A Cohort Study of Behavioral Problems and Intelligence in Children With High Prenatal Polychlorinated Biphenyl Exposure

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Background: In 1978, about 2000 persons in Taiwan were poisoned when their cooking oil was contaminated during manufacture with heat-degraded polychlorinated biphenyls, which are toxic, very widespread pollutants. The chemicals cannot be metabolized or excreted, and 8 of the first 39 children born to affected women died. When examined in 1985, 117 surviving children were found to have ectodermal defects, developmental delay, and disordered behavior. We have continued to observe the children.

Methods: From 1992 through 1995, 118 children born between 1978 and 1985 (during or after their mothers’ exposure) and 118 matched neighborhood control children had cognitive function measured yearly with the Wechsler Intelligence Scale for Children–Revised and behavioral problems measured with the Achenbach Child Behavior Checklist and the Rutter Child Behavior Scale A.

Results: The exposed children scored 3 points (P=.05) lower than control children for IQ; 3 points (P=.002) higher on the Child Behavior Checklist (an effect size similar to the sex difference); and 6 points (P<.001) higher on the Rutter scale (3 times the sex difference). Birth year × exposure interactions, testing whether children born long after the exposure were as affected as those born soon after, were small and not significant. Age × exposure interactions, testing whether the children improved relative to control children as they got older, were significant only for the Rutter scale.

Conclusions: Prenatal exposure to these compounds produces long-lasting cognitive and behavioral damage, but there is some evidence of recovery.

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POLYCHLORINATED biphenyls (PCBs), a group of industrial oils with 2 linked phenyl rings and various degrees of chlorination, were used widely between the 1930s and the 1970s, before they were banned in much of the world. They are still among the most ubiquitous and persistent of environmental contaminants and are detectable in most human beings worldwide. Polychlorinated biphenyls per se are toxic and teratogenic and can cause impaired learning and behavioral abnormalities in laboratory animals. In children, transplacental exposure even at low, background levels may produce subtle psychomotor, cognitive, and memory impairment. The most severe effects, however, from exposure to these compounds in children occurred among the offspring of women poisoned by complex mixtures of heat-degraded PCBs. Two such exposures have occurred, one in Japan in 1968 (referred to as Yusho) and the other in Taiwan in 1979 (Yucheng; the words mean “oil disease” in Japanese and Chinese, respectively). The PCBs used as heat exchangers in the processing of rice bran cooking oil leaked into the finished oil. The PCBs themselves were partially heat-degraded and thus contaminated by polychlorinated dibenzofurans (PCDFs) and other chlorinated, multi-ring compounds. Some of the PCDFs are extraordinarily toxic compounds, with potencies approaching that of 2,3,7,8-tetrachlorodibenzo-p-dioxin, a structurally similar compound that is the most toxic synthetic chemical known. The PCBs and PCDFs are not well excreted, and the women continued to have affected children for years after the exposure occurred. In Japan, the children born to affected women were “hypotonic, apathetic, and dull” as 9- and 10-year-olds, but there has been no formal study of them.

In Taiwan (the Yucheng incident), more than 2000 people consumed the con-
tminated oil for about 6 months during 1978 to 1979. In the first 3 years after the outbreak, 8 of the 39 children born to exposed women died. In 1985, we studied 117 of the 123 children with transplacental exposure (Yucheng children [hereafter referred to as exposed children]) and found ectodermal defects, developmental delay, more behavioral problems, and higher activity levels. These children have been followed up since 1985 with cognitive and behavioral testing. Between 1985 and 1992, the children’s cognitive test scores were not improving relative to control children as they got older, nor was the effect smaller in children who were born up to 6 years after the exposure had taken place.

From 1985 until 1992, the children’s behavior was studied with translations of the Raven’s Standard Progressive Matrices, and the Werry-Weiss-Peters scales of children’s activity. The exposed children had scores about 23% higher on the Rutter scale and about 15% higher on the Werry-Weiss-Peters scale. As with the cognitive testing, the difference in scores between the exposed children and control children did not diminish as the children aged nor by year of birth. Continued follow-up cognitive testing showed some diminution of effect in the oldest children studied with Raven’s Standard Progressive Matrices, but results of IQ and behavioral testing have not yet been reported. In this report, we present data from follow-up behavioral and cognitive testing of the same children by means of the Achenbach Child Behavior Checklist (CBCL), the Rutter Child Behavior Scale A, and the Wechsler Intelligence Scale for Children—Revised (WISC-R).

METHODS

SUBJECTS AND PROCEDURES

Beginning in 1984, the women who were registered with the Taiwan Provincial Health Department as being victims of Yucheng were located and all 123 living children, who had been born to 74 exposed women between June 1978 and March 1983, were identified. Because registration carried with it access to free medical services and because of the considerable local publicity, registration is believed to be complete. These children had transplacental exposure to the chemicals, and in some cases were breast-fed contaminated milk, but they were too young to have consumed the contaminated oil themselves. In April 1985, 117 of them attended a physical examination, and 118 exposed children participated in the cognitive and behavioral follow-up study. For each exposed child, 3 control children matched for age (within 13 days for those younger than 1 year, and within 1 month for those older), sex, neighborhood, maternal age (within 3 years), and socioeconomic status were identified and 1 was selected for the follow-up study. As follow-up proceeded, when a family of an exposed child moved or no longer participated, the corresponding control child was not examined. If a control child moved, one of the remaining 2 control children was invited.

The study has been approved by the several relevant committees on research risk during its duration, most recently by the committee on the protection of human subjects at National Cheng Kung University, Tainan, Taiwan. We obtained verbal consent from the parents and offered a small cash reimbursement (approximately $15 US). We asked for assent from children 10 years and older. Participation in this study did not affect the eligibility of the family for ongoing or subsequent care provided by the government for victims of Yucheng. The exposed child and his or her control child were given the WISC-R on the same day by the same examiner. All examiners held a bachelor’s degree in either special education or psychology. The supervising psychologist (N.-W.G.) trained the examiners. The Chinese version of the Achenbach CBCL and the Rutter scales were administered to parents as interviews. In 1993, the examiner also administered a demographic questionnaire.

The examiners were not specifically told of the exposure status of the family. However, some of the parents still had a distinctive skin condition related to their exposure, and some mentioned their exposure to the examiners. The exposed families were aware that they were participating in a follow-up study of the exposed children. The control families were told that they were participating in a general study of child development and behavior.

MEASUREMENTS

We used the CBCL to obtain standardized parental reports on children’s behavioral and emotional problems. The CBCL contains 118 specific behavioral and emotional problem items and 2 open-ended problem items. The responses were recorded as 0 if the parents reported that the problem item was not true of the child, 1 if the item was somewhat or sometimes true, and 2 if it was very true or often true. The parents were asked to score each item that described the child at the time the test was administered or within the previous 6 months. By summing 1s and 2s on all problem items, 8 syndromes, 2 second-order factors (internalizing and externalizing), and a total problem score were created. A Chinese version of the CBCL was used in this study. It has acceptable reliability and ability to discriminate between mainland Chinese children who were or were not referred for behavior problems. The CBCL scores are not normally distributed and so were transformed to T scores with a mean of 50 in the control children and an SD of 10, using the pooled (exposed and control) mean and collapsing over year of examination.

The Rutter Child Behavior Scale A is a parental questionnaire used to identify children likely to show some behavioral or emotional disorder; the 3 sections concern health problems, habits, and behaviors. We had used it in children younger than its minimum age of 9 years in the previous report on behavior in this cohort and had therefore added a “not applicable” category. It is designed for school children older than 9 years; although it overlaps the CBCL age range (4–16 years), it focuses more on problem behaviors. In our data, the correlation between CBCL and Rutter total scores was 0.44, and so they appear to capture somewhat different domains. We had also reported the results of a modified Werry-Weiss-Peters scale for activity, but the data for the older children had many answers missing or inapplicable and for the younger children there was much overlap with the CBCL, so we do not report those data herein.

We used the Chinese version of the WISC-R, which yielded verbal and performance scales, and combined them into a full-scale IQ.

STATISTICAL ANALYSES

After follow-up of these children from 1985 through 1992, we reported that the exposed children had more behavior problems and lower IQs than control children, and that the children born up to 6 years after their mothers were exposed were as severely affected as those born soon after the exposure took place. In addition, we had seen no narrowing of the difference
between the exposed and control groups as they got older. To test whether this remained true with 3 more years of follow-up, we first used paired $t$ tests to examine the cross-sectional differences in behavior scores and IQ between exposed children and control children, and then used multivariate mixed models designed for longitudinal data with repeated measures.$^{16}$ These mixed models account for the correlations in test scores when the same child is observed repeatedly, and they allow simultaneous estimation and statistical testing of multiple parameters. For these data, we were interested in effects of exposure, sex, and age of the child. We can also test for interaction between exposure and age, which measures whether the effect of exposure changed if the child was born longer after the mother’s exposure in 1978 to 1979. Mixed-model analyses were performed by SAS PROC MIXED procedure (SAS Institute Inc, Cary, NC). Fixed class variables in these models were subject identifier, sex, and exposure, and random variables included age and year of birth. All tests are 2-tailed.

### RESULTS

One hundred fifteen of the original 118 matched pairs of study children completed follow-up until 1991, 12 years after the exposure. We found and interviewed the families of 112 pairs (mean ± SD age, 10.1 ± 2 years; 51% male) in 1992, 100 (mean age, 11.3 ± 2 years; 51% male) in 1993, 105 (mean age, 12.5 ± 2 years; 52% male) in 1994, and 96 (mean age, 13.4 ± 2 years; 48% male) in 1995 (Table 1). The smaller numbers are due to loss of children and control children, and then used multivariate mixed models designed for longitudinal data with repeated measures.$^{16}$ These mixed models account for the correlations in test scores when the same child is observed repeatedly, and they allow simultaneous estimation and statistical testing of multiple parameters. For these data, we were interested in effects of exposure, sex, and age of the child. We can also test for interaction between exposure and age, which measures whether the effect of exposure changed if the child was born longer after the mother’s exposure in 1978 to 1979. Mixed-model analyses were performed by SAS PROC MIXED procedure (SAS Institute Inc, Cary, NC). Fixed class variables in these models were subject identifier, sex, and exposure, and random variables included age and year of birth. All tests are 2-tailed.

### Table 1. CBCL Scales, Rutter Child Behavior Scale, and IQ in Yucheng Children and Control Children in Taiwan, 1992-1995*$^{†}$

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<tbody>
<tr>
<td></td>
<td>Yucheng</td>
<td>Control</td>
<td>$P$ Value†</td>
<td>Yucheng</td>
</tr>
<tr>
<td>CBCL</td>
<td></td>
<td></td>
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<tr>
<td>Internalizing</td>
<td>51.3 (11.7)</td>
<td>47.7 (8.5)</td>
<td>0.06</td>
<td>49.4 (10.9)</td>
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<tr>
<td>Externalizing</td>
<td>52.8 (12.6)</td>
<td>48.9 (8.9)</td>
<td>0.04</td>
<td>49.8 (11.1)</td>
</tr>
<tr>
<td>Total</td>
<td>52.5 (12.3)</td>
<td>48.5 (9.2)</td>
<td>0.02</td>
<td>49.9 (11.5)</td>
</tr>
<tr>
<td>Rutter scale‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>14.9 (7.4)</td>
<td>11.3 (6.3)</td>
<td>&lt;0.001</td>
<td>11.6 (7.6)</td>
</tr>
<tr>
<td>IQ§</td>
<td>Full-scale IQ</td>
<td>100.0 (15.3)</td>
<td>104.4 (11.3)</td>
<td>0.002</td>
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</tbody>
</table>

$^{*}$All Child Behavior Checklist (CBCL) scale scores were standardized with a mean of 50 and an SD of 10 for all children, collapsing over the year at follow-up. Data are given as mean (SD). Data were based on 110 pairs of subjects (1 child with Yucheng paired with 1 control subject) in 1992, 94 pairs in 1993, 97 pairs in 1994, and 92 pairs in 1995.

$^{†}$Paired $t$ test.

$^{‡}$Data were based on 112 pairs in 1992, 100 pairs in 1993, 105 pairs in 1994, and 96 pairs in 1995.

In 1992, exposed children scored significantly higher on CBCL internalizing ($t_{109}=2.81, P= .006$), externalizing ($t_{109}=2.93, P= .004$), and total scale ($t_{109}=3.25, P= .002$) and on the Rutter scale ($t_{111}=4.05, P< .001$) than their control children, but significantly lower on full-scale IQ ($t_{112}=2.50, P= .01$). Very similar patterns were found for most behavior scales and full-scale IQ from 1993 through 1995 (Table 1).

For each psychological outcome, we constructed a multivariate mixed model that included age at testing, sex, and birth year. For the CBCL, the exposed children scored 2.8 points higher ($P= .002$) in a model in which boys scored 2.5 points higher ($P= .006$). The effect of age was small and not significant ($-0.06$ points per year; $P= .80$). Separate models for the internalizing and externalizing subscales gave similar results (Table 2). Interaction analyses on age by exposure showed that CBCL scale scores (total, $\beta=-0.63$, $t_{111}=1.74, P= .08$; internalizing, $\beta=-0.71$, $t_{110}=1.90, P= .06$; externalizing, $\beta=-0.52$, $t_{110}=1.47, P= .14$) declined with advancing age in exposed children, but the interactions were marginally or not significant. The interactions between year of birth and exposure were small and not significant (total scale, $\beta=0.49$, $t_{117}=1.07, P= .29$; internalizing, $\beta=0.54$, $t_{117}=1.13, P=.26$; externalizing, $\beta=0.33$, $t_{118}=0.73, P= .46$).

For the Rutter scale, the exposed children scored 6 points higher ($P<.001$) in a model in which boys scored 2 points higher ($P<.001$). There was a 0.7-point per year decline in scores with age ($P= .002$) and a similar decline with advancing year of birth ($P= .05$). The age $\times$ exposure interaction was significant ($-0.6$ additional point per year decline in those exposed; $P= .02$) (Table 3), but not the year of birth $\times$ exposure interaction ($\beta=0.39$, $t_{110}=1.92, P=.06$).

For the WISC, the exposed children scored 3 points ($P= .05$) lower than control children; there were significant main effects of age (0.67-point per year increase; $P<.001$) but not sex (girls were 0.4 point higher; $P= .80$) or year of birth (0.1 point per year; $P= .84$) (Table 3). The interaction terms for age $\times$ exposure ($\beta=0.15$, $t_{109}=0.40, P= .69$) and year of birth $\times$ exposure ($\beta=-0.30$, $t_{109}=0.35, P=.72$) were small and not significant.
We found that children born to mothers who were PCB-poisoned in 1979 continued to have mild but statistically significant effects on their behavior when tested in 1992 to 1995, when the children were up to 17 years old. On the Rutter scale, the statistically significant interaction between exposure and age is evidence of recovery, at a rate that is about the same size as the normal improvement in this test as the children age. On the CBCL, there is only marginal evidence of recovery. The lack of a significant interaction term between year of birth and exposure implies that even the youngest children, those born in 1985, are as severely affected as those born in 1979, right after the poisoning of their mothers. For cognitive function, we estimate a 3-point difference between the exposed and control groups, which is stable as the children age and the same in the younger and older children. Together with our previous observations, these data suggest that exposed children have a mild cognitive deficit up to at least 16 years of age.

The advantage of studies in the exposed cohort in general has been the etiologic clarity offered by the high exposure. The poisonings in Japan and Taiwan, although public health disasters, have provided some of the clearest evidence about the toxic side effects for human beings of these very widely dispersed agents. In this study, we have looked up with relatively few children unavailable, evaluation with instruments that are standard and interpretable in both clinical and community-derived groups of children, reasonable standardization data for the Chinese instruments, and evaluations of both the children's cognitive and behavioral function. The serial examinations coupled with longitudinal analysis techniques allow parsimonious data analysis with simultaneous testing of the hypotheses of interest.

We do not have individual exposure information from the children or the mothers. It is possible to measure PCBs and PCDFs in the fat of blood or adipose tissue. At the time that the study was started, the sample volume requirements for analyses were too high to be useful for children. We collected and analyzed a few samples on a pilot basis, but we had many samples in which the concentrations of PCBs and PCDFs were below the limit of detection and so obtained little quantitative information. We have no data from teachers or from clinical interviews of the children themselves, which might be helpful in interpreting the importance of behavior abnormalities reported by parents in school-aged children and adolescents. The number of children who were affected is fortunately small. The method of analysis that we used, while it allows estimation of both age and cohort effects, assumes linearity for the main effects and multiplicative interaction. Thus, for example, if there were recovery but not until the children reached a certain age, the models might not detect it. In addition, the models do not take full advantage of the matching, and thus for any specific age, they may not be as sensitive as a simple, paired comparison.

Behavior and activity levels, IQ, and school performance have been evaluated in several cohorts exposed perinatally to background levels of PCBs, including one in Michigan, one in North Carolina, and one in the


<table>
<thead>
<tr>
<th>Variables</th>
<th>β (SE)*</th>
<th>Statistics</th>
<th>β (SE)*</th>
<th>Statistics</th>
<th>β (SE)*</th>
<th>Statistics</th>
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<tbody>
<tr>
<td>Intercept</td>
<td>48.89 (2.22)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 22.01</td>
<td>45.37 (2.31)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 19.65</td>
<td>50.11 (2.13)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 23.54</td>
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<tr>
<td>Yucheng children (vs control)</td>
<td>2.77 (0.88)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 3.15</td>
<td>2.24 (0.91)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 2.45</td>
<td>2.55 (0.86)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 2.98</td>
</tr>
<tr>
<td>Age, y</td>
<td>-0.06 (0.24)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 0.25</td>
<td>0.48 (0.25)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 1.90</td>
<td>-0.21 (0.23)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 0.92</td>
</tr>
<tr>
<td>Year of birth</td>
<td>0.30 (0.31)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 0.97</td>
<td>0.42 (0.33)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 1.28</td>
<td>0.38 (0.29)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 1.29</td>
</tr>
<tr>
<td>Girls (vs boys)</td>
<td>-2.47 (0.88)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 2.80</td>
<td>-0.57 (0.92)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 0.62</td>
<td>-3.92 (0.86)</td>
<td>t&lt;sub&gt;29&lt;/sub&gt; = 4.56</td>
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*Estimated regression coefficients (SEs).
In Michigan, when the children were 4 years of age, a composite activity rating was not related to prenatal PCB exposure, but reduced activity was found among children with higher 4-year serum PCB levels. Among 395 Dutch children studied at age 42 months, there was a 3-point deficit on Kaufman preschool assessment battery scales among children at the high end of background prenatal exposure. Cognitive function was measured among the 10-year-olds in Michigan, and those with the highest prenatal exposure to PCBs had full-scale IQ scores about 6 points lower than the children with less exposure.

In North Carolina, using information abstracted from report cards from grades 3 and 4, children with higher PCB exposure, either prenatally or through breast milk, had fewer unsatisfactory marks on their work habits and conduct than those with lower exposures, but the associations were weak and not statistically significant. School grades were unaffected. There was no association between prenatal or postnatal PCB exposure and symptoms of hyperactivity reported by the parents.

Behavioral alterations appear in animals exposed perinatally to PCBs. The most consistent finding is hyperactivity among animals exposed to PCBs in utero, and it was observed in mice, male rats, and rhesus monkeys. One group of rhesus monkeys that had been exposed to PCBs perinatally was hyperactive at 6 and 12 months of age but was hypoactive at 44 months.

The continued mild behavioral disorder and cognitive deficits in these children is likely due to the persistence of the chemicals in their mothers, resulting in in utero PCB and PCDF exposure long after the exposure to the mother ceased. The biological mechanism by which PCBs and PCDFs cause behavioral and cognitive toxicity is unclear and is an area of ongoing laboratory investigation. In the intact animal, behavior and learning have been affected by perinatal PCB exposure in all species tested. Recent investigations have shown changes in hippocampal long-term potentiation, a fundamental plasticity process that reflects the neurophysiologic and biochemical changes that support learning at the synaptic level. One other possible mechanism is that the planar dioxygen-like congeners alter brain corticostereoid levels during development, which changes brain organization and the regulation of dopaminergic systems. The PCBs or possibly their hydroxylated metabolites can interfere with thyroid hormone and estrogen signaling.

Even though PCBs have not been manufactured since the late 1970s, all PCB-containing equipment will have to be disposed of in some way, and 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 PCB exposure can cause behavioral alterations at levels that do not cause clinical symptoms, but the effect is small and difficult to study. The exposed children are the only well-documented cohort with sufficient in utero PCB and PCDF exposure to cause obvious toxic effects. The behavioral and cognitive findings of this cohort may help us to understand the toxic effects of background PCB exposure and also provide new evidence for the causative link between prenatal exposure to toxic substances and behavioral and cognitive problems in children and adolescents.

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REFERENCES


