Growth Abnormalities in the Population Exposed *in Utero* and Early Postnatally to Polychlorinated Biphenyls and Dibenzofurans

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This article reviews the findings in children exposed to various levels of polychlorinated biphenyls (PCBs) and related compounds *in utero* and early postnatally. Yu-Cheng ("oil-disease") mothers were Taiwanese women exposed to PCBs and their heat-degradation products from the ingestion of contaminated rice oil in 1979. Children of these mothers were born growth retarded, with dysmorphic physical findings, and delayed cognitive development compared with unexposed children. In this article, findings in Yu-Cheng children born between 1978 and 1985 are summarized and compared with two other well-documented cohorts of children prenatally exposed to different levels of PCBs. Results of the investigation in Yu-Cheng children will provide important information about the toxicities, health effects, and mechanisms of PCB/PCDF exposure and demonstrate that the developing human is more sensitive than the adult to the toxic effects of these chemicals. — Environ Health Perspect 103(Suppl 6): 117–122 (1995)

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Background

Polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzodioxins (PCDDs) are ubiquitous environmental pollutants found throughout the world and in all human populations. The PCDFs and PCDDs are produced and released into the environment during many industrial processes such as chlorine bleaching, incineration, and manufacture or disposal of chlorine-containing products. PCBs were manufactured for many purposes, including lubricants for heavy machinery, dielectric fluid in transformers, and even for use as emersion oil for microscope slides. PCBs were recognized as potentially harmful environmental contaminants in the 1970s (*1*), and their use and manufacture were prohibited in many countries. Despite the ban on PCBs, PCBs, PCDFs, and PCDDs will be found in the environment for decades to come because of their long half-life in the environment (*2*).

The primary route of human exposure to these chemicals is through contaminated food such as meat and fresh-water fish (*3*). PCBs and their heat degradation products have long half-lives in humans (*4*), cross the placenta (*5,6*), and are excreted in breast milk. Prenatal exposure to PCBs and PCDDs have caused significant teratogenic and developmental toxicities in animals (*7*). In the human, transplacental and possibly transmammillary exposure has caused severe adverse effects (*8*). The developing human is more susceptible to PCB-induced toxic effects than the adult. The toxic effects seen in children are more severe and affect more organ systems than those seen in adults. These effects may persist throughout the child's entire life-span, while in the adult only part of the subject's life-span may be affected. The objective of this article will be to review the developmental toxicology data of the children most severely affected by these chemicals, the Yu-Cheng (Yu-Cheng means "oil disease" in Chinese) cohort of Taiwan, and compare these effects to those in their matched control subjects and two other PCB-exposed cohorts of U.S. children not so severely affected.

These three cohorts of children prenatally exposed to different levels of PCBs and related compounds all have been carefully followed. They are *a*) North Carolina children exposed to background PCB levels, *b*) children born to women who reported moderate consumption of Lake Michigan sport fish during pregnancy, and *c*) Taiwanese Yu-Cheng children. This article focuses on the Yu-Cheng children, with reference and comparison to findings of the other two groups.

Populations

Yu-Cheng Cohort

In 1979, over 2000 Taiwanese people ingested rice oil contaminated with PCBs and PCDFs. They developed chloracne, hyperpigmentation, peripheral neuropathy, and other signs and symptoms that later were called Yu-Cheng in Taiwan and were very similar to Yusho disease described in the 1970s in Japan. The outbreak and the discovery of the etiology of Yu-Cheng have been reviewed elsewhere (*9*). Repeated heating of the contaminated rice oil partially degraded the PCBs into PCDFs and polychlorinated terphenyls and quarterphenyls (PCTs and PCQs) (*10*). Some congeners of these PCDFs, e.g., 2,3,4,7,8-pentachloro-dibenzofurans (PnCDF), are

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highly toxic in animals, with potencies approaching those of the most toxic PCDDs, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in animal and *in vitro* studies (*11*).

Of 39 Yu-Cheng babies *in utero* during the time the mothers ingested the contaminated oil, eight died in the first few years of life (*9*). In September 1985, a field survey was conducted of 128 living children who were *in utero* during or after the period of oil contamination. History and physical examination of these children's development were performed and compared with those of 117 controls (*12*). The parents of 118 Yu-Cheng children gave permission for their children to be followed yearly. For the followup study, an unexposed child was selected as a control for each Yu-Cheng child, matched for neighborhood (same township), age (within 15 days for those under one year, and within one month for those older), sex, mother's age (within 3 years), parents' combined educational level (within about 3 years for the total), and occupation (within 1 class of 5 classes from unskilled laborer to professional).

Between the years 1985 and 1990, mental and cognitive development were studied regularly in these two groups of children. In February 1991, the Yu-Cheng children and their controls were invited to come to National Cheng Kung University Hospital for examination. Seventy-three of the 118 Yu-Cheng children and 69 of the control children (55 pairs) appeared and examinations were made of their growth profiles and structures of the joints. Again in 1992, these children were examined in the local health offices or in their homes by our investigators.

North Carolina/Michigan Cohorts

In North Carolina, 930 children born to mothers who had no unusual PCB exposure were followed from birth (*13*). In Michigan, 242 children whose mothers consumed moderate quantities of contaminated Lake Michigan fish and 71 children whose mothers did not eat such fish were followed from their birth (*8*). Levels of PCB exposure, growth, and development have been assessed in both cohorts.

Exposure Levels

In the Yu-Cheng cohort, the adults were estimated to have consumed an average of 1 g of PCBs and 3.8 mg of PCDFs during an average of 9 months of exposure to the contaminated oil (*14*). Serum PCB concentrations were measured in the mothers close to the end of pregnancy. The serum PCB values were log normally distributed in the exposed mothers; the arithmetic mean was 49.3 parts per billion (ppb), and the median was 26.8 ppb. Serum levels of PCDFs were not measured. However, Kashimoto et al. (*15*) measured blood levels of PCBs and PCDFs between 1979 and 1981 in a group of 113 Yu-Cheng patients in a school for the blind children in Taichung county, who had been exposed to the same contaminated rice oil as our subjects' mothers. They had average blood levels of 39 ppb PCBs and 76 part per trillion (ppt) PCDFs on a whole blood basis. Assuming an average hematocrit of 45 and lipid content of 0.35%, their values for total PCBs of 39 ppb in whole blood would be converted to 71 ppb in serum, approximately 40% higher than the average level of PCBs in our subjects' mothers around delivery. If we assume a 1:3 ratio in contents of PnCDF:1,2,3,4,7,8-hexachlorodibenzofurans (HxCDF) in the serum, Kashimoto's PCDF value of 76 ppt would be converted to approximately 10,000 ppt of PnCDF and 30,000 ppt of HxCDF on a serum lipid basis. If our subjects' mothers had similar PCDF and PCB serum ratios, their serum PnCDF level can be estimated as 6940 ppt, and HxCDF 20800 ppt on a serum lipid basis around the time of delivery of Yu-Cheng children. The average serum level in 20 subjects' mothers in February of 1992, i.e., about 10 years after previous measurements, was 1507 ppt of PnCDF and 3583 ppt of HxCDF on a serum lipid basis, and 9.6 ppb of total PCBs on a whole weight basis (Guo L, Ryan J, Hsu CC, unpublished data).

The average serum level in 14 serum samples of Yu-Cheng children in February 1991 was 167 ppt of PnCDF and 362 ppt of HxCDF on a serum lipid basis, and 1.5 ppb of total PCBs on a whole weight basis (*16*). The serum concentrations of PCBs and PCDFs were still much higher than those in a pooled serum sample of matched control children (0.5 ppb of PCBs, whole basis; 19 ppt PnCDF and 23 ppt HxCDF, lipid basis).

Maternal serum concentrations of PCBs averaged 4.7 to 5.9 ng/ml in the Michigan group, and infants' cord blood serum levels averaged 2.0 to 2.5 ng/ml (*17*). The relationship between maternal and cord serum level allows us a very rough estimate of a 1:2 ratio between cord and maternal serum levels.

The median maternal serum PCB level was 9.06 ppb, corresponding to the median milk PCB level of 1.77 ppm (fat basis) in the North Carolina cohort; median cord serum level was less than half the median maternal serum level (*18*). PCDFs were not measured in either U.S. study, but they tend not to be found at any substantial level in the U.S. exposures.

Cohorts History and Physical Findings

A summary of the history and physical findings that will be discussed is in Table 1.

Forty-nine newborns delivered to Yu-Cheng women between 1979 and 1985 had 500 g lower gestational age-adjusted birth weights than those of the controls (*19*). The deficits were present in both female and male exposed babies, and the first and second children born after the outbreak were more affected than the third child. A persistent delay in growth in Yu-Cheng children was observed by examination in 1985 (age range, 6 months–7 years) and again in 1991 (age range, 6–13 years). The Yu-Cheng children were 7% lighter ($p < 0.01$) and 3% shorter ($p < 0.05$) than controls (*12*). In February 1991, the Yu-Cheng children were still shorter than their controls by 3.1 cm (2.3%, $p < 0.01$), but weights did not differ between these two groups (*16*). There was no difference in the weight, joint laxity, total bone mineral density, and total and percent body fat between Yu-Cheng and control groups. Total lean mass and soft tissue mass were significantly lower in Yu-Cheng children.

Offspring of the Michigan group that had consumed fish with cord serum PCB levels of 5.0 ng/ml or more had decreased birth weights of approximately 160 to 190 g compared to the lower exposed children (*8*). At 4 years of age the PCB-induced growth-retarded children weighed 1.8 kg less than the children who were exposed the least (*20*). The effect on weight was significant for girls but not for boys. This reduction in weight correlated with their cord blood serum PCB level at birth but not with PCB levels at 4 years of age. These children also had reduced head circumferences of 0.6 to 0.7 cm at birth compared with those of their controls. Head circumferences were similar at time of re-examination at 4 years of age. In the North Carolina children, lower birth weights were not associated with high background PCB exposures.

Dermatological Findings

According to parents' histories, the Yu-Cheng children had increased rates of

Table 1. Health or physical findings in Yu-Cheng children compared with matched controls at different times of assessment.

Physical characteristic	Birth[a]	1985[b]	1991[c]
Weight	15% lower# (12)	7% lower** (12)	Not different (16)
Height		3% lower* (12)	3.1 cm (2.3%) shorter** (16)
Total lean mass			9.5% lower* (16)
Total body fat or percent body fat			Not different (16)
Skeletal mineralization			Not different (16)
Joint laxity			Not different (16)
Hyperpigmentation	43% vs 2%# (12)	Head or face: 11% vs 4%* (12)	None (22)
Dystrophic nails	25% vs 1%# (12)	Fingers: 16% vs 1%#	Grooving: 25% vs 1%# (22)
		Toes: 63% vs 21%# (12)	
Acne	13% vs 0%# (12)	17% vs 9% (including acne scars) (12)	None (22)
Frequency of respiratory infection		30/124 vs 5/115#	27/56 vs 8/56#
		(bronchitis or pneumonia in first 6 months) (12)	(more than once per month) (42)
Chronic otitis media			10/56 vs 0/56# (42)
Presence of soft neurological signs			10/27 vs 6/27 (29)
Latency in P300			7.6%–8.1% longer* (29)
Amplitude in P300			22%–24% lower* (29)
P-VEPs and SSEPs			Not different (29)

*$p<0.05$; **$p<0.01$; #$p<0.005$. [a]Data acquired by history. [b]Data acquired by examination of 128 Yu-Cheng and 117 control children. Age range 6 months to 7 years. [c]Data acquired by examination history of 56 pairs. Age range 6 to 13 years.

hyperpigmentation, eyelid swelling and discharge, deformed nails, acne, natal teeth, and swollen gums compared to controls (*21*). Examination in 1985 showed that the exposed children had more pigmented or dystrophic nails, acne, and hyperpigmentation. In the examination during 1991 and 1992, Yu-Cheng children had significantly higher risks of nail deformities than controls. However, there were no residual findings of acne or hyperpigmentation. The main nail findings were transverse coarse grooves and irregularly concaved depression in 25% of children (*22*), with predilection for thumbs, followed by big toes and other fingers. Those children born closer to the mothers' intoxication had more nail deformities than those born later. In some Yu-Cheng children, improvement of the nail changes was observed between 1991 and 1992 examination in that the coarse grooving had become irregular depressions (*22*). The typical nail changes found in prenatally exposed children but not in the directly exposed population suggested prenatal damage of the nail matrix. No abnormal dermatological findings were reported in the children from the Michigan or North Carolina cohorts.

Cognitive Developments

Of the 33 developmental milestones recorded, the Yu-Cheng parents reported 32 that were achieved later in their children than in controls, with many of these differences being statistically significant (*23*). A similar delay was observed by neurologist's examination.

A widely used instrument for evaluating high-risk children, the Bayley Scale of Infant Development, was administered to children 6 months to 2.5 years of age. The Bayley scale consists of two subscales, a mental development index and a psychomotor development index. Yu-Cheng children scored lower in both mental (100 vs 106, $p<0.05$) and psychomotor indexes (101 vs 108, $p<0.05$) compared to their controls (*23*).

In the assessment of cognitive development between 1985 and 1990 (*24*), the Yu-Cheng children scored approximately 5 points (0.30 SD) lower than their matched controls on the Stanford-Binet test at 4 and 5 years of age and approximately 5 points (0.40 SD) lower on the Wechsler Intelligence Scale for Children, Revised, at 6 and 7 years of age. The children born up to 6 years after their mothers' intoxication were affected in ways similar to those children born immediately after the episode.

Both U.S. studies used Brazelton Neonatal Behavioral Assessment Scales to evaluate psychoneurologic functioning in infants. Both studies detected primarily motor effects within the Brazelton Assessment in infants with the highest cord serum PCB levels. In the Michigan cohort assessed at 7 months (*20*), impaired cognitive functioning was seen on Fagan's test of visual recognition memory in children with cord serum PCB levels in the upper 25% of the cohort, i.e., 3.6 to 7.9 ng/ml. This level corresponds to maternal serum levels of approximately 7 to 17 ng/ml at birth. In the North Carolina cohort, children in the upper 5 to 10% of transplacental exposure to PCBs (greater than 3.5 ppm in maternal milk fat) were associated with lower psychomotor development indices, as determined by Bayley's test at 6, 12, 18, and 24 months of age (*25*). No association was detected between prenatal PCB exposure and Bayley's Mental Development Index. When the Michigan cohort was assessed at 4 years, a higher cord serum PCB level predicted poorer performance on verbal and memory subtests of McCarthy Scales of Children's Abilities. The highest exposed group, with cord serum PCB levels of 5.0 to 12.3 ng/ml (corresponding to maternal serum levels of 11–25 ng/ml), had most apparent deficits in both verbal and memory scale scores (*26*). However, no association was found between prenatal PCB exposure and McCarthy scores in the North Carolina cohort (*27*).

In the two U.S. studies, postnatal exposure to background levels of PCBs through breast milk did not affect developmental test scores (*25,26,28*).

Table 2 summarizes the cognitive and behavioral development at different age levels in Yu-Cheng children compared with those of their matched controls.

Neurological Findings

In February 1991, 27 pairs of Yu-Cheng and control children were randomly selected to have an extensive neurological evaluation with auditory event-related potentials (P300), pattern visual evoked potentials (P-VEPs), and short-latency somatosensory evoked potentials (SSEPs) (*29*). The P300 have proved to be useful in evaluating the function of information processing, in which latency relates to the speed of solving cognitive tasks (*30*), and

Table 2. Summary of results of cognitive and behavioral scores between Yu-Cheng children and their controls.[a]

Age	1	2	3	4	5	6	7	8	9	10	11
Bayley: mental scale[b]	–4.8 (18)	–6.7 (40)*									
Bayley: psychomotor scale[b]	–6.8 (18)	–7.9 (40)#									
Stanford–Binet IQ score[c]				–5.5 (87)*	–5.0 (95)#						
WISC–R full scale IQ score[c]						–4.7(100)**	–5.7 (87)#				
Rutter scale (health, habit and behavioral problems)[d]			2.3 (69)*	2.4 (80)#	1.8 (91)*	3.7 (110)#	3.1 (99)#	2.0 (83)*	3.5 (60)#	2.2 (39)	1.9 (27)
Activity scale[d]			7.1 (74)#	3.8 (87)*	4.7 (94)**	4.5 (110)#	4.0 (111)*	6.0 (89)#	3.6 (71)	4.0 (51)	4.1 (34)

*$p<0.05$; **$p<0.01$; #$p<0.005$. [a]Numbers shown are means of difference (Yu-Cheng minus control) and numbers of pairs (in parentheses). [b]From Yu et al. (*23*). [c]From Chen et al. (*24*). [d]From Hsu et al. (*38*).

amplitude relates to the frequency of the occurrence of target stimulus, reflecting the concentration ability (*31*). In children, low amplitude in P300 has been associated with attention deficits and reading disabilities (*32,33*) and greater latencies with cognitive impairments (*34*). P-VEPs and SSEPs are noninvasive techniques for evaluating visual and somatosensory afferent pathways from the peripheral to the central nervous system (*35,36*). No abnormalities were found in the neurological examinations of Yu-Cheng and control children. Soft neurological signs were present in both groups: 10 of 27 Yu-Cheng children and 6 of 27 control children. Prolonged latencies (356 vs 329 msec, $p<0.01$; and 356 vs 331 msec, $p<0.05$, at two scalp recording positions) and reduced amplitude (13.9 vs 17.3 mV, $p<0.05$; and 14.0 vs 17.1 mV, $p<0.05$, at two positions) were shown with P300, indicating slowed cognitive processing and attention deficits in Yu-Cheng children than in controls. Latencies were inversely correlated with WISC-R full-scale intelligent quotient (IQ). No conduction abnormalities were shown with P-VEPs and SSEPs. These findings suggested that sensory afferent pathways were not affected in Yu-Cheng children, and the reduced IQ scores might be due to slowed cognitive processing and/or attention deficits. Neither of the U.S. cohorts were assessed using these tools.

Behavior and Activity

Rutter's Child Behavior Scale A (*37*) was used to assess the behavior of Yu-Cheng and control children aged 3 or older. Rutter's Scale is a screening instrument, completed by main caretakers of the child, to identify children likely to show problems in health, habits, and behaviors. Higher scores on this scale represent more problems. Yu-Cheng children consistently scored higher than their controls between age 3 and 9 years (*38*). At present there are too few subjects tested at age 10 or older to determine whether the behavioral problems continued.

A Chinese version of the modified Werry-Weiss-Peters Activity Scale (*39*) was used for children aged 3 to 12 to evaluate the children's activity level. Yu-Cheng children scored 8 to 53% higher than their controls at each age, and the differences were significant in six age groups (*38*).

Both U.S. cohorts presented a different picture from Yu-Cheng children in the activity assessments. In the North Carolina cohort, using the information abstracted from report cards, no association was found between exposure and hyperactivity reported by parents (*40*). In Michigan, composite activity ratings were obtained based on examiners' ratings from two home visits and mothers' ratings on the Activity Scale of Buss and Plomin Emotionality Activity Sociability Temperament Survey for Children (*26,41*). The composite activity rating was negatively related to the 4-year serum PCB level in a dose-dependent fashion, and the children with serum PCB levels of 9 ng/ml or greater had the lowest activity ratings. Because the children's 4-year serum PCB levels were related to breast feeding, it is possible that postnatal exposure to PCBs had a different effect on activity than prenatal exposure. Another possibility is the nature of exposure to different mixtures; the Yu-Cheng children were exposed to much higher levels of PCDFs than the U.S. cohorts.

Immunology/Infectious Diseases

The Yu-Cheng children had histories of more frequent bronchitis, upper respiratory infections, and ear infections, as reported by the parents in 1985 and 1992 (*12,42*). On physical examination the Yu-Cheng children had more frequent chronic ear infections and abnormal auscultory findings of the chest. Neither of the U.S. cohorts reported similar findings.

Metabolic

Excessive or abnormal porphyrin production occurs as a result of altered enzyme activity in the heme biosynthesis pathway. Because 15% of heme is produced in the liver, damage to the hepatocyte membrane causes abnormal urinary porphyrin excretion, a condition known as hepatic porphyria (*43*). PCB exposure in animals caused type B hepatic porphyria, which is characterized by a urinary uroporphyrins/coprophyrins ratio of greater than one (*44*). Spot urine porphyrins were measured in 1985 for 75 Yu-Cheng children and 74 controls. Average total porphyrin excretion was higher in the Yu-Cheng children (95 vs 81 mg/l), and more Yu-Cheng children had total urinary porphyrin concentrations greater than 200 mg/l (11 vs 3%) (*45*).

Endocrine and Sexual Development

Calcium metabolism in the Yu-Cheng children was studied in 1985, since their physical examinations revealed tooth chipping and their parents had reported observing prenatal and fragile teeth (*12*). The children had essentially normal blood levels of parathyroid hormone, vitamin D, serum calcium, alkaline phosphatase, and phosphate, and no difference in skeletal mineralization was observed using Dual-photon absorptiometry compared to controls (*16*). In a preliminary study on sexual development (*46*), penile length was measured in 55 pairs of Yu-Cheng boys and their controls. Boys aged 11 to 14, who were born in the earlier years after their mothers' intoxications, had reduced penile length compared to those of their controls. The effects of PCBs/PCDFs on the reduced body height and length of penis might be due to hormonal effects of the toxins, since animals exposed to these chemicals have hormone dysfunction and altered sexual maturation (*47–50*). Further evaluation on sexual development is needed to confirm the above findings.

Later-born Yu-Cheng Children Cohort

Children born to Yu-Cheng mothers or Yu-Cheng fathers between July 1985 and December 1991 recently have been

identified (*51*). The effects of PCB/PCDF exposure on later-born children were examined with the Chinese Child Developmental Inventory (*52*). The PCB/PCDF toxicities of developmental delays were observed in the offspring with maternal exposure but not in those with paternal exposure.

Conclusion

The Yu-Cheng cohort represents one of the largest groups of children prenatally exposed to environmental PCBs/PCDFs. Although it has been 15 years since the Yu-Cheng outbreak, the chemicals still persist in mothers' bodies and the Yu-Cheng children continue to demonstrate adverse effects from their mothers' exposures. Careful followup and proper selection of controls of the Yu-Cheng children allowed epidemiologic studies to provide reliable information of physical, cognitive, and behavioral effects. Many research protocols presently are being carried out in the Yu-Cheng cohort and their control subjects. Assessment of neurobehavioral development, sexual development, and maturation will continue to be followed in Yu-Cheng children, as the earlier-born children will go through puberty in the next few years. Induction of cytochrome P450IA2 activity in the liver will be tested with the caffeine breath test (*53*), and the effect of altered enzyme activity on the metabolism of sexual hormones and sexual development will be examined. PCB and PCDF congener blood levels will be measured, and the relationship of blood chemical levels to physical findings will be evaluated. A better assessment of mothers' levels of exposure and continual followup examinations of children born to intoxicated mothers may provide important information on the dose–response relationships of PCBs and related chemicals to developmental toxicities.

There are several possible reasons why Yu-Cheng children were more severely affected than U.S. cohorts. The most likely reason is that the Yu-Cheng exposure involved PCBs with PCDFs and terphenyls and quaterphenyls; also the total exposure to PCBs and related chemicals were higher than those of the U.S. cohorts.

Despite widespread concern and a more careful attitude about PCB/PCDF/PCDD contamination in the environment, the potential for children's exposure to these chemicals is widespread through the food chain, improper incineration or disposal, or industrial accidents. Findings from studying the Yu-Cheng children will provide important information about the toxicities, health effects, and mechanisms of PCB/PCDF/PCDD exposure.

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