# Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age

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**Objective:** Our purpose was to evaluate whether effects of exposure to environmental levels of PCBs and dioxins on development in the Dutch cohort persist until school age.

**Study design:** In the Dutch PCB/dioxin study, cognitive and motor abilities were assessed with the McCarthy Scales of Children's Abilities in children at school age. During infancy, half of this population was fully breast-fed for at least ≥6 weeks and the other half formula fed. Prenatal exposure to PCBs was defined as the sum of PCB118, 138, 153, and 180 in maternal and cord plasma. In breast milk, additional measurements of 17 dioxins, 6 dioxin-like PCBs, and 20 nondioxin-like PCBs were done.

**Results:** Negative effects of prenatal PCB and dioxin exposure on cognitive and motor abilities were seen when parental and home characteristics were less optimal. These effects were not measurable in children raised in more optimal environments.

**Conclusions:.**Neurotoxic effects of prenatal PCB and dioxin exposure may persist into school age, resulting in subtle cognitive and motor developmental delays. More optimal intellectual stimulation provided by a more advantageous parental and home environment may counteract these effects of prenatal exposure to PCBs and dioxins on cognitive and motor abilities. (J Pediatr 2002;140:48-56)

Negative effects of prenatal exposure to environmental levels of PCBs and dioxins on child development have been described in a number of prospective long-term follow-up studies. Animal studies addressing effects of perinatal exposure on the developing central nervous system show direct effects on neuronal and glial cell development and disruption of neurotransmitters and several endocrine systems, such as thyroid and sex hormones, that may affect central nervous system development indirectly.[1,2] In humans, several epidemiologic studies have addressed these neurotoxic effects with cognitive and motor abilities as neurodevelopmental outcome. In the North Carolina cohort, lower psychomotor skills from 6 to 24 months of age were associated with higher prenatal PCB exposure.[3,4] At 3, 4, and 5 years of age, cognitive and motor abilities were not related to prenatal PCB levels.[5] In the Lake Michigan cohort, however, lower visual recognition memory at 7 months of age,[6] lower verbal and memory scores at 4 years of age,[7] and lower IQ scores at 11 years of age[8] were associated with higher prenatal PCB exposure. In the Oswego Study, negative effects of prenatal exposure on

| | |
|---|---|
| BF | Breast-fed |
| FF | Formula-fed |
| HOME | Home Observation for Measurement of the Environment |
| IUPAC | International Union of Pure and Applied Chemistry |
| GCI | General Cognitive Index |
| PCBs | Polychlorinated biphenyls |
| ΣPCB | Sum of PCBs IUPAC Nos. 118, 138, 153, and 180 |
| PCDDs | Polychlorinated dibenzo-*p*-dioxins |
| PCDFs | Polychlorinated dibenzo-*p*-furans |
| TEF | Toxic equivalence factor |
| TEQ | Toxic equivalent |
| TTEQ | Total TEQ: sum of the dioxin and dioxin-like PCB TEQs |

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visual recognition memory were described at 6 and 12 months of age.[9] In The Netherlands, a prospective follow-up study was started in 1989. In contrast to the previously described studies, half the study group was formula fed (FF) during infancy, representing children with mainly in utero exposure to PCBs and dioxins. The other half the group was breast-fed (BF) and were exposed postnatally to PCBs and dioxins through lactation. Prenatal PCB exposure was related to poorer neurologic condition at birth[10] and 18 months of age,[11] lower psychomotor abilities at 3 months of age,[12] and lower cognitive abilities at 42 months of age.[13] Postnatal PCB and dioxin exposure was only related to lower psychomotor abilities at 7 months of age.[12]

At 42 months of age, negative effects of prenatal PCB exposure on cognitive abilities were more pronounced in the FF than in the BF group,[13] although BF children were exposed to higher prenatal and postnatal PCB levels.[14] Children in the BF group had higher general cognitive abilities, as well as older mothers, parents with higher education levels and verbal IQs, and higher scores on the HOME questionnaire.[13] It was not clear whether nutrients in breast milk, or the more optimal parental and home environment often provided by families of breast-fed children, might have counteracted negative effects of prenatal PCB exposure.

At school age, the Dutch cohort was reassessed to examine the effects of perinatal exposure to PCBs and dioxins on cognitive and motor abilities, to explore the potential differences of these effects in FF and BF children, and to evaluate whether these effects are related to differences between the 2 feeding groups in parental and home environmental characteristics.

## METHODS

### *Patients*

The study population consisted of 418 healthy mother-infant pairs who were recruited from 1990 to 1992. Half the study population was from Rotterdam, a highly industrialized and densely populated area, and the other half from Gröningen, a semiurban area, in The Netherlands. The study design, recruitment process, and chemical analysis of PCBs and dioxins have been described in detail elsewhere.[15] All included mother-infant pairs were white, and pregnancy and delivery had been without complications. Only first or second term-born infants were included. In addition to women who intended to use formula feeding, women who intended to breast-feed their children for at least 6 weeks were also included. All infants in the FF group received formula from a single batch (Almiron M2, Nutricia NV, Zoetermeer, The Netherlands) from birth until 7 months of age. In this formula, concentrations of both PCBs and dioxins were below the detection limit. The medical ethics committee of the University Hospital Rotterdam/Sophia Children's Hospital and the Academical Hospital Groningen approved the study design. The parents gave informed consent.

### *Test Material*

The Dutch version of the McCarthy Scales of Children's Abilities[16,17] was used to assess cognitive and motor abilities at 6.5 years of age. The McCarthy Scales of Children's Abilities consists of 18 subtests from which 6 subscales are composed: verbal, perceptual-performal, quantitative, memory, and motor subscale (mean, 50; SD, 10). An age-standardized General Cognitive Index (GCI) (mean, 100; SD, 15) is derived from the sum of the verbal, perceptual-performal, and quantitative subscales. Effects of PCB and dioxin exposure on the GCI and the memory and motor scales will be evaluated.

### *Assessment of Exposure Variables*

Plasma samples were collected from the mothers during the last month of pregnancy and cord plasma samples were collected immediately after birth. These samples were analyzed for 4 PCB congeners, International Union for Pure and Applied Chemistry (IUPAC) Nos. 118, 138, 153, and 180.[15,18] Two weeks after delivery, a 24-hour representative breast milk sample was collected from the mothers who were breast feeding their children. Breast milk samples were analyzed for 17 dioxins (PCDDs and PCDFs), 6 dioxin-like PCBs (IUPAC Nos. 77, 105, 118, 126, 156, and 169), and 20 nondioxin-like PCBs (IUPAC Nos. 28, 52, 66, 70, 99, 101, 128, 137, 138, 141, 151, 153, 170, 177, 180, 183, 187, 194, 195, and 202).[15,19] Toxic potency of the mixture of dioxins and dioxin-like PCBs was expressed by the TEF approach,[20] TEQs were calculated by multiplying the concentration of each congener by its TEF value.

Prenatal exposure to PCBs in the total study population is defined as the sum of the concentrations of the 4 PCB congeners measured in maternal plasma ($\Sigma PCB_{maternal}$) and in cord plasma ($\Sigma PCB_{cord}$). The breast milk samples were used as indirect measures of prenatal exposure to PCBs and dioxins.[21] In the BF group, therefore, 3 additional prenatal exposure measurements were defined: the TTEQ value (the sum of the TEQ values of the 17 dioxins and the 6 dioxin-like PCBs), $\Sigma PCB_{milk}$ (the sum of PCB118, 138, 153, and 180), $\Sigma PCB_{20\ nondioxin\ PCBs}$ (the sum of 20 nondioxin-like PCBs).

Postnatal exposure to PCBs and dioxins through lactation was estimated in the BF group by multiplying, respectively, breast milk levels of TTEQ, $\Sigma PCB_{milk}$, and $\Sigma PCB_{20\ nondioxin\ PCBs}$ with the number of weeks of breast feeding.

### *Assessment of Covariables*

Variables that may influence child neurodevelopment were assessed. These variables included birth weight, duration of gestation, fetal exposure to alcohol and cigarette smoking, maternal age at birth, parental education level, and pari-

ty (items on a questionnaire addressing obstetric, social, economic, and perinatal conditions[22]), type of feeding during infancy, duration of breast-feeding, and infant sex. The quality of intellectual stimulation and emotional support provided by the child's home environment was assessed by the Home Observation for Measurement of the Environment (HOME).[23] The verbal IQ of the parent who spent the most time with the child (usually the mother) was measured by 2 subtests, Information and Vocabulary, from the Dutch version of the Wechsler Adult Intelligence Scale (WAIS).[24]

### *Statistical Analysis*

We used a Student *t* test, $\chi^2$ test, and Mann-Whitney *U* test to compare groups for a single variable. PCB and dioxin levels were positively skewed and were, therefore, normalized by a natural logarithmic transformation (LnExposure). Effects of PCB and dioxin exposure on cognitive and motor abilities were studied by means of multiple regression analyses. Variables that were likely to affect cognitive and motor abilities, based on literature and clinical knowledge, were included in the regression model as a fixed set of explanatory variables. These variables were (1) type of feeding during infancy (BF or FF) and (2) duration of breast feeding (0 for FF children), (3) sex, (4) age at examination, (5) highest education level of the parents (*low*, primary school, secondary school not finished; *middle*, secondary school finished; *high*, high school finished, professional, and university training), (6) parental verbal IQ, and (7) HOME score. Because 2 examiners, 1 in each study center, carried out the cognitive and motor assessment, the variable study center was included in the fixed set to adjust for interrater variability. In addition, covariables were selected by means of partial F tests. Variables with a relation ($P \leq .2$) with ≥1 of the exposure variables and ≥1 of the 6 subscales of the McCarthy Scales of Children's Abilities, adjusted for the variables in the fixed set, were included in the final regression model. These variables were considered potential confounders for effects of PCB and dioxin exposure on cognitive and motor abilities. Candidate confounders were alcohol use (yes/no) and smoking (yes/no) during pregnancy, duration of gestation (weeks), birth weight (grams), maternal age at birth, and parity (first or second born). In the final regression model, the variables included were study center, sex, parity, type of feeding, duration of breast feeding, maternal age at birth, parental education level, parental verbal IQ, HOME score, and age at examination.

To evaluate effects of prenatal PCB exposure in the 2 feeding groups separately, an interaction variable (the product of feeding type and LnΣPCB) "feeding type × LnΣPCB" was included in the regression model.

Interaction effects, first-order (eg, linear interaction) and second-order interaction effects (eg, parabolic interaction) of PCB and dioxin exposure, and the variables in the regression model that were significantly different for the 2 feeding groups (eg, maternal age, parental education and verbal IQ, and HOME scores) were explored in separate analyses. Because of the explorative nature of this study, no correction for multiple testing was made, and 2-tailed *P* values <.05 were considered significant. Nonetheless, all relevant interactions, including the nonsignificant ones, will be presented together with the actually calculated *P* values.

## RESULTS

At school age, 376 children (90%) of the original cohort of 418 children (189 from Rotterdam, 187 from Groningen) were willing to participate in the follow-up assessment. Forty-two children were lost to follow-up, 21 because of a lack of interest, 20 because of emigration, and 1 because of death in an accident. Four children were excluded from data analyses because of circumstances that are known to influence the score on the McCarthy scales of Children's Abilities, other than PCB and dioxin exposure (eg, Turner's syndrome, pervasive development disorder, Volkmann's contracture after a humerus fracture, and attention deficit hyperactivity disorder treated with methylphenidate hydrochloride). Five children failed to finish all subtests of the McCarthy Scales of Children's Abilities; these were GCIs (n = 5), memory (n = 2), and motor scores (n = 4) and they were not included in the data analyses. Prenatal PCB and dioxin levels of the children that did not participate in the study at 6.5 years of age and the participating children were similar. However, nonparticipating children were significantly more likely to be FF and BF for shorter periods. Maternal age, parental education level, and verbal IQ scores were significantly lower in this group (Table I). In addition, more boys than girls did not participate at school age. The mean age at examination of the total group was 6.7 years (± 0.3; 6.1-7.3 years) (Table II). The mean GCI and scores on the memory and motor scales were comparable to a normal population. Maternal age, parental education level and verbal IQ, HOME scores, and prenatal PCB exposure levels were significantly higher in the BF group than in the FF group, as were the mean (not adjusted) GCI and memory scores (Table II).

Results of multiple regression analyses on GCI, memory, and motor scores by using maternal PCB levels are presented in Table III. Significant effects using cord PCB levels ($P \leq .05$), are presented in the text, and for reasons of clarity, are not shown in Table III or in the figures.

Prenatal PCB levels were not related to GCI, memory, and motor skills, after adjustment for covariables (Table III, *A*). In Table III, *B,* results of multiple regression analyses evaluating the effects of prenatal PCB exposure on the GCI, memory, and motor scores in the 2 feeding groups are presented. Effects of

prenatal PCB exposure on the GCI, memory, and motor scores were not significantly different for BF and FF children. In the 2 feeding groups separately, prenatal PCB exposure was not related to GCI or memory skills. In FF children, however, higher maternal PCB levels tended to be related to lower motor scores (Table III, *B*).

In Table III, *C* to *F*, results of multiple linear regression analyses are presented, including the following interaction variables in the regression models, respectively: "$\text{LnΣPCB}_{\text{maternal}}\times$maternal age," "maternal age$^2$," and "$\text{LnΣPCB}_{\text{maternal}}\times$maternal age$^2$" (because the interaction effect of $\text{LnΣPCB}_{\text{maternal}}$ and maternal age was of parabolic nature) (*C*), "$\text{LnΣPCB}_{\text{maternal}}\times$parental education level" (*D*), "$\text{LnΣPCB}_{\text{maternal}}\times$ parental verbal IQ" (*E*), "$\text{LnΣPCB}_{\text{maternal}}\times$HOME" (*F*). In the Figure (*A* to *D*), these interaction effects are visualized by presenting the effects of doubling maternal PCB exposure on GCI, memory, and motor scores in relation to maternal age (*A*), parental education level (*B*), parental verbal IQ (*C*) and HOME score (*D*).

Effects of prenatal PCB exposure on the GCI were significantly modified by maternal age (combined $P_{\text{PCBcord, mat.age}}$ [$P_{\text{PCBcord}\times\text{mat.age}}$ and $P_{\text{PCBcord}\times(\text{mat.age})^2}$] = .003) and parental verbal IQ ($P_{\text{PCBcord}\times\text{VIQ}}$ = .004). Negative effects of prenatal PCB exposure on the GCI were seen in children born to younger mothers and to parents with lower verbal IQ scores; these effects, however, were not evident with increasing maternal age and parental verbal IQ. Similar relations were seen exploring effect modification of prenatal PCB exposure by parental education level.

Effects of prenatal PCB exposure on memory skills were significantly modified by maternal age (combined $P_{\text{PCBcord, mat.age}}$ = .027) and parental verbal IQ ($P_{\text{PCBcord}\times\text{VIQ}}$ = .050). Negative effects of prenatal PCB exposure on memory skills appeared to decrease when maternal age and parental verbal IQ increased.

***Table I.*** Significant differences in characteristics of participating and nonparticipating children at school age

| Characteristics | Participants | Nonparticipants | *P* value |
|---|---|---|---|
| Sex (male/female) | 190/182 | 32/14 | .019* |
| BF/FF | 194/178 | 15/31 | .018* |
| Breast-feeding period (wk) | 24.2 ± 15.2 | 13.8 ± 5.4 | .005† |
| Maternal age (y) | 29.2 ± 3.8 | 27.9 ± 4.1 | .030† |
| Parental education (low/medium/high) | 37/112/223 | 8/24/14 | .001* |
| Parental verbal IQ | 119.2 ± 15.9 | 111.0 ± 17.0 | .005† |

Values are numbers or means ± SD. Parental education level: *low*, primary school, secondary school not finished; *middle*, secondary school finished; *high*, high school finished, professional and university training; *Parental verbal IQ*, score on 2 subtests, Information and Vocabulary, of the Wechsler Adult Intelligence Scale, assessed from 1 of the parents. *$\chi^2$ test. †Mann-Whitney *U* test.

Effects of prenatal PCB exposure on motor skills were significantly modified by parental verbal IQ ($P_{\text{PCBcord}\times\text{VIQ}}$ = .021) and HOME scores. Negative effects of prenatal PCB exposure on the motor scores were seen to decrease in children born from parents with higher verbal IQ and higher HOME scores.

In the BF group, levels of the TTEQ, $\text{ΣPCB}_{\text{milk}}$, and $\text{ΣPCB}_{\text{20 nondioxin-like PCBs}}$ in breast milk were not significantly related to GCI, memory, and motor scores when adjusted for confounding variables. Effects of prenatal TTEQ exposure on motor skills were modified by parental verbal IQ levels ($\beta_{\text{TTEQ}}$ = –48.005, *P* = .036; $\beta_{\text{TTEQ}\times\text{VIQ}}$ = .386, *P* = .036). Negative effects of prenatal TTEQ exposure were seen to decrease in children born to parents with higher verbal IQs.

Postnatal exposure to PCBs and dioxins through lactation was not significantly related to GCI, memory, and motor scores, and effects of postnatal exposure were not significantly modified by parental and home environmental characteristics.

## DISCUSSION

In the Dutch PCB and dioxin study at school age, subtle effects of prenatal exposure to PCBs and dioxins were seen on cognitive and motor abilities. At 42 months[13] and at 6.5 years of age, FF children had significantly lower cognitive abilities than BF children. In the FF group in our cohort, parental and home environmental characteristics are less optimal compared with these characteristics in the BF group. Effects of prenatal PCB exposure on cognitive abilities of children at 42 months of age were more pronounced in the FF group than in the BF group, although BF children were exposed to higher prenatal exposure levels and higher postnatal exposure levels of PCBs and dioxins in particular. To explore whether these differences in effect were related to nutritional benefits of breast feeding or to more advantaged parental and home characteristics, we evaluated whether effects of PCB and dioxin exposure were modified by parental and home characteristics that were significantly different for the 2 feeding groups. The present results give evidence for effect modification by parental and home environmental conditions in the total cohort. The adverse effects of prenatal PCB exposure were more pronounced when parental and home characteristics were less optimal, whereas these effects were not evident when parental and home characteristics were more advantageous. At school age, differences in vulnerability to prenatal exposure to PCBs between the BF and FF groups were not statistically different. Differ-

***Table II.*** Characteristics of the study population

| Characteristics | Total (n = 372) | BF (n = 194) | FF (n = 178) |
|---|---|---|---|
| Study center (Rotterdam), n (%) | 186 (50.0) | 96 (49.5 ) | 90 (50.6) |
| Sex (male), n (%) | 190 (51.3) | 105 (54.1) | 85 (47.8) |
| Parity (firstborn), n (%) | 179 (48.1) | 100 (51.5) | 79 (44.4) |
| Breast feeding period (wk) | | 20 (6-78) | |
| Maternal age at birth (y)* | 29.2 ± 3.8 | 29.7 ± 3.5 | 28.7 ± 4.0 |
| Parental education level at birth† | | | |
| Low, n (%) | 37 (9.9) | 8 (4.1) | 29 (16.3) |
| Middle, n (%) | 112 (30.1) | 36 (18.6) | 76 (42.7) |
| High, n (%) | 223 (59.8) | 150 (77.3) | 73 (41.0) |
| Parental verbal IQ† | 119.2 ± 15.9 | 125.2 ± 11.8 | 112.55 ± 17.1 |
| HOME† | 47.8 ± 3.2 | 48.5 ± 2.9 | 47.0 ± 3.3 |
| Exposure variables | | | |
| $\Sigma PCB_{maternal}$ (μg/L)† | 2.04 (0.59-7.35) | 2.22 (0.73-7.35) | 1.85 (0.59-5.08) |
| $\Sigma PCB_{cord}$ (μg/L)† | 0.38 (0.08-2.08) | 0.38 (0.08-2.08) | 0.34 (0.08-1.98) |
| TTEQ (μg/kg fat) | | 63.30 (24.16-136.54) | |
| $\Sigma PCB_{milk}$ (μg/kg fat) | | 403.66 (158.35-1226.38) | |
| $\Sigma PCB_{20\ non\text{-}dioxin\ PCBs}$ (μg/kg fat) | | 451.05 (186.11-1121.02) | |
| Cognitive and motor assessment at school age, McCarthy Scales of Children's Abilities | | | |
| GCI† | 104.7 ± 12.6 | 108.2 ± 11.7 | 100.8 ± 12.4 |
| Memory† | 46.5 ± 7.6 | 48.2 ± 7.2 | 44.7 ± 7.7 |
| Motor | 52.2 ± 9.8 | 52.3 ± 9.2 | 52.06 ± 10.5 |

Values are numbers (percentages), means ± SD or medians (range). Parental education level: *low*, primary school, secondary school not finished; *middle*, secondary school finished; *high*, high school finished, professional and university training. *Parental verbal IQ*, score on 2 subtests, Information and Vocabulary, of the Wechsler Adult Intelligence Scale, assessed from 1 of the parents. *HOME*, Home Observation for the Measurement of the Environment at school age. *PCB*, sum of PCB congeners IUPAC Nos. 118, 138, 153, and 180; *TTEQ*, sum of the dioxin TEQs and dioxin-like PCB TEQs in breast milk.
*$P \leq .05$. †$P \leq .01$, difference between BF and FF groups.

ences in vulnerability to effects, however, were related to more subtle differences in parental and home environmental characteristics, varying across both feeding groups. These results suggest, therefore, that the differences in vulnerability of the BF and FF children, seen at 42 months of age, were more likely to be related to parental and home characteristics than to beneficial effects of breast-feeding per se.

In some neurotoxic epidemiologic studies, effects of exposure to these compounds on child development were also seen to be related to socioeconomic risk factors.[25-28] Children from lower social economic backgrounds were more vulnerable to negative cognitive effects of prenatal exposure to lead than children in more advantaged families. Comparable effects have also been reported in studies of low-birth-weight children where in children at high biologic risk, favorable early parental and home characteristics could compensate for or mask developmental delays.[29-33] The results of the present study give evidence for counteracting processes or for "cumulative deficits" in respect of effects of prenatal exposure to PCBs on cognitive and motor abilities. Cognitive and motor development is influenced by many factors, and not all of them were controlled for in this study. Whether the interaction effects presented here reflect not measured variables such as subtle parent-child interaction aspects or aspects related to self-esteem and emotional development is not known. On the one hand, maternal age at birth is related with higher PCB and dioxin levels, and conversely, with higher education levels, verbal IQs, and HOME environment scores. There is no reason to believe that maternal age itself is directly related to cognitive or motor outcome; factors associated with maternal age are more likely to explain the reported interaction effects. We suggest that these factors include among others that older mothers may more consciously choose for parenthood and may have different parental values and orientation toward child development than younger mothers. Effect modification of PCB and dioxin exposure by maternal age at birth, parental education level, verbal IQ, and HOME scores could not be analyzed in one regression analysis because these interaction variables correlated highly with each other. We therefore choose a statistical procedure in which effect modification of exposure

***Table III.*** Estimated effects of $Ln\Sigma PCB_{maternal}$ on the 3 outcome variables GCI, memory and motor scores on the McCarthy Scales of Children's Abilities.

| | | GCI (n = 353) | | | Memory (n = 354) | | | Motor (n = 352) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $Ln\Sigma PCB_{maternal}$ | Regression coefficient | SE | *P* value | Regression coefficient | SE | *P* value | Regression coefficient | SE | *P* value |
| A* | PCB | –0.14 | 1.58 | .929 | –0.36 | 1.02 | .725 | –2.45 | 1.45 | .092 |
| B* | PCB in BF | –0.01 | 2.00 | .996 | –0.25 | 1.30 | .844 | –1.28 | 1.84 | .486 |
| | PCB in FF | –0.30 | 2.22 | .891 | –0.49 | 1.44 | .733 | –3.92 | 2.04 | .055 |
| | PCB×FT (BF = 0) | –0.29 | 2.79 | .916 | –0.24 | 1.81 | .896 | –2.64 | 2.56 | .305 |
| C* | PCB | –147.51 | 50.44 | .004 | –82.58 | 32.89 | .013 | –77.99 | 46.78 | .096 |
| | PCB×Mat. age | 9.37 | 3.41 | .006 | 5.38 | 2.22 | .016 | 4.73 | 3.16 | .132 |
| | PCB×Mat. age$^2$ | –0.15 | 0.06 | .011 | –0.09 | 0.04 | .021 | –0.07 | 0.05 | .166 |
| D* | PCB | –5.84 | 3.29 | .077 | –3.25 | 2.14 | .129 | –5.93 | 3.05 | .052 |
| | PCB×Education† | 3.75 | 1.92 | .052 | 1.92 | 1.25 | .125 | 2.41 | 1.78 | .177 |
| E* | PCB | –26.06 | 10.37 | .012 | –16.49 | 6.72 | .015 | –21.24 | 9.58 | .027 |
| | PCB×VIQ | 0.22 | 0.09 | .012 | 0.13 | 0.06 | .016 | 0.16 | 0.08 | .048 |
| F* | PCB | –26.92 | 22.79 | .238 | –12.99 | 14.75 | .380 | –46.65 | 20.92 | .026 |
| | PCB×HOME | 0.60 | 0.48 | .240 | 0.26 | 0.31 | .392 | 0.92 | 0.44 | .035 |

In A, the regression coefficient of $Ln\Sigma PCB_{maternal}$, SE of the mean, and *P* value are presented assuming no effect modification. In B, the regression coefficient of $Ln\Sigma PCB_{maternal}$, SE of the mean, and *P* value are presented for the BF and FF groups, respectively, and the statistical difference in effect of $Ln\Sigma PCB_{maternal}$ between the feeding groups is indicated by the regression coefficient, SE of the mean, and *P* value of the interaction variable "PCB×FT." In C, D, E, and F, the regression coefficient, SE of the mean, and *P* value of the interaction variable indicate the effect modification of $Ln\Sigma PCB_{maternal}$ by maternal age, parental education level, parental verbal IQ, and HOME score, respectively. For each outcome variable, 6 separate regression analyses (A-F) are presented according to various effect modification of $Ln\Sigma PCB_{maternal}$.
*Results of regression analysis, adjusted for study center, sex, age at examination, type of feeding, duration of breast feeding in weeks, maternal age, parental education, parental verbal IQ, HOME score, and parity. †Education is used as a linear trend variable: *0*, low; *1*, middle; *2*, high maximal education level of both parents. *PCB*, $Ln\Sigma PCB_{maternal}$; *GCI*, General Cognitive Index; *FT*, Feeding type (BF or FF); *Mat.age*, maternal age at birth; *VIQ*, parental verbal IQ; *HOME*, Home Observation for the Measurement of the Environment, at school age.

by parental and home environmental characteristics was explored separately. Consequently, we are not able to differentiate the relative effects of the several aspects of parental and home characteristics.

It should be stressed here that the study population consists of families that were motivated to participate in this study for 7 years. Parental and home characteristics of this group are likely to be more advantaged than the average Dutch population. These results suggest that effect of exposure to these environmental pollutants on cognitive and motor abilities might be more pronounced in less advantaged populations.

As cognitive outcome variables, we used the GCI and memory scales of the McCarthy Scales of Children's Abilities. The GCI scale is a composite scale of 3 subscales, verbal, perceptual-performal, and quantitative. Because of the complex nature of this study, we decided not to include these subscales in the analyses and use only the composite GCI scale, memory, and motor scales as outcome variables.

In the present study, the demonstrated effects of cord plasma PCB levels on cognitive and motor abilities are generally comparable to those using maternal PCB levels. In the BF group, prenatal exposure to TTEQ was associated with lower motor scores in children born to parents with lower verbal IQ scores. Exposure to nondioxin-like PCBs and $\Sigma PCB_{milk}$ showed comparable relationships, although they did not reach significance. In the environment, PCBs and dioxins are present as complex mixtures of various congeners that may vary in metabolism and toxicity. The sum of PCBs 118, 138, 153, and 180 consists of the 4 most abundant congeners, constituting 46% of the total PCBs.[34] In our cohort TTEQ levels, the sum of the nondioxin-like PCBs, and the sum of the 4 PCBs in breast milk and in maternal and cord plasma, correlated highly.[35] It is uncertain whether described effects of the sum of the 4 PCBs in plasma might also reflect effects of dioxins and other related organochlorine compounds and their metabolites.

In agreement with the results at 42 months of age in this cohort,[13] and other epidemiologic studies,[3-5,7-9] our results show that postnatal exposure to PCBs and dioxins through lactation was not related to cognitive and motor abilities at school age. Prenatally, the developing central nervous system seems to be more susceptible to harmful effects of these compounds than during the early postnatal period.

In contrast to the examined effects at school age, negative effects at preschool age of prenatal PCB exposure on cognitive abilities were seen in the total co-

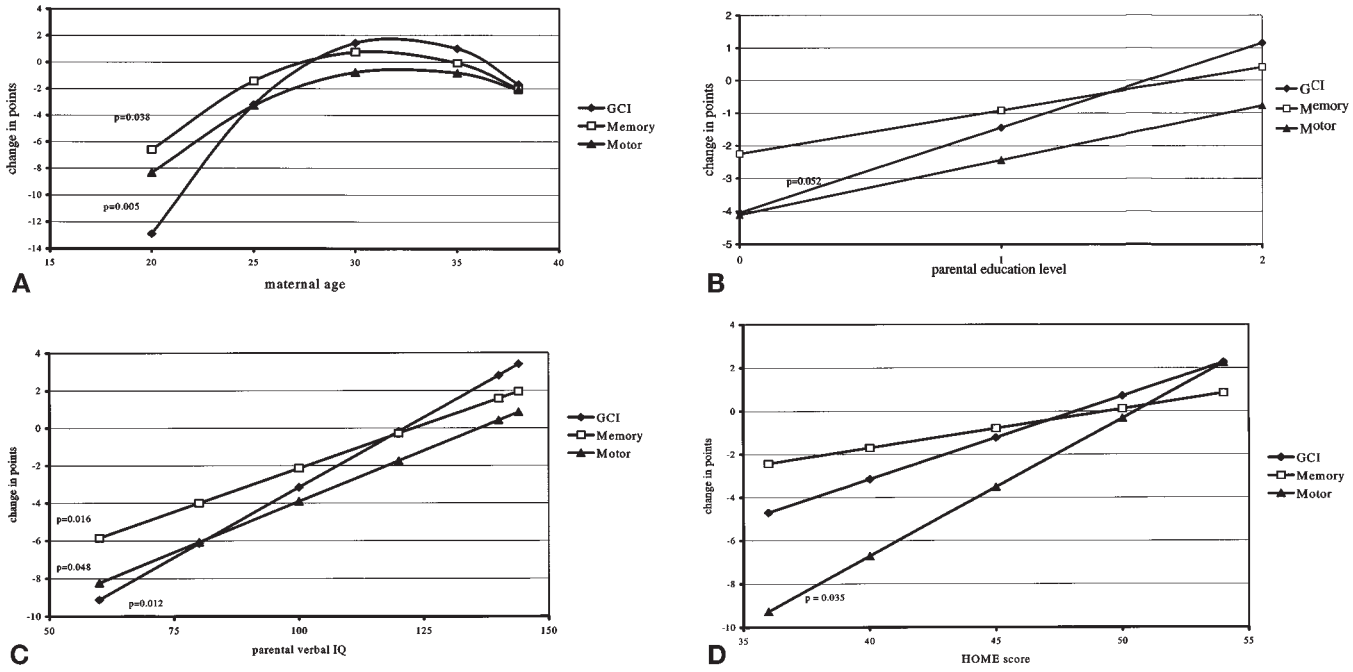


***Figure.*** Effect of doubling prenatal PCB exposure on GCI, memory, and motor skills in relation to **(A)** maternal age, **(B)** parental education level, **(C)** parental verbal IQ, **(D)** HOME score.
The y-axis represents the effect on the GCI, memory, and motor scales of doubling maternal PCB levels as it is modified by maternal age, parental education level, parental verbal IQ, and HOME score. The *P* values indicate significance of modification of the PCB effect by maternal age, parental education level, parental verbal IQ, and HOME score, respectively. In **A**, the PCB effect on motor skills is not significantly different from a constant effect of –1.70 (= –2.45Ln[2]). In **B**, the PCB effect on memory and motor skills is not significantly different from a constant effect of –0.25 (= –0.36Ln[2]) and –1.7 (= –2.45Ln[2]), respectively. In **D**, the PCB effect on GCI and memory skills is not significantly different from a constant effect of –0.1 (= –0.14Ln[2]) and –0.25 (= –0.36Ln[2]), respectively.

hort. This difference could be explained by a number of factors. At school age, children who participated in the follow-up had significantly higher parental and home characteristics compared with the nonparticipating children. The higher mean levels of these background variables might explain that no effect of prenatal PCB exposure is seen in the total cohort, adjusting for the mean population levels of the confounders. The interaction effects seen at school age between PCB and dioxin exposure and parental and home characteristics show the importance of the distribution of these variables in a cohort. Differences in the results of effects of prenatal PCB exposure could also reflect differences in the test materials used to assess cognitive abilities. At 42 months of age, the Kaufman-ABC[36] was used, and at school age, the McCarthy Scales of Children's Abilities was used. These developmental tests assess different neuropsychologic functions to compose a general cognitive index. The McCarthy Scales of Children's Abilities were also used in the North Carolina cohort[5] (at 3-5 years of age) and in the Lake Michigan cohort[7] at 4 years of age. In both study populations, no relationship between prenatal PCB exposure and the GCI were seen; in the Lake Michigan cohort, prenatal PCB exposure was related to lower memory skills and lower scores on the verbal scale. In comparing effects seen in different cohorts, we have to consider differences in exposure levels between these cohorts that are difficult to compare because of differences in analytic methods used to measure exposure. There is reason to believe that exposure levels in the Dutch cohort and the Lake Michigan cohort are roughly comparable, whereas exposure levels in the North Carolina cohort are suspected to be lower.[13]

We conclude that neurotoxic effects of prenatal PCB and dioxin exposure may persist into school age and may result in subtle cognitive and motor developmental delays. Parental and home environmental characteristics influenced the consequences of these neurotoxic effects for cognitive and motor abilities. When these characteristics were less optimal, negative effects of prenatal PCB exposure were seen on cognitive and motor abilities, whereas these negative effects of prenatal PCB exposure were not measurable in children raised in more optimal environments. These data indicate that children might be at risk to these neurotoxic pollutants because of prenatal exposure to PCBs and dioxins. Follow-up studies into adulthood in children exposed to different levels of these contaminants, while growing up in different environments, should be conducted to investigate the future implications of our findings.

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## *50 Years Ago in The Journal of Pediatrics*

### USES OF PLAY IN THE TREATMENT OF CHILDREN

*Bernstein I. J Pediatr 1951;39:503-8.*

Play has long been recognized as an important activity for children, and Dr Bernstein's words are as true today as when they were written 50 years ago. Play provides the opportunity to express wishes, act out fantasies, and "work through" fears and other feelings related to real life challenges. By nature, children are dependent and subject to the whims and directives of the adults who care for them. In the world of play, the tables are turned and helplessness and frustration diminish, if only temporarily, as the child takes control and achieves a sense of mastery. Play is a *naturally* occurring phenomenon and serves as a primary means of expression for the child whose cognitive capacities for language and self-reflection are less developed. Thus, play has value as a diagnostic and research tool for physicians because it allows us, through observation, to gain information that otherwise may be difficult to obtain.

The central focus of this article, however, is the use of play as a psychotherapeutic modality. In the child who has emotional problems, play serves as a means of working through issues. This technique is still often used in child psychotherapy, although typically not in isolation, and sometimes not at all. Largely because of the psychiatric climate of his day, Bernstein spoke of play therapy as a useful component within the context of child *psychoanalytic* therapy. Although play clearly provides insight into the child's inner world, the dynamic interventions used in the past are more often replaced with cognitive–behavioral strategies today. That is, interpreting conflicts has been replaced by identifying and labeling thoughts and feelings. The differences are perhaps subtle, however, and the process is truly very similar, as are the materials used. The items in the playroom are typically simple and allow for creativity and self-expression without externally imposed direction. In her seminal work (originally published in 1947), Virginia Axline[1] advanced the notion of "non-directive" play therapy, in which the therapist takes a much less active role. Many therapists currently adhere to her principles, although the degree to which they are truly nondirective varies. Moreover, today's climate tends to emphasize behavioral techniques, and parent training is often used as an adjunct to individual play therapy with the child.

The value of play in child psychotherapy remains a constant, and it will continue to be used for another 50 years.

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