70277

GE Corporate
Environmental Programs

John G. Haggard
Engineering Project Manager
Hudson River

General Electric Company
1 Computer Drive South, Albany, NY 12205
518 458-6619 Dial Comm: 8*920-9000
Fax: 518 458-9247

October 4, 1991

Douglas J. Tomchuk
Remedial Project Manager
U.S. Environmental Protection Agency
Emergency & Remedial Response Division
26 Federal Plaza - Room 747
New York, NY 10276

Re: New Information on PCB Toxicity

Dear Mr. Tomchuk:

Enclosed is a recently published article with particular significance to the Hudson River Reassessment RI/FS:

> Effects of Perinatal Polychlorinated Biphenyls and Dichlorodiphenyl Dichloroethene on Later Development: Beth C. Galden, PhD, and Walter J. Rogan, MD; Journal of Pediatrics, July 1991

The results of this study did not confirm the earlier finding of developmental problems. We request you consider this significant information in your work on the Hudson River Reassessment RI/FS. Please place a copy of this article in the Hudson River Reassessment RI/FS.

Very truly yours,

John G. Haggard
Technical Project Manager

Enclosure

cc: Al D'Bernardo, TAM's (w/enclosure)
Yvette Lowney, Gradient Corp. (w/enclosure)
Peter Grant, EPA-Region II (w/enclosure)

804041

Effects of perinatal polychlorinated biphenyls and dichlorodiphenyl dichloroethene on later development

Beth C. Gladen, PhD, and Walter J. Rogan, MD

From the Statistics and Biomathematics Branch and Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

Objective: Determining whether early developmental effects of perinatal exposure to polychlorinated biphenyls (PCBs) or dichlorodiphenyl dichloroethene (DDE) persist.
Design: Cohort followed from birth; ages now 5½ to 10½ years.
Setting: General community.
Participants: Volunteer sample of 859 children, of whom 712 had been examined with the McCarthy Scales of Children's Abilities at 3, 4, or 5 years; 506 sent report cards.
Interventions: None.
Measurements and results: Neither transplacental nor breast-feeding exposure to PCBs or DDE affected McCarthy scores at 3, 4, or 5 years. There was no statistically significant relationship between poorer grades and PCB or DDE exposure by either route.
Conclusions: The deficits seen in these children on the Bayley Scales of Infant Development through 2 years of age are no longer apparent. (J Pediatr 1991; 119:58-63)

Polychlorinated biphenyls are insulating oils that were heavily used worldwide from their introduction in the 1930s until their ban in the 1970s. They are highly prevalent in human tissue.[1, 2] Polychlorinated biphenyls are toxic; in particular, neural and developmental effects have been seen.[3] Dichlorodiphenyl dichloroethene is the most stable derivative of the pesticide DDT; DDT was banned in the United States in 1972, but by that time DDT and DDE had also appeared in human tissue.[2, 4] These compounds are fat soluble and have long half-lives in human beings; they are also trace contaminants of the food supply. Both compounds cross the placenta, and thus both the fetus and the nursing infant are exposed. The ubiquitous background exposure to these chemicals, which accounts for their presence in human tissue, is much lower than that from breast-feeding. Cow milk and commercial formulas are essentially free of these residues.

In 1978 we began a study in which we measured the amounts of PCBs and DDE in human milk and followed the children from birth for various outcomes. The mothers did not have occupational or other special exposure but simply the usual background exposure. We have reported motor abnormalities at birth[5] and psychomotor delay up to 2 years of age[6] associated with the highest 5% of transplacental exposure to PCBs. We looked for but have not found developmental or other toxic effects attributable to exposure through breast-feeding[7]; small exposures to the fetus appear to have greater impact than large exposures to the nursing infant through milk. We report the results of continued developmental testing of the same children to school age, and some aspects of their school performance, in relation to their exposure to PCBs and DDE early in life.

DDE	Dichlorodiphenyl dichloroethene
DDT	Dichlorodiphenyl trichloroethane
PCB	Polychlorinated biphenyl

Submitted for publication Oct. 26, 1990; accepted Jan. 16, 1991.
Reprint requests: Beth C. Gladen, PhD, Statistics and Biomathematics Branch, Mail Drop B3-02, National Institute of Environmental Health Sciences, PO Box 12233, Research Triangle Park, NC 27709.
9/20/28097

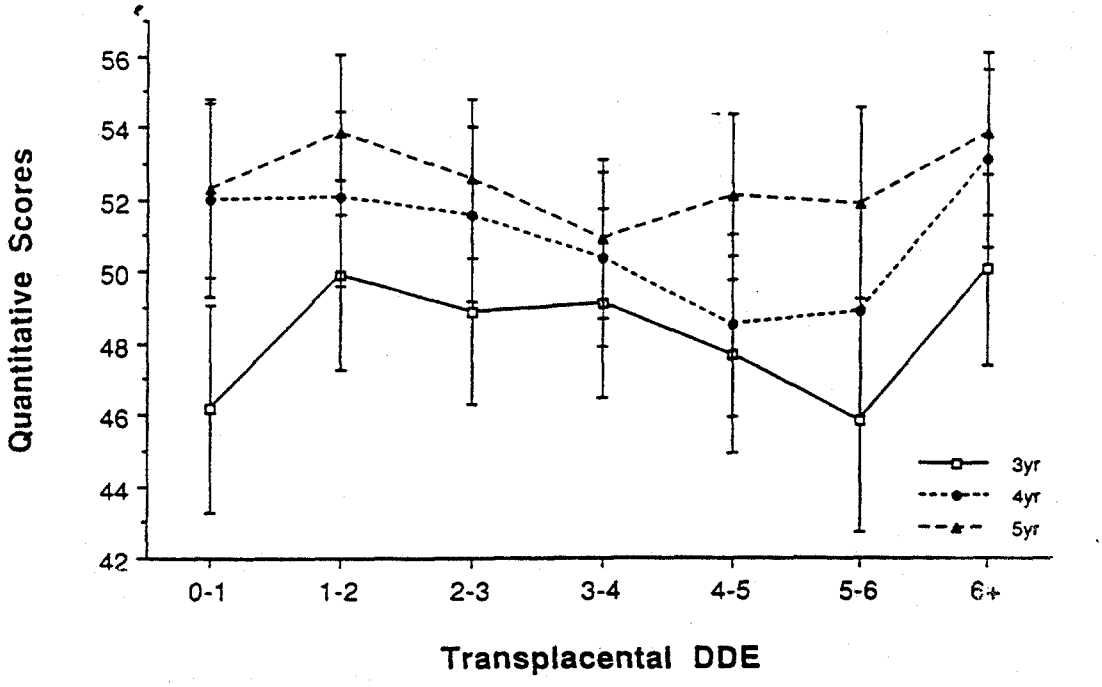

Fig. 1. Relationship between quantitative McCarthy scores and prenatal exposure to DDE (parts per million, fat basis). Data expressed as adjusted means and standard errors, adjusted for factors described in Methods section.

METHODS

The methods of this study have been reported previously.[8] Briefly, we enrolled 859 newborn infants between 1978 and 1982 and then followed them actively from birth to 5 years of age; information collected included questionnaires, medical records, and results of physical and developmental examinations. We also collected samples of maternal milk, maternal blood, cord blood, and placenta for chemical analysis. Informed consent was obtained from the parents of all children.

Outcome measures. We administered the McCarthy Scales of Children's Abilities[9] at 3, 4, and 5 years of age. We attempted to have the children who had moved examined by a local psychologist. We obtained scores on 645 children at 3 years, 628 at 4 years, and 636 at 5 years of age.

In 1988 we wrote to parents and asked for copies of report cards. We received at least one report card for each of 506 children. We used only those report cards from grade 3 or later. We obtained usable report cards for 366 children; the parents of 140 children sent report cards only from before grade 3.

We abstracted grades for English and mathematics from the report cards. If there was a summary grade, we used that; if there were separate grades for subcategories (such as vocabulary or reading), we averaged all the subcategories. We converted grades to numeric scores as follows: A = 4, B = 3, C = 2, D or F = 1; excellent = 4, good = 3, satisfactory = 2, unsatisfactory = 1; commendable = 4, satisfactory = 2.5, unsatisfactory = 1; satisfactory = 2.5, unsatisfactory = 1; and high pass = 4, pass = 2.5, fail = 1. We used report cards from grades 3, 4, and 5; if we had more than one, we averaged them.

Table I. Distribution of information obtained, by age

Age (yr)	Report card	McCarthy score	Both	Neither	Total
5.5-6	0	0	0	1	1
6-6.5	0	6	0	2	8
6.5-7	0	29	0	6	35
7-7.5	0	32	0	6	38
7.5-8	0	59	4	13	76
8-8.5	2	55	40	13	110
8.5-9	8	67	73	26	174
9-9.5	6	55	94	24	179
9.5-10	7	43	92	26	168
10-10.5	1	24	39	6	70
TOTAL	24	370	342	123	859

Children are classified by their age and the information we have on them. Age is as of Oct. 1, 1988, which is approximately when the solicitation for report cards was mailed. Possible information shown is from any report cards, any McCarthy scores, both, or neither. Report cards from kindergarten, and grades 1 and 2 do not count.

Exposure measures. Prenatal exposure is a function of the concentration of chemical agent in maternal fat during pregnancy. To estimate this exposure, we took all the samples that we had from a given woman, scaled them to be comparable (with the milk sample collected at or near birth

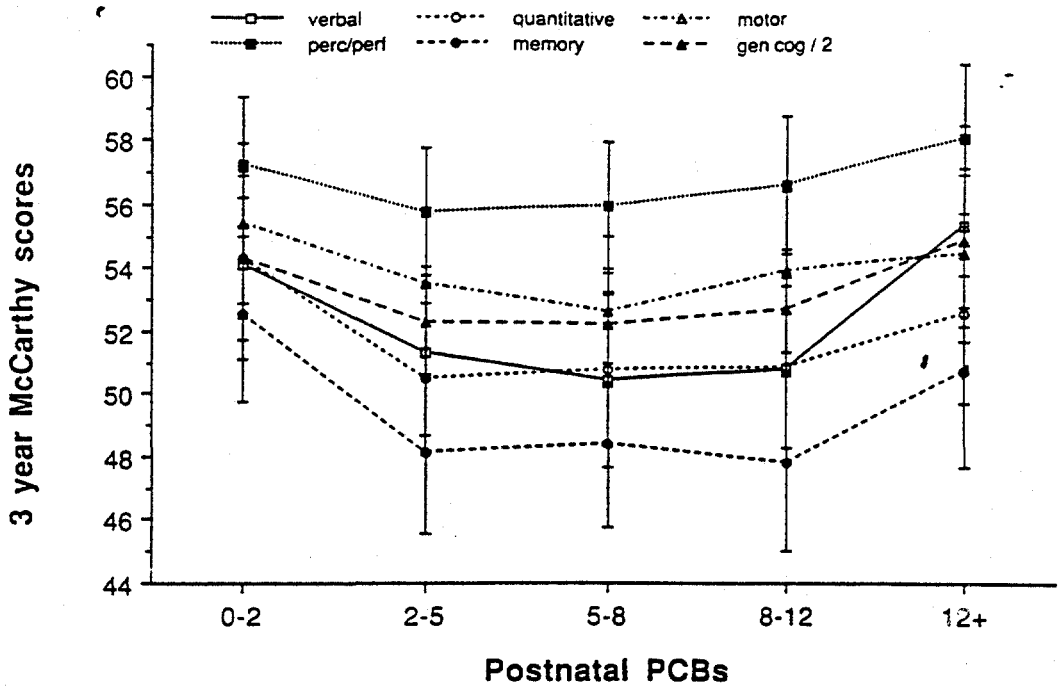

Fig. 2. Relationship between McCarthy scores at 3 years of age and postnatal exposure to PCBs (milligrams). Data expressed as adjusted means and standard errors, adjusted for factors described in Methods section. Means for general cognitive score have been divided by 2 to allow them to be displayed on same scale as others. *perc/perf*, Perceptual performance; *gen cog/2*, one-half general cognitive score.

as the base), and averaged them; details have been given elsewhere.[5, 8]

For practical purposes, breast-feeding is the only postnatal exposure for about the first year of life. The chemicals accumulate in the child, so the dose of interest is the cumulative postnatal exposure. We estimated this dose by combining information on the duration of breast-feeding and the concentration of chemical in milk. The calculations for the estimated exposures are shown in detail elsewhere.[7] About 88% of the children in this study were fed human milk.

We did not measure the chemical levels in the child because with the techniques available at the time, 10 ml of blood were required; however, several studies have shown that the major determinant of the amount of these chemicals stored in young children is breast-feeding.[10-13]

Statistical analysis. McCarthy scores were analyzed by analysis of covariance. Transplacental exposure to PCBs was divided into eight categories, and postnatal exposure through breast-feeding was divided into five; transplacental and postnatal exposures to DDE were divided into seven and five categories, respectively. Covariates included were the identity of the examiner, maternal age, race, occupation, education, smoking, drinking, child's gender, number of older siblings, and feeding pattern (bottle feeding or breast-feeding of short, medium, long, or very long duration). Analyses of transplacental exposure included all children; those of postnatal exposure included only breast-fed children. English and mathematics grades were analyzed in the same way, except that the term in the models that identified the examiner was not included. Statements that differences were not significant indicate that p values were >0.10; smaller p values are given explicitly.

RESULTS

Table I shows response rates by age. Of the original 859 children, 83% had taken at least one McCarthy examination. Those who were examined had the same maternal distribution of PCBs and DDE as those who did not; however, those who had McCarthy examinations were more likely to be breast fed and to be breast fed longer. They did not differ on the Bayley Psychomotor scale at any time point, but those who had taken McCarthy examinations were higher on the Mental scale (7 points [$p = 0.003$] at 18 months of age, 7 points [$p = 0.06$] at 24 months of age). To look at further response bias for report cards, we limited attention to those who had any McCarthy scores and were at least 8 years of age at the time of the mailing; 58% of these children supplied report cards. Those who did and those who did not supply report cards did not differ in maternal PCB or

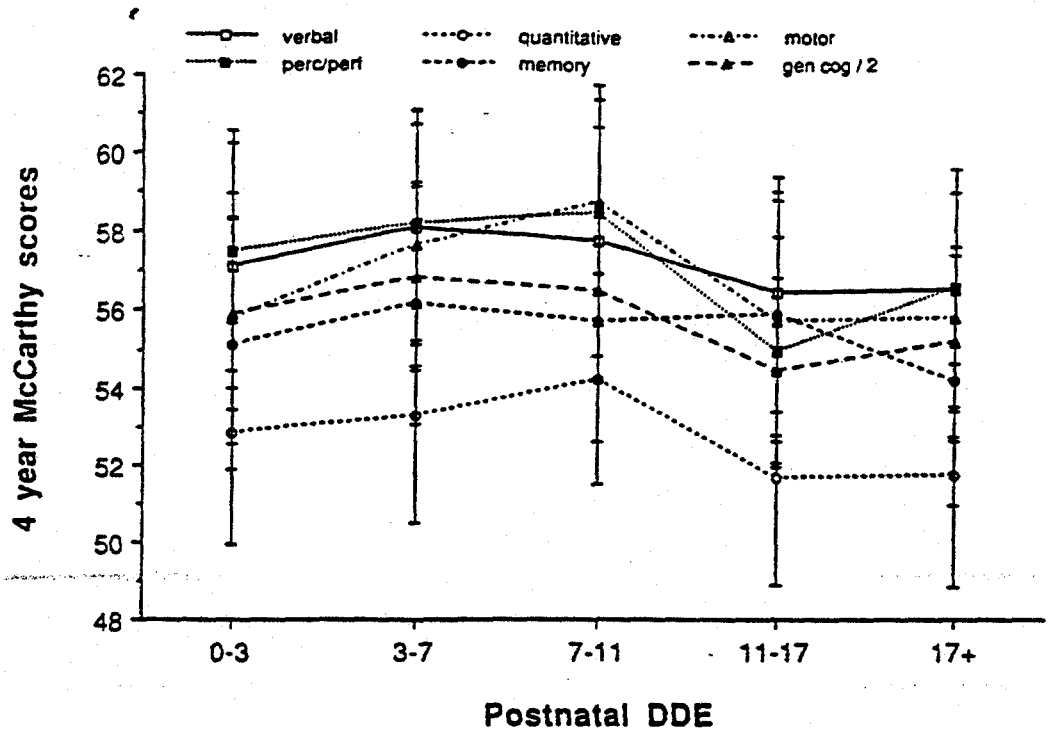

Fig. 3. Relationship between McCarthy scores at 4 years of age and postnatal exposure to DDE (milligrams). Data expressed as adjusted means and standard errors, adjusted for factors described in Methods section. Means for general cognitive score have been divided by 2 to allow them to be displayed on same scale as others. *Perc/perf*, Perceptual performance; *gen cog/2*, one-half general cognitive score.

DDE levels nor in breast-feeding patterns. There was again no difference on the Psychomotor scale, but those with report cards had higher scores on the Mental scale (4 points [$p = 0.01$] at 18 months of age, 5 points [$p = 0.003$] at 24 months of age).

No association was found between transplacental PCB exposure and McCarthy scores. The quantitative score varied among the transplacental DDE exposure categories at 3 years ($p = 0.06$), 4 years ($p = 0.06$), and 5 years of age ($p = 0.05$), but the pattern was not suggestive of dose and response; subjects in both low and high DDE categories had high scores, and categories in the middle had lower scores. Adjusted means are shown in Fig. 1.

For postnatal exposure, some variation by exposure was beyond that expected by chance, but the patterns again did not suggest cause and effect. All scores of children at 3 years of age showed similar patterns in relationship to PCB exposure; lower scores were associated with the middle categories (Fig. 2); differences among the groups were marginally significant on verbal ($p = 0.06$) and memory ($p = 0.08$) scales. In these same children at 4 and 5 years of age, no relationship to PCBs was found. For DDE, scores at all years showed similar patterns; higher scores were associated with the middle categories, and the differences were marginally significant for motor ($p = 0.05$) and perceptual performance ($p = 0.10$) at 4 years of age (Fig. 3).

Grades in English and mathematics had no statistically significant relationship to either transplacental PCB or DDE exposure (Table II). Differences among postnatal DDE categories were marginally significant ($p = 0.10$) for English grades; higher levels of DDE were associated with poorer grades. There was no significant relationship between English or mathematics grades and postnatal PCB exposure. Results were similar whether all report cards were averaged or only grade 3 reports were used. Both English ($p = 0.005$) and mathematics ($p = 0.0001$) grades were significantly related to the 5-year General Cognitive McCarthy scale.

DISCUSSION

In these data the association of prenatal PCB exposure with delayed development, seen previously up to 2 years of age in these children,[6] does not persist. We were also unable to confirm an association, seen in a similar study in Michigan, between prenatal PCB exposure and scores on the McCarthy Memory and Verbal scales at 4 years of age.[14] We saw no consistent associations between exposure to either PCBs or DDE through breast-feeding and the McCar-

Table II. Grades versus prenatal and postnatal exposure to PCBs and DDE

	English	Mathematics
By prenatal PCB exposure (ppm, fat basis)		
Up to 0.9	3.54 ± 0.23	3.69 ± 0.30
1-1½	3.57 ± 0.20	3.52 ± 0.26
1½-2	3.50 ± 0.20	3.52 ± 0.26
2-2½	3.64 ± 0.20	3.70 ± 0.25
2½-3	3.61 ± 0.22	3.48 ± 0.28
3-3½	3.54 ± 0.24	3.45 ± 0.32
3½-4	3.70 ± 0.25	3.62 ± 0.33
>4	3.66 ± 0.24	3.56 ± 0.32
By prenatal DDE exposure (ppm, fat basis)		
Up to 1	3.62 ± 0.22	3.70 ± 0.28
1-2	3.69 ± 0.21	3.68 ± 0.26
2-3	3.67 ± 0.20	3.58 ± 0.26
3-4	3.67 ± 0.21	3.71 ± 0.26
4-5	3.48 ± 0.21	3.44 ± 0.27
5-6	3.52 ± 0.23	3.34 ± 0.30
>6	3.53 ± 0.23	3.51 ± 0.29
Among breast-fed subjects, by postnatal PCB exposure (mg)		
Up to 2	3.64 ± 0.21	3.62 ± 0.28
2-5	3.68 ± 0.19	3.62 ± 0.25
5-8	3.78 ± 0.20	3.73 ± 0.26
8-12	3.80 ± 0.20	3.67 ± 0.26
>12	3.75 ± 0.22	3.59 ± 0.29
Among breast-fed subjects, by postnatal DDE exposure (mg)		
Up to 3	3.86 ± 0.20	3.78 ± 0.27
3-7	3.73 ± 0.19	3.63 ± 0.26
7-11	3.76 ± 0.19	3.62 ± 0.25
11-17	3.78 ± 0.19	3.69 ± 0.26
>17	3.51 ± 0.21	3.51 ± 0.29

Data expressed as adjusted means ± SE; the factors for which they are adjusted are listed in the Methods section.

thy Scales, nor did we see any significant associations with our measures of school performance.

In laboratory experiments designed to evaluate the effects on the nervous system of prenatal exposure to PCBs, changes in activity levels of the offspring are the most commonly reported effects.[3] Evidence is also good that prenatal exposure affects learning, but motor function has not been so consistently affected.

There have been two episodes in Asia of epidemic PCB poisoning as a result of the contamination of rice bran oil; however, in both instances the PCBs were themselves contaminated with the highly toxic polychlorinated dibenzofurans. In both incidents, women who were pregnant during or after the outbreak bore affected children. After the 1968 outbreak in Japan, Harada[15] described the children as apathetic and dull, with IQs in the 70s; formal testing of the children was not done. After the 1979 outbreak in Taiwan, children exposed transplacentally were determined to be developmentally delayed according to all instruments used except the Verbal subscale of the Wechsler Intelligence Scale for Children.[16]

The developmental deficits seen at earlier ages were on the Bayley Psychomotor scale; we saw no relationship between exposure and the McCarthy Motor scale. This scale may not be an exact analogue of the Bayley Psychomotor scale, so the failure to see effects may relate to the different abilities assessed by the two tests. However, the McCarthy Scales use common, standard tasks to assess motor function. Alternate explanations for the lack of persistence of deficits are that (1) the children have recovered or that (2), as they have grown, their relatively fixed body burdens have declined by dilution and the concentration of agent at some critical site is below threshold levels. This possibility is not excluded by the animal experiments, which were carried out at higher doses, and is consistent with the idea that many of the persistent toxic effects seen in the Asian outbreaks were attributable to the presence of polychlorinated dibenzofurans.

Whether differences in dose or exposure account for the failure to replicate the association seen in Michigan between prenatal exposure to PCBs and the McCarthy Verbal and Memory scales at 4 years of age is difficult to know. The reported levels seen in the two cohorts overlap. However, the analytic methods used in the two studies differed, so levels cannot be compared directly.

We can, of course, exclude effects only within the resolving power of the measures that we used, and report cards in particular are relatively crude. However, our measures are sensitive enough to detect the modest relationship between the McCarthy General Cognitive scale and scholastic grades.[17-19] Thus, despite the difficulties posed by negative findings, we find the results from this large and reasonably well documented cohort to be reassuring.

We thank Nancy Carreras, Pam Hardy, Mary Tully, Jon Tingelstad, and James Thullen for long-term collaboration and data collection, and James McKinney for chemical analysis.

REFERENCES

1. Jensen AA. Background levels in humans. In: Kimbrough RD, Jensen AA, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. 2nd rev. ed. New York: Elsevier, 1989:345-80. (Topics in environmental health; vol 4.)
2. Jensen AA. Chemical contaminants in human milk. Residue Rev 1983;89:1-128.
3. Tilson HA, Jacobson JL, Rogan WJ. Polychlorinated biphenyls and the developing nervous system: cross-species comparisons. Neurotoxicol Teratol 1990;12:239-48.
4. Environmental Protection Agency. DDT: a review of scientific and economic aspects of the decision to ban its use as a pesticide. Washington, DC: U.S. Environmental Protection Agency; 1975.
5. Rogan WJ, Gladen BC, McKinney JD, et al. Neonatal effects of transplacental exposure to PCBs and DDE. J PEDIATR 1986;109:335-41.
6. Rogan WJ, Gladen BC. PCBs, DDE, and child development at 18 and 24 months. Ann Epidemiol (in press).

7. Rogan WJ, Gladen BC, McKinney JD, et al. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects on growth, morbidity, and duration of lactation. Am J Public Health 1987;77:1294-7.
8. Rogan WJ, Gladen BC, McKinney JD, et al. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects of maternal factors and previous lactation. Am J Public Health 1986;76:172-7.
9. Kaufman AS, Kaufman NL. Clinical evaluation of young children with the McCarthy scales. New York: Grune & Stratton, 1977.
10. Kuwabara K, Yakushiji T, Watanabe I, et al. Relationship between breast feeding and PCB residues in blood of the children whose mothers were occupationally exposed to PCBs. Int Arch Occup Environ Health 1978;41:189-97.
11. Niessen KH, Ramolla J, Binder M, Brugmann G, Hofmann U. Chlorinated hydrocarbons in adipose tissue of infants and toddlers: inventory and studies on their association with uptake of mother's milk. Eur J Pediatr 1984;142:238-43.
12. Yakushiji T, Watanabe I, Kuwabara K, et al. Postnatal transfer of PCBs from exposed mothers to their babies: influence of breast-feeding. Arch Environ Health 1984;39:368-75.
13. Jacobson JL, Humphrey HEB, Jacobson SW, Schantz SL, Mullin MD, Welch R. Determinants of polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), and dichlorodiphenyl trichloroethane (DDT) levels in the sera of young children. Am J Public Health 1989;79:1401-4.
14. Jacobson JL, Jacobson SW, Humphrey HEB. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J PEDIATR 1990;116:38-45.
15. Harada M. Intrauterine poisoning: clinical and epidemiological studies and significance of the problem. Bull Inst Constitutional Med Kumamoto Univ 1976;25(suppl):26-74.
16. Rogan WJ, Gladen BC, Hung KL, et al. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science 1988;241:334-6.
17. Kaufman AS. Comparison of the WPSSI, Stanford-Binet, and McCarthy scales as predictors of first-grade achievement. Percept Motor Skills 1973;36:67-73.
18. Massoth NA. The McCarthy Scales of Children's Abilities as a predictor of achievement: a five-year follow-up. Psychol Schools 1985;22:10-3.
19. Funk SG, Sturner RA, Green JA. Preschool prediction of early school performance: relationship of McCarthy Scales of Children's Abilities prior to school entry to achievement in kindergarten, first, and second grades. J School Psychol 1986;24:181-94.