

# Effect of prenatal exposure to polychlorinated biphenyls on cognitive development in children: a longitudinal study in Taiwan

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**Background** From 1978 to 1979, a group of people in Taiwan were exposed to high levels of heat-degraded polychlorinated biphenyls (PCBs) owing to accidental ingestion of contaminated rice oil. Children born to mothers following the exposure ('Yucheng' children) were known to have hyperpigmented skin and other dysmorphology after birth.

**Aims** To determine the effect of prenatal exposure to PCBs on cognitive development in Yucheng children.

**Method** One hundred and eighteen Yucheng children prenatally exposed to PCBs and degradation products, and community-matched control children who were exposed to background levels only, were followed from 1985 to 1998. The Bayley Scale for Infant Development, Chinese version of the Stanford-Binet IQ Test, Raven's Coloured Progressive Matrices and Raven's Standardised Progressive Matrices were used to assess the cognitive development of these children.

**Results** The Yucheng children scored lower than control children on each of these methods of measurement between the ages of 2 and 12 years.

**Conclusions** Prenatal exposure to PCBs and their derivatives has long-term adverse effects on cognitive development in humans.

**Declaration of interest** None. Funding from the National Science Council, Taiwan (see Acknowledgements).

Polychlorinated biphenyls (PCBs) were widely used as a dielectric in transformers and capacitors, as well as in cables, small electric parts, etc. They became worldwide contaminants by 1969, after which use was prohibited in many developed countries. Polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzodioxins (PCDDs) can be released as by-products of many industrial processes. The former compounds are the most toxic degradation products of PCBs. All these substances have been found in the blood and adipose tissues of people all over the world (Kimbrough, 1985; Jensen, 1987).

Typical human exposures come from environmental contamination of the food supply, and from occupational exposures. Two epidemics of intoxication with heat-degraded PCBs have occurred: in Japan in the 1960s, and in the 'Yucheng' ('oil disease') episode in Taiwan in the 1970s. The cause of these two Asian episodes was consumption of rice-bran cooking oils contaminated with PCBs during processing. The aim of this paper is to summarise the effect of prenatal exposure to PCBs and their derivatives on the cognitive development of children born to mothers who were exposed in the Yucheng epidemic.

## METHOD

### Subjects

In the summer of 1985, we conducted the first field survey of all living children who had been born to mothers poisoned by PCBs and their derivatives in the 1978-1979 incident. A total of 118 children, born between June 1978 and March 1985, entered this study after their parents had given permission. One hundred and eighteen unexposed children were selected as a paired control group, individually matched by gender, age (age difference less than 15 days for those under 1 year of age and less than 1 month for those over 1 year). The difference in the mothers' ages in each pair

was less than 3 years. We also matched for socio-economic status and residential location of the parents. The socio-economic status ratings for the children were based on the educational levels of both parents and the occupational status of the parent with the higher occupational level. The five-point system used to score educational level was: 1 point for 6 years or less of education; 2 points for 7-9 years; 3 points for 10-12 years; 4 points for college level (13-16 years); and 5 points for postgraduate level (more than 16 years). The five-point system for occupational status was: unskilled, 1 point; semi-skilled worker, 2 points; skilled worker, 3 points; semi-professional, 4 points; and professional, 5 points. The total scores of these three variables can range from 3 to 15. As expected, there was no difference in age and socio-economic status scores between Yucheng children and the matched control children. One field study has been conducted each year since 1985.

### Measurements

Four cognitive measurement tools, according to the different ages of the subjects, were used in this study. These were the Bayley Scales for Infant Development (BSID) for those aged from 6 months to 30 months, the Chinese version of the Stanford-Binet IQ Test for those aged 30 months to 6 years, Raven's Coloured Progressive Matrices (CPM) for those aged 5-9 years, and Raven's Standard Progressive Matrices (SPM) for those aged above 9 years. These tests were administered annually to all the children at their homes. Because these cognitive measurement tools have their own age-range limitations, each subject's score was individualised according to the subject's actual age on the date of testing. The Yucheng child and the control child were tested on the same day by the same tester, and random cross-validations were carried out by a senior clinical psychologist (N.W.G.). The examiners were unaware of the children's history of exposure. All examiners held bachelor's degrees in either special education or psychology and were trained and supervised by our senior clinical psychologist.

### Analysis

Student's *t*-test was used to compare the difference in scores at each age level between each of the 118 Yucheng children and their matched controls.

## RESULTS

Data from 1985 to 1998 are available. The mean age of the Yucheng children and the control children on the standard date, 31 August 1985, was 3.6 years.

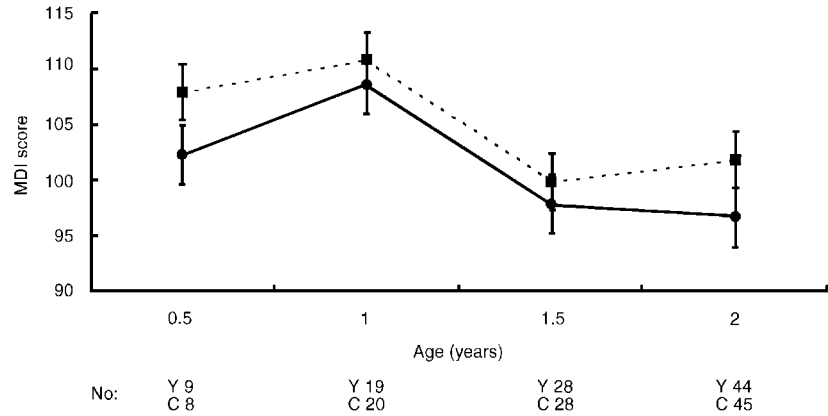
Figures 1 and 2 show comparisons of Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores for Yucheng children and their controls from 6 months to 2 years. The Yucheng children scored lower than the control children at each age level on the MDI scale, and at three out of four levels on the PDI scale, but because of relatively small numbers only one difference – PDI scale at 2 years – was significant at the 0.05 level. Figure 3 shows comparisons of the two groups on Stanford–Binet IQs by age level from 2 years to 5 years. Here also the Yucheng children scored lower at each of the four age levels, significant differences being noted at ages 4 and 5 years. The differences between these two groups at different age levels ranged from 2 to 7 points.

Figures 4 and 5 show the comparisons of the two groups on CPM and SPM at age levels 5–8 years and 9–15 years, respectively. The Yucheng children scored lower than the control children in CPM at ages 5, 6, 7 and 8 years, significant differences being noted at ages 7 and 8 years. Differences between Yucheng children and controls on SPM scores were all in the same direction, and were significant at ages 11 and 12 years. Significant differences were not found after 12 years, suggesting a tendency for the Yucheng children to catch up gradually from around 13 years, a finding that deserves clarification.

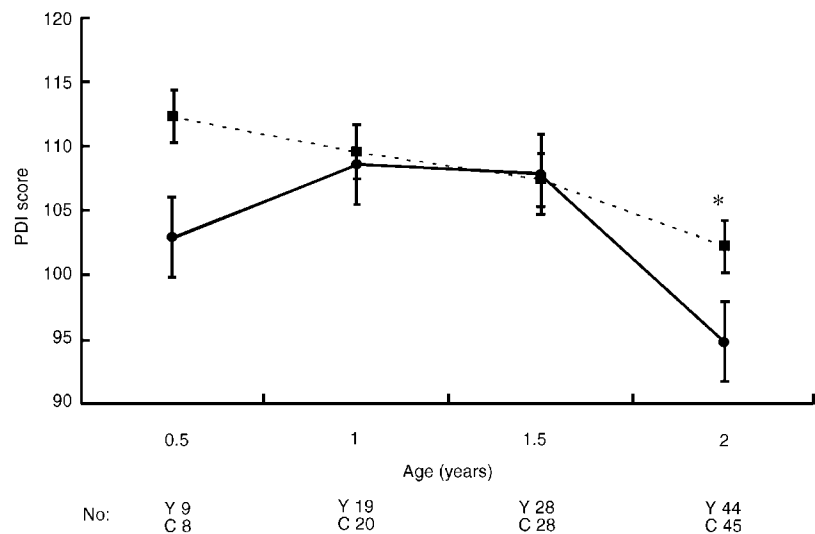
## DISCUSSION

### Effects of PCBs on children

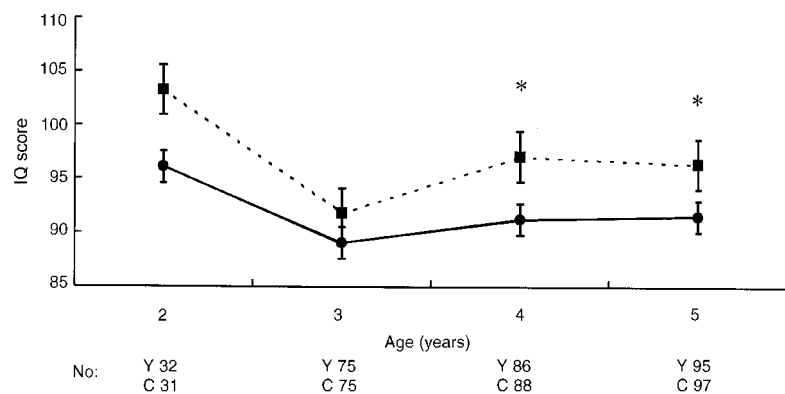
The PCBs had been partially heat-degraded, and were further contaminated with high levels of PCDFs and polychlorinated quarterphenyls (Masuda *et al*, 1986). In 1979, over 2000 persons in Taiwan were intoxicated by heat-degraded PCBs (Hsu *et al*, 1985). Children exposed prenatally to PCBs/PCDFs (Yucheng children) had higher prenatal mortality and lower birth-weight; dysmorphic features at birth such as hyperpigmentation, neonatal teeth, and deformed nails; and delays of developmental milestones (Miller, 1985; Rogan *et al*, 1988). These symptoms were caused not only by PCBs but by their heat-



**Fig. 1** Mental development index (MDI) of the Bayley scale in Yucheng (Y) children (●) and control (C) children (■) in each age group; error bars represent 1 s.e.



**Fig. 2** Psychomotor development index (PDI) of the Bayley scale in Yucheng (Y) children (●) and control (C) children (■) in each age group; error bars represent 1 s.e., \* $P < 0.05$ .



**Fig. 3** Scores of Stanford–Binet IQ test in Yucheng (Y) children (●) and control (C) children (■) in each age group; error bars represent 1 s.e., \* $P < 0.05$ .

degraded products, PCDFs (Kashimoto *et al*, 1985). In humans PCBs, PCDFs and PCDDs have long half-lives, and these compounds have been found to have significant

developmental toxicity in animals (Tilson *et al*, 1990). They are known to cross the placenta and affect the foetus (Kodama & Ota, 1980).

Cognitive development in children prenatally exposed to PCBs and their contaminants has been carefully studied in four cohorts of humans.

(a) Japanese investigators followed 11 Japanese *Yusho* (the same two Chinese characters as Yucheng, i.e. oil disease, as pronounced in Japanese) children living on an isolated small island and found that 6 years later they appeared to be apathetic and inactive, with IQs averaging 70 (Harada, 1976). Harada did not specify the measurement tool used and no control children were studied. Rogan *et al* (1988), who cross-sectionally examined 117 children born between 1978 and 1985 to Taiwanese Yucheng women, reported that congenitally exposed children showed delayed developmental milestones and deficits on formal developmental testing.

(b) A Michigan cohort included 313 newborns, 242 of whose mothers had consumed Lake Michigan fish presumed to be contaminated by PCBs. These exposed infants showed impaired visual recognition memory at age 7 months, which persisted up to age 4 years (Jacobson *et al*, 1985; Jacobson *et al*, 1990).

(c) In North Carolina, children in an exposed cohort were found to have neurological anomalies at birth (Rogan *et al*, 1986) and developmental delays in gross motor function during infancy (Gladen *et al*, 1988).

(d) In Taiwan, previous long-term follow-up studies had noted a consistent tendency which indicated that Yucheng children scored lower on each kind of measurement tool at each age level (Chen *et al*, 1992; Lai *et al*, 1994).

**Findings in auditory event-related potentials**

Chen & Hsu (1994) compared the auditory event-related potentials (P300) in 27 pairs of Yucheng and control children in 1991. This method offers considerable promise as a means of testing children with disorders of cognitive function. Prolonged latencies and reduced amplitude were shown with P300 in Yucheng children, indicating slow cognitive processing and attention deficits. The P300 latencies were also found to be inversely correlated with Wechsler Intelligence Scale for Children-Revised (WISC-R) full-scale IQs. These findings suggest that the reduced developmental quotient and IQ scores in the Yucheng children may have a neurophysiological basis.

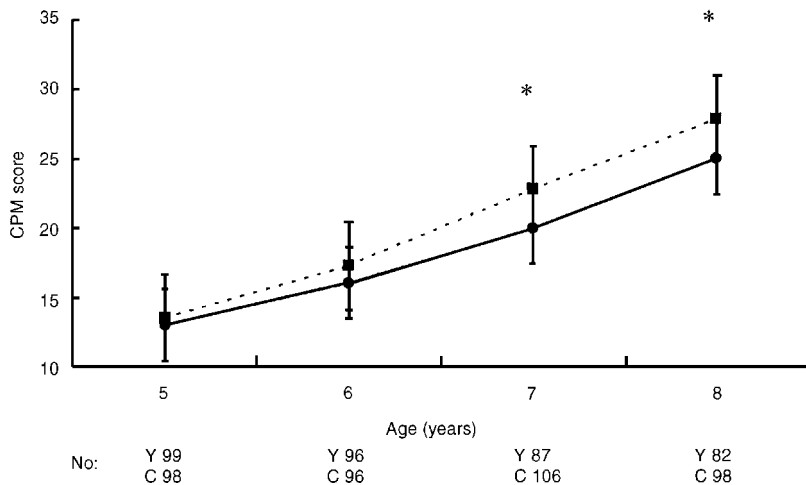
**Other factors that could affect the results**

Yucheng children and control children were similar with respect to socio-economic status, educational level and parental ages. None of the exposed families had any psychiatric history, none of the exposed mothers had ever smoked, and only two exposed mothers had drunk alcohol regularly before – though not after – marriage.

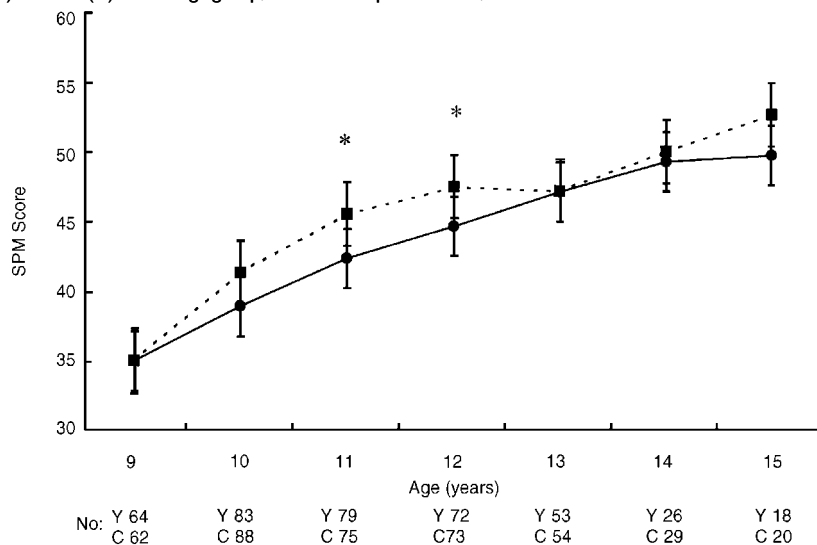
So far as the possibility of learning effects caused by repeated measures are concerned, it appears that the learning increments by children of the two groups were similar.

Serum levels of PCDFs were not previously measured for the mothers of our subjects. Kashimoto *et al* (1985) reported mean blood levels of PCBs and PCDFs in a group of 113 *Yusho* patients as 39 parts per billion (p.p.b.) and 0.076 p.p.b., respectively. In 1991, analysis of serum levels in a randomly selected subgroup of Yucheng children in this study (Guo *et al*, 1994; Ryan *et al*, 1994) showed median levels of 106 ng/kg lipid, 160 ng/kg lipid and 1.3 ng/kg whole weight for 2,3,4,7,8-PnCDF, 1,2,3,4,7,8-HxCDF and total PCBs, respectively: levels much higher than those of a pooled serum sample of the matched control children (19 ng/kg, 23 ng/kg and 0.17 ng/kg, respectively).

Raven's Progressive Matrices are considered to be relatively culture-fair and have been used to evaluate the general intelligence factor, i.e. Spearman's *g* factor (Raven, 1983; Raven *et al*, 1985). These matrices assess a person's ability to form comparisons and to reason by analogy as well as to show to what extent the subject is capable of organising spatial perceptions



**Fig. 4** Scores of Raven's Coloured Progressive Matrices (CPM) in Yucheng (Y) children (●) and control (C) children (■) in each age group; error bars represent 1 s.e., \*P < 0.05.



**Fig. 5** Scores of Raven's Standardised Progressive Matrices (SPM) in Yucheng (Y) children (●) and control (C) children (■) in each age group; error bars represent 1 s.e., \*P < 0.05.

into systematically related wholes. Our findings of reduced CPM and SPM scores were consistent with results of the previous assessments in the Yucheng children. A tendency towards a ceiling effect in the SPM scores has been noted since the 1998 field survey, and we are now trying to use another measurement tool, Advanced Progressive Matrices (APM), to minimise this effect.

There may be several reasons why the cognitive functions of Yucheng children were more severely affected than those of the Michigan and North Carolina cohorts. The main reasons may be that Yucheng exposure involved PCBs with PCDFs, terphenyls and quarterphenyls, and that the total quantity of exposure to PCBs and related chemicals was much higher than in the US cohorts.

Although many studies have been done on the toxicity and mechanisms of PCBs and related compounds, the two Asian outbreaks represent the only known cases of clinically obvious PCB/PCDF poisoning in large groups of adults and children. This particular study is the only prospective longitudinal follow-up study on more than 100 prenatally exposed children. Findings from studying the vicissitudes and possible correlates of the adverse effects on Yucheng children as they grow older will provide important information about the toxicity, health effects and mechanisms of prenatal exposure to PCBs, CDFs and PCDDs.

## CLINICAL IMPLICATIONS

A recent report on serum levels in the Yucheng cohort indicated that the Yucheng mothers had serum levels about seven times that of the background level 13 years after the exposure episode (Ryan *et al*, 1994). Some of the background population, especially those who consume large amounts of food from contaminated sources such as Lake Michigan fish, may have similar serum levels to the Yucheng mothers.

Our findings of poorer cognitive development in Yucheng children indicate that subsets of the general population can be at risk of cognitive changes, even with background levels of exposure.

## LIMITATIONS

Following the cognitive development of the Yucheng children as they grow to adulthood will shed more light on the long-term

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adverse effects of prenatal exposure to PCBs, PCDFs and PCDDs.

Because of the expense of the procedure, we have been unable to carry out further analysis of serum levels of PCBs and their degradation products. We hope to have more samples analysed at National Cheng-Kung University, Taiwan, in order to assess the dose-response relationship. We also need more sophisticated measurement tools to evaluate the cognitive development, neuropsychological and other psychiatric problems in the Yucheng children.

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