A 6-Year Follow-Up of Behavior and Activity Disorders in the Taiwan Yu-cheng Children

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A B S T R A C T

Objectives. The relationship of behavior and activity levels to the interval between outbreak and year of birth and to age of the children is explored in Taiwanese children exposed in utero to heat-degraded polychlorinated biphenyls (PCBs)—the Yu-cheng children. Additionally, the relationship of the scores to chemical, physical, and cognitive findings is described.

Methods. With Rutter's Child Behavior Scale A and a modified Werry-Weiss-Peters Activity Scale, 118 Yu-cheng children and matched controls were followed biannually from 1985 to 1991.

Results. At each year, the Yu-cheng children scored 7% to 43% worse (mean = 23%) than control children on the Rutter scale. At any fixed age, the Yu-cheng children scored 11% to 63% (mean = 28%) worse. The effect for children born later did not differ from that for those born earlier; neither was there any improvement as the children aged. A similar but weaker picture was seen for the activity score. These behavioral findings were not related to physical or cognitive findings or to serum PCB levels.

Conclusions. In utero exposure to heat-degraded PCBs appears to cause mildly disordered behavior and increased activity level; the effect persists over time and is similar in children born up to 6 years after the mothers were exposed. (*Am J Public Health.* 1994;84: 415–421)

Introduction

Polychlorinated biphenyls (PCBs), a group of compounds with two linked phenyl rings and various degrees of chlorination, were used widely in industry between the 1930s and 1970s,[1] and have since become ubiquitous and persistent environmental contaminants because of their resistance to chemical and thermal degradation.[2] The most common source of general population exposure is low-level contamination of the food chain; other known sources of exposure, like the workplace or contaminated sport fish, can produce higher body burdens.[3,4] PCBs are readily absorbed when ingested, can persist in fat tissue for years,[5,6] and can cross the placenta to affect the fetus.[7,8] Commercial grade PCBs per se are teratogenic, causing malformations in mice[9] and pigs,[10] and decreased intrauterine growth and survival in monkeys, rabbits, and rats.[11] In utero exposure has also increased motor activity and impaired learning in mice,[12–14] male rats,[15] and rhesus monkeys.[16–18]

Thus far, however, birth defects in human beings have been documented only after maternal exposure to a complex mixture of heat-degraded PCBs. Two such exposures have occurred, one in Japan (called Yusho, or "oil disease") in 1968[19] and one (Yu-cheng, the episode studied here) in Taiwan in 1979.[20] In both instances, PCBs were used as heat exchangers and thus were contaminated by their heat-degraded by-products, polychlorinated dibenzofurans, terphenyls, and quarterphenyls. These chemicals leaked into and became mixed with rice bran oil. Children born to women who had consumed the contaminated oil were found to have ectodermal defects, including hyperpigmentation, deformed nails, and natal teeth; intrauterine growth delay; and developmental delay.[21–23] The Japanese Yusho children were described as hypotonic, apathetic, and dull at 9 and 10 years old.[22]

In the Taiwan incident, more than 2000 people who had consumed the contaminated oil for up to about 9 months between June 1978 and October 1979 were included in the Yu-cheng registry.[20] In the first 3 years after the outbreak, babies born to exposed women had a high infant mortality rate.[20] Surviving children were found to have ectodermal defects, developmental delay, more behavioral problems, and higher activity levels.[23–33] Followed from 1985 to 1991 with cognitive and behavioral tests, these children were also found to have poorer cognitive development up to 7 years of age.[28]

We examine here the behavior and activity level of the children born to exposed women. We explore both the relationship of the behavior and activity scores to the interval between outbreak and year of birth, and the possibility that the effect of exposure diminishes as the children age. We also describe the re-

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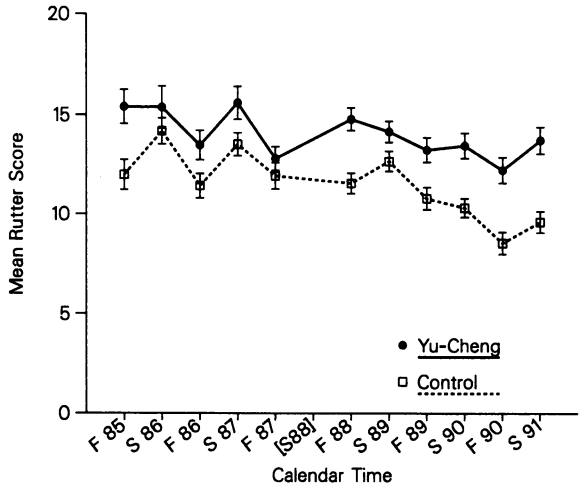


Note. F = fall, S = spring; behavior levels were not evaluated in spring 1988.

FIGURE 1—Mean Rutter scores by calendar time, Yu-cheng and control children.

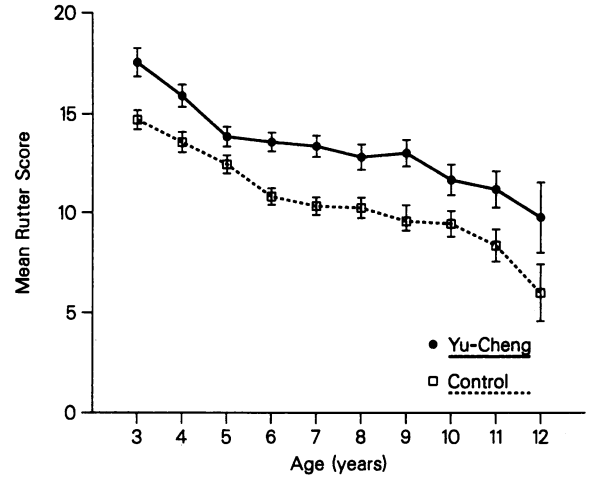


FIGURE 2—Mean Rutter scores by age, Yu-cheng and control children.

lationship of the behavior and activity scores to chemical, physical, and cognitive findings.

Methods

Study Subjects

The procedure used to identify the study children has been described in detail elsewhere.[23] Briefly, 132 living children, born to exposed women between June 1978 and February 1985, were identified. These children are referred to as "Yu-cheng children." One hundred and eighteen of them participated in a 6-year cognitive and behavioral follow-up study. For each Yu-cheng child, a control matched on age (within 15 days for those under 1 year, and within 1 month for older children), sex, neighborhood, maternal age (within 3 years), and socioeconomic status was selected for the follow-up study.

Behavioral and Activity Measurement Scales

There was no validated Chinese instrument for assessing children's behavior in 1985. Our group has clinical experience with behavioral disorders in Chinese children, and the items on Rutter's Child Behavior Scale A,[34] which had been validated in British children aged 9 to 12, appeared to be culture fair. The scale is a screening instrument to identify children likely to show some emotional or behavioral disorder; the three sections concern health problems, habits, and behaviors. The questionnaire was modified so that all items allowed a "not applicable" answer, and the parents used this option for younger children in whom one would expect that some of the behaviors asked about could not have occurred. There was a strong relationship between the percentage of not applicable answers and age: 21% for children under age 1, 11% for ages 1 to 2, 4.5% for ages 3 to 4, and less than 1% for ages 5 and over. Chinese parents reported a much higher frequency of behavioral problems in all children, including controls, than one would expect from the results in British children: 48% of the Yu-cheng children and 25.5% of the control children aged 9 to 12 years met Rutter's criterion for a behavioral disorder, compared with 15.1% and 8.1% of the British boys and girls, respectively, of the same ages. Nevertheless, it seemed justified to use the Rutter scale from age 3 years on because less than 5% of the questions were not applicable to children outside the 9- to 12-year age group, and because there were simultaneous control children and so the "normal" values for the instrument did not have to be used. However, it should be borne in mind that it is not known whether these higher scores in the Yu-cheng children, which represent more behavioral problems, are associated with the psychiatric diagnoses with which they are associated in British children. The test-retest reliability was assessed on 30 mothers with a 2-week interval between ratings, and the correlation between the scores on the two occasions was .82.[35]

A modified Werry-Weiss-Peters Activity Scale,[36] which had been validated in Chinese children aged 3 to 11,[37] was used to evaluate the children's activity level. Both behavior and activity questionnaires were filled out by a parent with instructions from an interviewer. The matched control was always evaluated on the same day as the Yu-cheng child. The evaluations were conducted twice a year between fall 1985 and spring 1991, except for spring 1988.

Data Analysis

Paired *t* tests were used to compare the mean Rutter behavior or activity scores between Yu-cheng and control children at each time point or age. Student's *t* tests were used to compare the mean scores of Yu-cheng children who had physical stigmata at birth or in the 1985 survey with the scores of those who did not, and to compare the scores of children who had detectable PCBs with the scores of those who did not. Simple regression analyses were used to test the relationship of the scores to maternal PCB values and IQ score.

Results

One hundred and fifteen of the original 118 Yu-cheng children com-

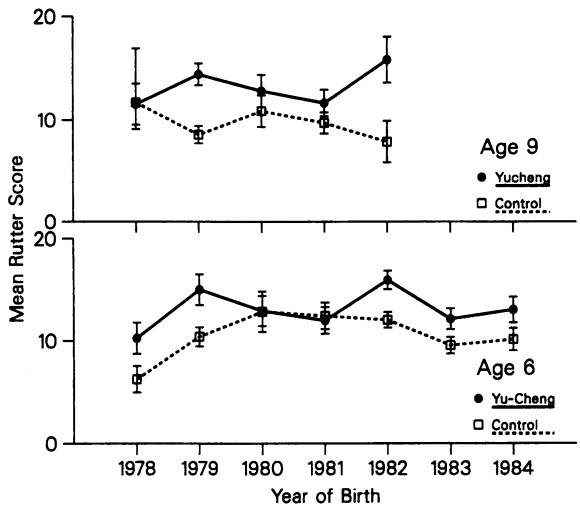


FIGURE 3—Mean Rutter scores at ages 6 and 9 by year of birth, Yu-cheng and control children.

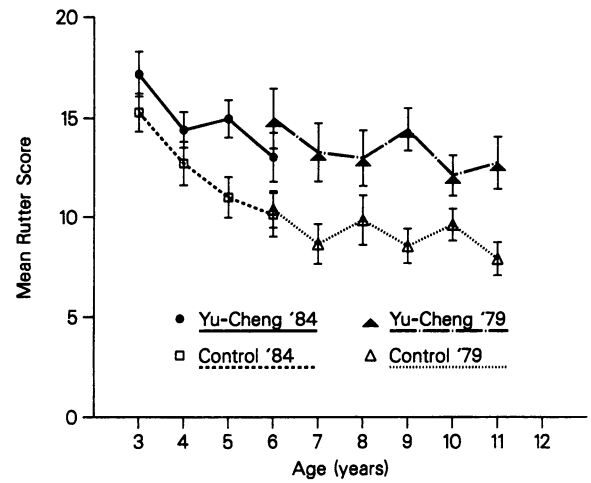


FIGURE 4—Mean Rutter scores for 1979 and 1984 birth cohorts, by age, Yu-cheng and control children.

pleted the 6-year follow-up study, as did their matched controls. The other three Yu-cheng children were removed from the study by their parents in early test rounds, and their corresponding controls were not evaluated further.

Because the children were born over a 7-year period, they were of different ages in any one round of follow-up. When children of different ages were combined and behavior scores analyzed by test time, the Yu-cheng children were found to have scored 7% to 43% (mean = 23%) higher than the control children on the Rutter scale at every time point (Figure 1); all differences were statistically significant except for those in spring 1986 and fall 1987. If analysis was done by age and the scores from different time points were combined, the Yu-cheng children scored 11% to 63% (mean = 28%) higher than their controls at each age (Figure 2); all differences were statistically significant except those for the 12-year-olds, for which there were only 17 pairs.

To examine whether children born longer after the exposure are less affected, the children were separated by year of birth. Figure 3 shows mean Rutter scores for all children aged 6 and 9 arrayed by year of birth. Except for the 1978 birth cohort at age 9 and the 1980 and 1981 birth cohorts at age 6, Yu-cheng children consistently scored higher than their controls. There was no consistent trend toward decreased differences in scores of Yu-cheng and control children as the interval between the exposure and year of birth increased. Pictures at other ages are similar.

To see whether the behavioral abnormality in the children persists as they grow, a given birth cohort was examined over time. The Rutter scores of the 1979 and the 1984 birth cohorts, arrayed by age, are shown in Figure 4. The difference between the Yu-cheng and the control children did not decrease as the children grew older.

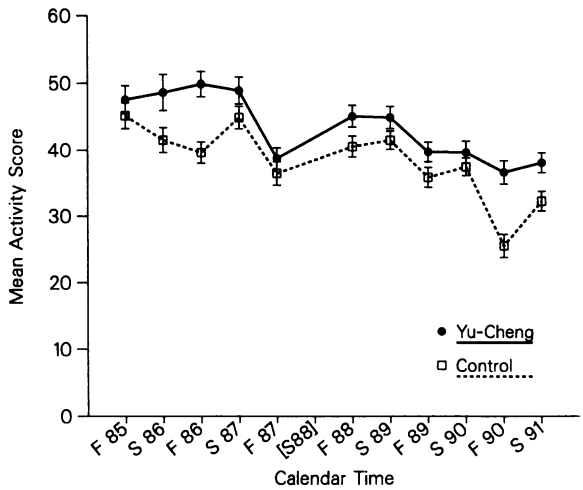
A similar but weaker picture was seen for the activity score. At each round, Yu-cheng children had a mean activity score 5% to 44% higher than the control children (Figure 5), and the differences were statistically significant at seven time points; Yu-cheng children scored 8% to 53% higher than their controls at each age (Figure 6), and the differences were significant in six age groups. The average differences across calendar time or across age were both highly significant.

There is information on physical findings, cognitive scores, and PCB levels of the Yu-cheng children from previous studies.[23,25,28,38] When the Rutter and activity scores of Yu-cheng children with various historical or physical stigmata were compared with the scores of those children without the stigmata, there did not appear to be any consistent trend. Children with physical signs had a higher mean score at some ages and a lower score at others (Table 1). Cognitive scores, PCB detectability, maternal serum PCB levels, and breast-feeding mode did not have consistent relationships to Rutter or activity scores, either.

Discussion

The data show that in utero exposure to PCBs and their heat-degraded contaminants is associated with mildly disordered behavior and increased activity level. The effects persisted as the children aged, and they appeared to be similar in children born up to 6 years after the mother was exposed. This is the first study to report the long-term effects of in utero exposure to heat-degraded PCBs on children's behavior and activity level.

Some of the children still have visible Yu-cheng–related physical stigmata, such as abnormal patterns of pigmentation, hypoplastic nails, and teeth that are very susceptible to caries. Since both the behavior questionnaire and the activity checklist were filled out by a parent, the perception of the parent that his or her child is "abnormal" may contribute to the differences in reported behavior and activity. So far, we have not seen consistent relationships between either cognitive[38] or behavioral function in the children and the presence of the physical stigmata of the syndrome. In general, the physical signs are subtle, and among children old enough to attend school, the results of teacher ratings on each child's maladaptive behavior and activity level are thus far



Note. F = fall, S = spring; activity levels were not evaluated in spring 1988.

FIGURE 5—Mean activity scores by calendar time, Yu-cheng and control children.

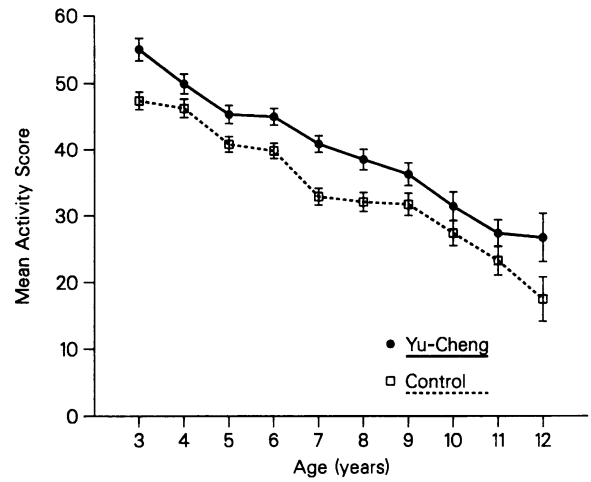


FIGURE 6—Mean activity scores by age, Yu-cheng and control children.

consistent with the parent's rating.[26,29,32,33] We believe the teachers are less likely to be aware of the child's exposure status and are thus not sensitized to the child's behavior. It is also possible that the perception that the child is damaged, regardless of whether there are physical signs, may in fact affect a parent's attitude in rearing the child and produce the abnormal behavior.

Yu-cheng children had persistent cognitive deficits up to 7 years of age.[28] The observed association between in utero PCB exposure and persistent behavior and activity level alteration may be secondary to the cognitive developmental delay. Our data did not show consistent and significant associations between cognitive scores and behavioral scores for the Yu-cheng children. This suggests that the developmental delay observed in these children did not produce secondary behavioral problems.

The finding of no consistent relationships between behavior/activity scores and physical findings, cognitive scores, and serum PCB levels is consistent with our previous report,[38] in which we found inconsistent relationships between cognitive developmental scores and physical stigmata and serum PCB levels. It is possible that our measures of dose did not accurately reflect the children's in utero exposure; that the congeners responsible for the physical stigmata may not have been those responsible for the cognitive delay or the disordered behavior; or that different mechanisms were involved in the physical stigmata, cognitive delay, and disordered behavior.

We matched the control children with the Yu-cheng children on age, sex, neighborhood, maternal age, and socioeconomic status. None of the exposed families had any psychiatric history, none of the exposed mothers had ever smoked, and only two exposed mothers had ever drunk regularly. However, other factors that we did not measure could have caused residual confounding; these factors may include parity, temperament of the mother, child-rearing attitudes or behaviors, and family and parental stresses. There is, however, no a priori reason to believe that control families differed in stress levels, attitudes, or illnesses other than those caused by exposure.

The Japanese Yusho children were described as hypotonic, apathetic, and dull at 9 and 10 years old.[22] However, since these children were not randomly selected and no controls were compared, the observation may not represent the whole picture of Yusho children.

Behavior and activity levels were evaluated in two US cohorts—one in Michigan, the other in North Carolina—exposed perinatally to background levels of PCBs. In North Carolina, using the information abstracted from report cards, researchers found no significant relationship between PCB exposure, either prenatally or through breast milk, and the child's work habit or conduct grades.[39] The study also found no association between exposure and hyperactivity reported by parents.[39] In the Michigan study, which used the reports from mothers and examiners when the children were 4 years of age, a composite activity rating was not related to prenatal PCB exposure.[40] The negative results in the two US cohorts were probably due to the low dose of PCBs and the virtual absence of polychlorinated dibenzofurans in the US exposures.

The Michigan study did find reduced activity among children with higher 4-year serum PCB levels.[40] These PCB levels were related to the children's breast-feeding history and not to their prenatal exposure, and the effect was seen only in children who had been breast-fed for more than 1 year and whose mothers had above average breast milk PCB levels. Breast-feeding has the potential to transfer much more of these chemicals to the child than does transplacental exposure. The Michigan findings were consistent with findings from two laboratory studies that found that postnatal exposure to PCBs reduced the activity level.[41–43] In our study, breast-feeding was not found to have a consistent association with the child's activity level among the Yu-cheng children. However, Yu-cheng mothers were advised not to breast-feed their children, and only 30 did.

Behavioral alterations appear in animals exposed perinatally to PCBs.[44]

The most consistent finding has been hyperactivity among animals—namely, mice, male rats, and rhesus monkeys—exposed in utero.[12-18] One group of rhesus monkeys exposed perinatally were hyperactive at 6 and 12 months of age but were hypoactive at 44 months.[16] The authors suggest that the altered behavior was a delayed and possibly permanent effect of the early exposure.

The continued mildly disordered behavior in these children is likely due to the persistence of the chemicals in their mothers, which resulted in the child's in utero exposure long after the mother's exposure to the chemicals ceased. Even though the levels in the mothers were declining, there appeared to be sufficient agent to be toxic for at least 6 years after the exposure. The persistent effect observed as the children aged may have been due to either continued internal exposure to PCBs/polychlorinated dibenzofurans stored in the body or permanent structural changes.

The biological mechanism that causes behavioral toxicity is unclear. It has been suggested that the PCB congeners responsible for neurochemical changes are different from the dioxin-like coplanar congeners that bind the Ah receptor and cause immunotoxicity, enzyme induction, and possible carcinogenesis.[45] After exposure of intact pigtail macaques (*Macaca nemestrina*) to two PCB mixtures, ortho- and ortho-, para-substituted congeners were found in the nigra-striatal system and the hippocampus, and the presence of these congeners correlated with decreases in the dopamine content in these brain regions.[45,46] Thus, these orthosubstituted nonplanar congeners may be responsible for the observed changes in in vivo neurochemistry. This suggestion is supported by the observation that there were no consistent relationships between behavioral scores and physical findings in the Yu-cheng children. One other possible mechanism is that the planar dioxin-like congeners alter brain steroid levels during development, which changes brain organization and the regulation of dopaminergic systems.[45]

The findings of mildly yet persistently disordered behavior and higher activity levels among the Yu-cheng children in this study is of public health significance. Even though PCBs have not been manufactured since the late 1970s, all PCB-containing equipment will have to be disposed of in some way. There will continue to be a risk of exposure to workers and the general population through accidents, improper disposal practices, transport of equipment containing huge amounts of PCBs, and contaminated animals and food. Prenatal exposure can cause activity alteration at a level that does not cause obvious clinical symptoms. The Yu-cheng children are the only well-documented cohort with sufficient in utero exposure to cause obvious toxicity. The behavioral and activity findings from this cohort may help us understand the toxicity that background exposure may cause. We will continue to follow these children and evaluate their health outcomes to understand the disease process. □

TABLE 1—Relationship between Physical, Cognitive, and Chemical Findings and Rutter Scores, Yu-cheng Children

	4 Years of Age		6 Years of Age		9 Years of Age	
	Mean ± SE	(n)	Mean ± SE	(n)	Mean ± SE	(n)
Neonatal eyelid swelling						
Yes	18.9 ± 1.7	(26)*	13.4 ± 1.3	(37)	13.6 ± 1.3	(19)
No	15.4 ± 0.5	(117)	13.8 ± 0.5	(141)	12.8 ± 0.8	(62)
Neonatal hyperpigmentation						
Yes	17.7 ± 1.0	(57)**	13.4 ± 0.7	(75)	13.3 ± 1.0	(44)
No	15.0 ± 0.6	(86)	13.9 ± 0.7	(103)	12.7 ± 0.9	(37)
Neonatal deformed/small nails						
Yes	19.1 ± 1.6	(32)**	12.1 ± 0.8	(44)**	14.2 ± 1.1	(24)
No	15.2 ± 0.5	(111)	14.2 ± 0.06	(134)	12.5 ± 0.8	(57)
History of bronchitis/pneumonia in first 6 months						
Yes	18.5 ± 1.5	(26)**	14.2 ± 1.0	(43)	13.8 ± 1.1	(24)
No	15.5 ± 0.6	(117)	13.5 ± 0.5	(135)	12.7 ± 0.8	(57)
History of toenail deformity						
Yes	18.0 ± 1.3	(39)*	13.6 ± 0.8	(51)	14.1 ± 1.1	(28)
No	15.4 ± 0.6	(102)	13.8 ± 0.6	(125)	12.4 ± 0.8	(53)
Deformed/pigmented toenails at initial examination						
Yes	15.9 ± 0.7	(90)	12.7 ± 0.6	(114)**	13.0 ± 0.8	(59)
No	16.4 ± 0.7	(53)	15.4 ± 0.8	(64)	13.2 ± 1.1	(22)
Cognitive score[a]						
<100	16.7 ± 0.8	(51)**	13.9 ± 0.8	(77)	13.2 ± 1.2	(26)
≥100	13.8 ± 0.9	(35)	13.4 ± 1.5	(19)	12.5 ± 1.7	(14)
Detectable child's serum PCBs						
Yes	17.1 ± 1.2	(14)	11.2 ± 1.2	(23)**	13.3 ± 1.9	(13)
No	16.7 ± 1.3	(11)	18.3 ± 2.0	(11)	14.5 ± 4.7	(4)
Maternal serum PCB level						
≤25 ppb[b]	17.1 ± 0.9	(72)*	13.5 ± 0.6	(88)	14.6 ± 1.0	(31)**
>25 ppb	14.9 ± 0.7	(61)	13.5 ± 0.8	(77)	11.1 ± 0.9	(42)
Feeding mode						
Breast-fed	18.7 ± 1.8	(19)*	13.3 ± 0.8	(46)	13.6 ± 1.0	(29)
Bottle-fed	15.5 ± 0.6	(124)	13.9 ± 0.6	(132)	13.2 ± 0.8	(51)

[a]Stanford-Binet test for age 4, and Webster Intelligence Scale for Children, Revised (WISC-R) for ages 6 and 9.
[b]Median value.
*Groups differ at $P < .10$ by t test; **groups differ at $P < .05$ by t test.

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