	0.72	0.08	0.23	0.01	0.85
95	−0.07	0.25	0.02	0.71	−0.04	0.47	−0.05	0.38	−0.01	0.88	0.00	0.99	−0.11	0.08	0.06	0.31	0.01	0.83	0.06	0.33	−0.04	0.55	−0.06	0.37	0.01	0.88
52	−0.06	0.32	0.01	0.81	−0.04	0.47	−0.07	0.28	−0.02	0.79	0.03	0.60	−0.11	0.07	0.07	0.24	0.03	0.68	−0.03	0.62	−0.06	0.31	−0.02	0.73	0.03	0.66
74	−0.08	0.20	0.00	0.96	−0.01	0.83	−0.07	0.23	−0.01	0.92	0.01	0.85	−0.05	0.44	0.06	0.34	−0.06	0.30	−0.07	0.25	0.03	0.64	0.07	0.24	0.05	0.44
105	**−0.16**	0.01	−0.01	0.91	−0.09	0.16	−0.03	0.58	−0.05	0.40	−0.04	0.56	−0.01	0.88	0.05	0.38	−0.08	0.18	−0.07	0.29	−0.02	0.75	−0.03	0.66	−0.04	0.55
149[+123][k]	−0.08	0.17	0.02	0.72	0.00	0.98	−0.06	0.35	0.02	0.80	−0.03	0.62	**−0.13**	0.04	0.05	0.37	0.02	0.70	0.06	0.32	−0.07	0.23	−0.07	0.28	−0.08	0.22
187	−0.04	0.48	−0.06	0.36	−0.10	0.11	**−0.14**	0.02	−0.09	0.13	−0.05	0.47	−0.05	0.38	0.01	0.91	−0.09	0.15	−0.12	0.05	0.01	0.90	−0.04	0.57	−0.06	0.36
70	−0.02	0.73	0.06	0.36	−0.03	0.61	−0.06	0.33	0.02	0.76	0.01	0.85	−0.09	0.13	0.11	0.07	0.01	0.91	0.02	0.77	−0.03	0.65	−0.05	0.39	0.03	0.65

	RPM (n=268)		VMIS (n=269)		NMIS (n=269)		DRIS (n=269)		CMIS (n=269)		BCAE (n=236)		LTR (n=269)		STM (n=266)		PSD (n=268)		APG (n=263)		VPG (n=269)		CKN (n=250)		FRG (n=258)	
PCBs (ppb)	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***
84	0.02	0.73	0.02	0.70	−0.04	0.56	−0.04	0.53	0.00	0.98	−0.02	0.77	**−0.14**	0.03	0.09	0.15	0.01	0.84	0.04	0.54	−0.07	0.28	−0.03	0.69	−0.02	0.73

Abbreviations: RPM= Ravens Progressive Matrices; VMIS = TOMAL Verbal Memory Index; NMIS= TOMAL Non-verbal Memory Index; DRIS = TOMAL Delayed Recall Index; CMIS = TOMAL Composite Memory Index; BCAE = WJ-R Broad Cognitive Ability Extended; LTR = WJ-R Long Term Retrieval; STM = WJ-R Short Term Memory; PSD = WJ-R Processing Speed; APG = WJ-R Auditory Processing; VPG = WJ-R Visual Processing; CKN = WJ-R Comprehension-knowledge; FRG = WJ-R Fluid Reasoning.

Bold denotes p<0.05.

[*] Only those congeners that were found to be significantly correlated with the outcome variables are shown in the detected in <50% or >10% group.

[a] Values below the mdl were calculated following the EPA recommended method for estimating non-detected values as described in Schell et al., 2003.

[b] Values below the detection limit have been replaced by the value midway between the detection limit and zero.

[c] ΣDioxin-like congeners in >50% of the sample= IUPAC#s 105,118,149[+123].

[d] ΣDioxin-like congeners in >10% of the sample= IUPAC#s 77,105,118,149[+123],156.

[e] ΣNondioxin-like congeners in >50% of the sample = IUPAC#s 52,70,84,74,87,95,99,101[+90],110,138[+163+164],153,180,187.

[f] ΣNondioxin-like congeners in >10% of the sample = IUPAC#s 52,70,84,74,87,95,99,101[+90],110,138[+163+164],153,180,187,132,146,158,170,183,199,28,31,44,47[+59],66,130,141,151,174,177,18,196,29,33,8,92,97,128,144,15,172,176,190,203,24[+27],40,42,49,53,56,71.

[g] ΣPersistent PCBs detected in >50% of the sample = IUPAC#s 74,99,105,118,138[+163+164],153,180,187

[h] ΣPersistent PCBs detected in >10% of the sample = IUPAC#s 74,99,105,118,138[+163+164],153,180,187,47[+59],28,66,77,130,158,199,128,146,156,170,172,177,183,190,196,203.

[i] ΣLowPersistent PCBs detected in >50% of the sample = IUPAC#s 52,70,84,95,110,101[+90],87.

[j] ΣLowPersistent PCBs detected in >10% of the sample = IUPAC#s 52,70,84,95,110,101[+90],87,8,18,29,31,33,40,42,44,49,53,56,71,92,97,132,141,144,151,174,176,24[+27],15.

[k] Bracket indicates 'minor' congener based on aroclor concentration (Frame, 1997).