NEUROCOGNITIVE EFFECTS OF ACCIDENTAL EXPOSURE TO PCBS AND PCDFS IN TAIWANESE YUCHENG COHORT

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Abstract
In 1979, approximately 2000 people were exposed to rice oil contaminated by polychlorinated biphenyls (PCBs) and dibenzofurans (PCDFs) in central Taiwan. This investigation was conducted to compare neurocognitive functioning between people exposed to PCBs/PCDFs and unexposed sex- and age-matched neighbors. A retrospective cohort study among exposed and unexposed subjects aged 60 years or older with prospective outcome measurements was conducted. Neurocognitive tests including cognition, memory modalities, learning, motor and sensory function, mood and daily activity were evaluated. Totally 166 (57%) exposed and 162 (61%) controls completed this study. Exposed subjects were found to have reduced functioning in attention and digit span (ADS), visual memory span (VMS), learning ability, trials 4 and 5 of visual memory recalls (VMR) ($p < 0.05 \sim 0.0002$), and 30-minute delayed recall of VMR ($p=0.06$). There were no difference in Mini-Mental State Examination (MMSE), digit symbol (DS), motor, sensory, depression (by GDS-S) and activity of daily life (ADL) between the groups. We conclude that neurocognitive deficits in certain aspects of attention, visual memory, and learning ability were found in people previously exposed to PCBs/PCDFs.

Introduction
PCBs and PCDFs are persistent environmental pollutants that induce a broad spectrum of toxic effects in mammalian species.[1] Over 2000 Taiwanese people in 1978-79 ingested rice oil accidentally contaminated with PCBs and PCDFs.[2] They developed chloracne, hyperkeratosis, peripheral neuropathy, and other signs and symptoms. Such event was called "Yucheng" meaning "oil-syndrome" in Chinese. Children of Yucheng mothers prenatally exposed to the toxicants had intrauterine growth retardation, dysmorphic and hyperpigmented skin and nails, and reduced neurocognitive development.[3] However, information concerning the effects of PCBs/PCDFs on neurocognitive functioning among directly exposed population is lacking.

Materials and Methods

The details of this cohort and the matched unexposed subjects are described previously.[2] All subjects had ceased exposure since 1980 with notification of the Yucheng event. For the neurocognitive functioning study, only Yucheng and unexposed subjects aged 60 years or older were recruited. A phone-interview was conducted to review medical history and general health status. The individuals were then invited to participate in neurocognitive examinations by home visit. Among those agreed to participate, neurocognitive tests were administered by interviewers during one home visits, with a standardized neurobehavioral battery, including intelligence, verbal, learning and memory, visual-constructive and organizational skills, sensory tactile function and motor performance. The Mini-Mental State Examination (MMSE), Attention and digit span (ADS) of the WAIS-R, the Digit Symbol (DS), the Verbal Memory Recalls (VMR) with 30 minutes delayed recall test, Visual Memory Span (VMS) from the WMS-R, a Finger-Tapping Serial, the Sensory Tactile Performance, the Geriatric Depression Scale-Short Form (GDS-S), and the Activity of Daily Life (ADL) scale was used. All tests were estimated to require 90 minutes. Test-retest was performed in a random sampling of 20 subjects, with stable reliability in MMSE (0.85), DS (0.66), ADS (0.69), VMS (0.73) and delayed recall (0.77) after 4 months.

Results and Discussion
A total of 166 (57%) exposed and 162 (61%) unexposed subjects completed the study satisfactorily. Average age was 69.5 ± 5.9 years (range, 60.0 to 91.1 years), and the mean educational level was 4.3 ± 3.5 yrs. Exposed participants had a lower performance than did controls on most neurocognitive tests. The average testing time

was 72.9 ± 22.1 minutes. The body height, weight, body mass index (BMI), self-reported smoking habit, and consumption of alcohol of the participants were not different between exposed and unexposed groups. The exposed subjects exhibited a greater decline in the test scores than the controls, with significance in learning ability, trials 4 and 5 of the VMR, ADS-forward, ADS-total, VMS-backward, VMS-total, and trending for significance in total VMR and delayed recall (Table 1). No differences in MMSE, DS, ADL, GDS-S, and motor and sensory modality were noted by adjusted potential confounding.

Our scores, on average, were similar to the data from people in northern Taiwan, but slightly higher than the data from the south.[4,5] Variable test items and cultural and learning differences were presumed to render the MMSE hard to use as an indicator of a toxic effect. In the VMR, the summation of five recall trials showed a tendency toward significance (p=0.06), with significance in trial 4 (p=0.02) and trial 5 (p=0.02). The exposed participants had a lower learning ability than the non-exposed subjects before and after adjusting the confounders (p=0.04 vs. p=0.03). The 30-minute delayed recall also showed a trending decline in the exposed group (p=0.06). The exposed subjects had lower cognitive scores than the controls in the VMS-backward (p=0.05), VMS-total (p=0.04), ADS-total (p=0.001), and ADS-forward (p=0.0002), with clear statistical difference. However, there was a negative correlation in the executive Finger-Tapping serials and GDS-S, with higher scores reflecting worse outcomes, and a positive correlation in sensory and perceptive modalities and ADL, with higher scores indicating better outcomes, although without statistical significance between the two comparisons. All the above findings pointed to the learning and memory domains, no matter whether visual or auditory, short-term or long-term. These observations were similar to those in an adult cohort of Michigan Lake fish eaters, exposure to PCBs, that impaired neuropsychological tests was found in certain areas of memory and learning. [6]

The effects of serum PCBs and cognitive performance were also tested using linear or multivariate regression models. PCB levels were estimated in drawn pooled blood, from 1980 to 1982, using gas chromatographic mass analysis. The linear decay of serum PCBs by years, similar to changes in environmental PCB levels over time, was reported in the literature (Blank et al. 2000). When we stratified PCBs into variables of higher (≧90 ppb), medium (31-89 ppb) and lower (≦30 ppb) exposures, non-significant trending declines in the 30-minute delayed recall (p=0.15), ADS-backward (p=0.25), VMS-forward (p=0.20), VMS-backward (p=0.19), DS (p=0.67), learning ability (p=0.06), VMR total recalls (p=0.49), trial 4 (p=0.17), and trial 5 (p=0.15) were identified. However, the effects of medium and high PCB level in ADS-forward (p=0.002) were clearly seen in the post-hoc analysis (Table 4).

In conclusion, this study found neurocognitive deficits in certain aspects of attention, visual memory, and learning ability in people previously exposed to PCBs/PCDFs as compared to unexposed neighbors.

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Table1. Neurocognitive tests of exposed and control groups, adjusting for potential confounders.

Study subjects (N)	Control (162)	Exposed (166)		
Tests \ Scores	Mean±SE	Mean±SE	Crude P	Adjusted P
MMSE	24.10±0.24	23.58±0.23	0 .23	0.12
Trials of VMR	28.48±0.62	26.89±0.59	0.59	0.06+
Learning ability	3.65±0.22	2.97±0.21	0.21	0.03*
Delayed recall in 30 min	5.60±0.23	5.01±0.22	0.22	0.06+
DS	24.82±0.90	22.49±0.88	0.88	0.07
ADS-forward	12.13±0.19	11.10±0.18	0.18	0.0002*
ADS-backward	4.44±0.16	4.09±0.16	0.16	0.12
ADS-total	16.55±0.30	15.20±0.28	0.28	0.001*
VMS-forward	6.97±0.13	6.70±0.12	0.12	0.13
VMS-backward	4.80±0.14	4.43±0.13	0.13	0.05*
VMS-total	11.76±0.23	11.11±0.22	0.22	0.04*
Finger tapping serials				
Dominant hand	26.27±0.80	27.04±0.76	0.76	0.49
Non-dominant hand	23.46±0.75	25.41±0.72	0.72	0.07
Luria's Sensory Scores				
Dominant hand	52.19±0.75	51.92±0.72	0.72	0.97
Non dominant hand	42.19±0.70	41.69±0.66	0.66	0.70
2-point discrimination	12.96±0.18	12.75±0.18	0.18	0.42
GDS-S	6.85±0.24	6.82±0.21	0.21	0.89
ADL	97.6±1.20	96.3±1.07	1.07	0.29

1. Adjusted for age, sex and education, with significant (*), and trending for significance (+).
2. MMSE=Mini-mental state examination, VMR=verbal memory recalls, DS=digit symbol, ADS=attention and digit span, VMS=visual memory span, GDS-S=geriatric depression scale-short form, ADL=activity of daily life.

Table 2. Stratified PCB levels and the correlation in certain domains through adjusting the covariates.

	Control (N=162)	PCB≧0,≦30ppb (N=42)	PCB>30,<90 ppb (N=63)	PCB≧90ppb (N=43)	P value
Variable	Mean (±SE)	Mean (±SE)	Mean (±SE)	Mean (±SE)	
Verbal Memory Recalls (Total trials)	28.4 (±0.7)	27.5 (±1.3)	26.6 (±1.0)	27.1 (±1.3)	0.49
Trial 4	6.7 (±0.2)	6.1 (±0.4)	6.0 (±0.3)	6.5 (±0.4)	0.17
Trial 5	7.0 (±0.2)	6.5 (±0.4)	6.2 (±0.3)	6.6 (±0.4)	0.15
Learning ability	3.6 (±0.2)	2.7 (±0.5)	2.7 (±0.4)	3.5 (±0.4)	0.06
Delayed recall in 30 min	5.6 (±0.2)	5.4 (±0.5)	5.2 (±0.4)	4.4 (±0.5)	0.15
DS	25.1 (±1.3)	24.3 (±2.2)	23.3 (±2.1)	21.9 (±2.0)	0.67
ADS-Forward	12.1 (±0.2)	11.8 (±0.4)	11.1* (±0.3)	11.0* (±0.4)	0.002*
ADS-Backward	4.5 (±0.2)	4.4 (±0.4)	4.3 (±0.3)	3.7 (±0.3)	0.25
VMS-Forward	7.0 (±0.1)	7.1 (±0.3)	6.8 (±0.3)	6.4 (±0.3)	0.20
VMS-backward	4.8 (±0.2)	4.5 (±0.3)	4.7 (±0.3)	4.1 (±0.3)	0.19

1. *Post-hoc* Tukey HSD for dosing response with significance (*). DS=digit symbol, ADS=attention and digit span, VMS=visual memory span. SE=standard error. (18 exposed subjects had no PCB level).