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# Gestational exposure to polychlorinated biphenyls and dibenzofurans induced asymmetric hearing loss: Yucheng children study

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ABSTRACT

*Introduction:* In 1979, approximately 2000 people in central Taiwan were exposed to polychlorinated biphenyls and dibenzofurans (PCBs/PCDFs) due to ingestion of contaminated rice oil. The children born to mothers exposed to PCBs/PCDFs were called Yucheng children. We conducted a follow-up study to examine the association between gestational PCBs/PCDFS exposure and auditory function in Yucheng children's early adulthood.

*Methods:* In 1985 and early 1992, Yucheng children and their age, gender, socio-economic matched unexposed referent children were recruited for physical examination and long-term follow-ups. In 2007, Yucheng children and referent children were invited to participate in a health examination, including assessment of pure-tone air-conduction thresholds and distortion product otoacoustic emissions (DPOAEs) test. Gestational exposure to PCBs/PCDFs in Yucheng children were estimated by back-extrapolation of their mother's serum concentration to the time of childbirth.

*Results:* A total of 86 Yucheng children (51.2% males) and 97 referent children (50.5% males) were included for analysis. No difference was found in demographic characteristics between two groups. Among the Yucheng children, 53 had estimated PCBs/PCDFs concentrations. We found that Yucheng children were at higher risk of having elevated hearing threshold at low frequencies in the right ear. Estimated maternal concentrations of 2,3,4,7,8-pnCDF at the time of birth were associated with increased hearing thresholds and decreased DPOAEs amplitudes at low frequencies in the right ear.

*Conclusion:* Gestational exposure to PCBs/PCDFs caused adverse asymmetrical hearing effects detectable even in early adulthood.



## 1. Introduction

Polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) are widespread environmental pollutants. The use of these chemicals are currently banned or restricted in most developed countries. However, because of the chemicals' persistence in the environment, high background concentrations are still found as seen in several large-scale epidemiologic studies in the general population (Patterson et al., 2008, 2009; Wong et al., 2008). Due to the worldwide ubiquitous background exposure, PCDDs, PCDFs, and PCBs are still a concern to human health. PCBs have been suggested as neurotoxicants especially when exposed during prenatal and early postnatal periods, and known to cause neurological effects including neurocognitive deficits, behavioral problems, and auditory impairments (Boucher et al., 2010; Grandjean and Landrigan,

*Abbreviations:* PCBs, polychlorinated biphenyls; PCDFs, polychlorinated dibenzofurans; DPOAE, distortion product otoacoustic emissions

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2006; Schantz, 1996; Schantz et al., 2003; Tilson et al., 1998). We and others have reported neurological adverse effects in the children prenatally exposed to PCBs and PCDFs (Chen et al., 1992; Jacobson and Jacobson, 1996; Lin et al., 2008).

Several animal studies have demonstrated auditory deficits after gestational PCB exposure. In rats, gestational exposure to a commercial PCB mixture, Aroclor 1254, resulted in low-frequency hearing loss (Goldey et al., 1995; Lasky et al., 2002). The rats with gestational exposure to a mixture of 35% Aroclor 1242, 35% Aroclor 1248, 15% Aroclor 1254, and 15% Aroclor 1260 had decreased hearing function as measured by an objective method, distortion product otoacoustic emissions (DPOAE), including reduced amplitudes and elevated thresholds across a wide range of frequencies (Powers et al., 2006, 2009). More recently, a study suggested an additive effect of PCBs and polybrominated diphenyl ethers (PBDEs) on cochlear function, evidenced by reduced DPOAE amplitudes and increased DPOAE thresholds in rats (Poon et al., 2011).

Further investigation on the auditory pathway showed that rats exposed to Aroclor 1254 decreased amplitude of the early brainstem auditory evoked response (BAER) peaks, a measurement for the damage in the brainstem auditory pathways (Herr et al., 1996). The authors suggested that the deficit might exist at the level of the cochlea and/or auditory nerve. A recent study in rats confirmed PCB-52 and PCB-180 effect on elevation BAER threshold. This study also indicated that different PCB congeners had varied potencies, as PCB-52 had greater effect on BAER threshold than PCB-180 (Lilienthal et al., 2011).

In humans, studies on auditory effects of gestational exposure to PCBs are limited. A study in 7-year-old children in Faroe Islands found a positive association between prenatal PCB exposure and auditory thresholds at frequencies 250 and 12,000 Hz in only the left ear (Grandjean et al., 2001). In a follow-up study of mother-child pairs in 12 U.S. centers, higher PCB concentration in maternal serum was related to increased hearing thresholds at 2000 Hz in the left ear, and 4000 Hz in the right ear when the children were 8 years of age (Longnecker et al., 2004). Swedish boys, born to fishermen's wives and sisters in east coast, who were exposed to organochlorine, according to plasma PCBs concentrations (Grimvall et al., 1997; Rylander et al., 1997), had higher prevalence of hearing loss as compared to boys born to fisherman families in west coast, where exposure to PCBs was low. However, somehow conflicting results were also found, that the boys from fisherman's families of east coast did not have poorer hearing ability as compared to the local reference population, who were not highly exposed to PCBs (Rylander and Hagmar 2000).

In 1978–1979, an episode of mass exposure to toxic agents occurred in central Taiwan. Approximately 2000 victims ingested rice oil contaminated with PCBs (Kanechlor-500) and their pyrolytic products (Hsu et al., 1985). After an average of 9–10 months of exposure, the etiology was confirmed by health authority that one specific brand of rice oil was contaminated and was the causal agent of this mass poisoning. Repeated heating of the PCBs resulted in generation of PCDFs and polychlorinated quaterphenyls (PCQs). Based on the interviews with 98 Yucheng patients, average consumption was estimated to be 1 g (range = 0.7–1.4) of PCBs and 3.8 mg (range = 1.8–5.6) of PCDFs (Lan et al., 1981), averagely. More than 13 years after the Yucheng incident, Yucheng mothers continued to have detectable serum concentrations of PCB/PCDF congeners that were many times higher than that of the unexposed controls (Guo et al., 1997). The children born to mothers exposed to PCBs and related compounds were called Yucheng children. Our previous study showed that Yucheng children had a higher incidence of otitis media than referent children (Chao et al., 1997). No auditory assessment was performed during that time. We therefore conducted a follow-up study to test the hypothesis whether children prenatally exposed to PCBs and PCDFs had higher risk of developing auditory deficits, as compared to their referent children. We also examined whether hearing effects were associated with gestational PCBs/PCDFS exposure or exposure to specific congeners in the Yucheng children.

## 2. Material and methods

### 2.1. Subjects

This study was approved by the Institutional Review Board of The National Taiwan University Medical Center. The study candidates were from two groups, the exposed Yucheng children who were born between June 1978 and December 1998 to mothers exposed to PCBs and PCDFs (Chen et al., 1992; Guo et al., 1994). The other group was from the previously identified referent group of children. For each Yucheng child, one unexposed child was selected as a control by matching for neighborhood (lived/born within the same township), age (within 15 days of age for those under 1 year, and within 1 month of age for those older), gender, mother's age (within 3 years of age), parents' combined educational level (within 3 years), and occupation (within 1 class of 5 classes from unskilled laborer to professional). A total of 240 exposed and 240 unexposed were entered into follow-up. In 2007, a health survey was conducted in three townships, where a total of 184 Yucheng children and 184 referent children were found and invited to participate in a health examination. An informed consent was obtained before examination and tests.

### 2.2. Methods of measurements

Demographic data were collected by using a structured questionnaire. Otoscopic ear examination was carried out by an otolaryngologist (H. P. Wu) before hearing tests. Participants with ear disease or other pathologies related to hearing loss were excluded. Blood samples from all children were collected for measurements of serum concentrations of cholesterol and triglycerides. All interviewers, physicians, and testers were blinded as to the exposure status of the participants.

### 2.3. Pure tone audiometry

Pure tone audiograms were obtained for each ear in all subjects, employing a standard threshold search procedure using a clinical audiometer (Unity PC Audiometer SD 100, Copenhagen, Denmark). Pure tone thresholds were obtained from 250 to 8000 Hz, via headphones. All pure tone threshold tests were conducted in a sound-proofed booth.

### 2.4. Distortion product otoacoustic emissions testing

Distortion product otoacoustic emissions (DPOAEs) were elicited by two continuous, primary tones at frequencies $f1$ and $f2$ ($f2$:$f1$ was fixed at 1.22), generated by two separate transducers (Etymotic Research; ER2, Elk Grove Village, IL, USA) connected to a digital signal processing board (DSP) (SmartOAE; Intelligent Hearing Systems, Miami, FL, USA). Two short plastic tubes connected the transducer outputs to the OAE probe (Etymotic Research; ER10B+), which also contained a miniature low-noise microphone for emission detection. The tapered end of the probe was extended with a short, soft silicon tip and the probe was inserted deeply and tightly into the external ear canal. The microphone detected the overall acoustic signal in the external ear canal during tone stimulation. Its response was preamplified (+40 dB) then analyzed by the SmartOAE DSP board. The stimulation and

detection process were automatically controlled by using a PC computer driven by SmartOAE software (Intelligent Hearing Systems, version 3.72). This software, based on Fourier transformation calculation, generated the stimulations through two independent channels, checked the actual levels of stimulating tones, and computed the complex response at frequency $2f1–f2$. The testing frequency range of $f2$ was 1.5–6 kHz, and the two primaries, $L1$ and $L2$, were set at 65 and 55 dB SPL. Amplitudes of DPOAEs were measured at selected frequencies. Data are described with respect to $f2$ frequency since the generator site of the $2f1–f2$ distortion product has been most closely correlated with the $f2$ frequency place in the cochlea.

### 2.5. Maternal exposure data

Due to a broad coverage of media about this event, all the women who were followed ceased using rice oil. Since the government halted the manufacturing and sale of the contaminated oil, further exposure was unlikely. However, the toxic compounds were known to have long body half-lives, and Yucheng mothers with a high body burden continued to transfer the toxic substances to their fetuses even several years later.

Maternal blood concentrations of PCBs and PCDFs were available from 53 children of 47 mothers. The blood samples were collected between 1994 and 2003, stored at −80 °C, and sent on dry ice to the U.S. Centers for Disease Control and Prevention for the measurements of PCB, PCDF, and PCDD congeners (Lambert et al., 2006). In brief, high resolution gas chromatography (GC)/mass spectrometry (MS) (Patterson et al., 1987) was used for the measurement of 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF. Ortho-substituted PCBs were analyzed by a Hewlett-Packard 5890 gas chromatograph (GC) (Hewlett-Packard, Houston, TX) using an electron-capture detector, including 2,3′,4,4′,5-PeCB (IUPAC118), 2,2′,4,4′,5,5′-HxCB (IUPAC153), 2,2′,3,4,4′,5′-HxCB (IUPAC138), 2,3,3′,4,4′,5-HxCB (IUPAC156), 2,2′,3,3′,4,4′,5-HpCB (IUPAC170), 2,2′,3,4,4′,5,5′-HpCB (IUPAC180) Values were reported on a lipid weight basis in parts per trillion (ppt) by dividing the congeners on a whole-weight basis by total serum lipid content, estimated from measurements of triglycerides, and total cholesterol (Phillips et al., 1989).

Yucheng children were born between June 1978 and December 1998, i.e., earlier than the time we got maternal exposure data. Thus, gestational exposure was estimated by back-extrapolation from the mothers' serum concentrations. The half-life used for back extrapolation of each congener was based on a review article, which was specific for Yucheng and Yusho cohorts (Ogura, 2004), namely 1.7 years for PCB-118, 3.9 years for PCB-153, 4.8 years for PCB-138, 4.9 years for PCB-156, 5.4 years for PCB-180, 5.5 years for PCB-170, 3.1 years for 2,3,4,7,8-pnCDF, and 3.3 years for 1,2,3,4,7,8-hxCDF.

### 2.6. Statistical analysis

Statistical analysis was performed using SAS version 9.3 and JMP version 5.0 software. Basic demographic data were summarized as total numbers and percentage for categorical variables. Differences of categorical variables were then compared by using Chi-square tests. Logistic regression was performed using elevated pure tone auditory thresholds ($>20$ vs. $\leq 20$) at different frequencies as dependent variables, and exposure status (Yucheng children vs. referent children) as independent variable. Linear regression was performed using log-transformed pure tone auditory thresholds or log-transformed DPOAEs as dependent variables, and maternal serum concentrations at pregnancy of log-transformed maternal PCDFs and marker-PCBs concentrations (at birth) as independent variable. All regression models were adjusted for potential confounding factors of hearing loss, such as age, gender, body mass index (Curhan et al., 2013), total cholesterol (Longnecker et al., 2004), and triglyceride (Chau et al., 2010; Longnecker et al., 2004).

## 3. Results

Among the 184 Yucheng children invited, 86 agreed to participate in this examination. Among the 184 referent children, 97 agreed to participate. The Yucheng and referent children were of similar age, gender, body mass index, total cholesterol, and triglyceride (Table 1). Among Yucheng children, non-participants had average age of $21.3 \pm 3.8$, 51.0% males. Among referents, non-participants had average age of $21.3 \pm 3.8$, 51.7% males. These were not different from participants (data not shown).

For pure tone auditory at frequencies from 250 Hz to 8000 Hz, hearing threshold of $>20$ dB was more frequently observed at 250 Hz, 500 Hz, and 2000 Hz among Yucheng children as compared to the referents. Estimated maternal concentrations of PCBs and PCDFs at the time of birth are shown in Table 2.

Table 3 shows results of logistic regression using elevated pure tone auditory thresholds ($>20$ vs. $\leq 20$) at different frequencies as dependent variables, and exposure status (Yucheng vs. referent), age, gender, body mass index, total cholesterol, and triglyceride as independent variables. Yucheng children were at higher risk of elevated hearing threshold in the right ear at frequencies 250 Hz, 500 Hz, and 2000 Hz, as compared to the referents.

Table 4 shows linear regression using log-transformed pure tone auditory thresholds as dependent variable and log-transformed maternal serum concentrations of PCDFs and marker-PCBs as independent variable. Maternal concentrations of 2,3,4,7,8-pnCDF at the time of delivery were found associated with pure tone auditory thresholds at frequency 250 Hz, 500 Hz, 1000 Hz, and average threshold level of right ear, and 500 Hz, 4000 Hz, and average threshold level of the left ear, after adjusting for age, gender, body mass index, total cholesterol, and triglyceride.

Maternal concentrations of 1,2,3,4,7,8-hxCDF were associated with pure tone auditory thresholds at frequency 4000 Hz of the left ear. There was no association found between maternal marker-PCB concentrations and pure tone auditory thresholds.

Table 5 shows linear regression using log-transformed DPOAEs as dependent variable and maternal serum concentrations at pregnancy of log-transformed maternal PCDFs and marker-PCBs concentrations (at birth) as independent variable. Maternal concentrations of 2,3,4,7,8-pnCDF at delivery were found negatively associated with DPOAE amplitudes at 1500 Hz, 2000 Hz, average amplitude of right ear, and average amplitude of left ear. The results were unchanged when adding 1,2,3,4,7,8-hxCDF or the sum of marker-PCBs in the model of regression analysis (data not shown).

## 4. Discussion

This is the first paper describing adverse hearing effects in children with gestational exposure to PCBs and PCDFs. The main damage to hearing threshold by such exposure was found at low frequencies. Such damage was related to gestational exposure to 2,3,4,7,8-pnCDF, but not to the marker-PCB congeners.

The mechanism of PCBs-induced auditory deficits has been suggested in prenatally exposed animals. Thyroid hormone is necessary for normal cochlear development (Uziel, 1986), and perinatal exposure to Aroclor 1254 is known to markedly reduce serum thyroid hormones in rats (Goldey et al., 1995; Morse et al.,

**Table 1**
Characteristics in Yucheng children and their neighborhood referents at time of study.

| Demographic variable | Yucheng children $N=86$ | | Referent children $N=97$ | | *P*-value |
|---|---|---|---|---|---|
| **Age (years)**[a] | | | | | |
| Mean and range | 21.1 | 8.7–28.7 | 21.2 | 10.9–29.1 | 0.91 |
| $>21.3$ | 43 | 50.0% | 46 | 47.4% | 0.73 |
| $\leq 21.3$ | 43 | 50.0% | 51 | 52.6% | |
| **Gender** | | | | | |
| Male | 44 | 51.2% | 49 | 50.5% | 0.93 |
| Female | 42 | 48.8% | 48 | 49.5% | |
| **Body mass index**[a] | | | | | |
| $>21.25$ | 43 | 50.0% | 47 | 48.5% | 0.83 |
| $\leq 21.25$ | 43 | 50.0% | 50 | 51.5% | |
| **Total cholesterol (mg/dL)**[a] | | | | | |
| $>163$ | 44 | 51.2% | 49 | 50.5% | 0.93 |
| $\leq 163$ | 42 | 48.8% | 48 | 49.5% | |
| **Triglyceride (mg/dL)**[a] | | | | | |
| $>71$ | 48 | 55.8% | 44 | 45.4% | 0.16 |
| $\leq 71$ | 38 | 44.2% | 53 | 54.6% | |
| **Right ear hearing threshold $>20$ dB** | ***N*** | **(%)** | ***N*** | **(%)** | ***P*-value** |
| Average threshold level (dB) | 14 | 16.3 | 8 | 8.2 | 0.09 |
| 250 Hz | 13 | 15.1 | 5 | 5.2 | **0.02** |
| 500 Hz | 11 | 12.8 | 4 | 4.1 | **0.03** |
| 1000 Hz | 13 | 15.1 | 11 | 11.3 | 0.45 |
| 2000 Hz | 15 | 17.4 | 3 | 3.1 | $<$ **0.01** |
| 4000 Hz | 14 | 16.3 | 10 | 10.3 | 0.23 |
| 8000 Hz | 15 | 17.4 | 8 | 8.2 | 0.06 |
| **Left ear hearing threshold $>20$ dB** | ***N*** | **(%)** | ***N*** | **(%)** | ***P*-value** |
| Average threshold level (dB) | 11 | 12.8 | 9 | 9.3 | 0.58 |
| 250 Hz | 7 | 8.1 | 8 | 8.2 | 0.98 |
| 500 Hz | 7 | 8.1 | 7 | 7.2 | 0.81 |
| 1000 Hz | 11 | 12.8 | 8 | 8.2 | 0.31 |
| 2000 Hz | 9 | 10.5 | 11 | 11.3 | 0.85 |
| 4000 Hz | 15 | 17.4 | 15 | 15.5 | 0.71 |
| 8000 Hz | 9 | 10.5 | 9 | 9.3 | 0.78 |

[a] Divided by median level of all subjects; dB: decibel.

1996). As a result, perinatally exposed animals had reduced auditory startle amplitudes especially in lower testing frequencies (Goldey et al., 1995). Those rats perinatally exposed to higher doses of Aroclor 1254 (4 and 8 mg/kg per day from gestational day 6 through postnatal day 21) had irreversible hearing damage. Replacement therapy with thyroxine injection ameliorated the hearing loss caused by gestational Aroclor 1254 exposure (Goldey and Crofton, 1998). The cochlea was specifically indicated as the likely site of action since other investigators found loss of outer hair cells in rats perinatally exposed to PCBs (Crofton et al., 2000). As for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and PCDFs, the auditory effects in rodents of gestational exposure to these chemicals has not been reported, despite several reports documenting reduced serum thyroxine levels in animals exposed to TCDD (Bastomsky, 1977; Mc Kinney et al., 1985; Potter et al., 1983, 1986; Gorski and Rozman, 1987; Roth et al., 1988; Lans et al., 1990). Since the reduction in thyroxine levels was strong in animals exposed to TCDD, one might assume that gestational exposure to TCDD might cause similar auditory effects. Despite an elevated rate of reported goiter in Yucheng women (Guo et al., 1999), hypothyroidism was not increased in Yucheng as compared to their controls. However, thyroid function was not measured when the Yucheng mothers were pregnant. The possibility of sub-clinical hypothyroidism in Yucheng mothers as a cause of their children's hearing damage cannot be totally ruled out.

**Table 2**
Estimated maternal concentrations of PCBs and PCDFs at the time of birth ($N=53$).

| Congeners | Concentrations (median, interquartile range) |
|---|---|
| **PCBs (ng/g lipid)** | |
| PCB-118 | 9.87(1.08–16.48) |
| PCB-153 | 270.42(19.64–809.56) |
| PCB-138 | 301.23(29.55–1166.61) |
| PCB-156 | 152.14(6.23–511.61) |
| PCB-180 | 289.61(9.15–825.74) |
| PCB-170 | 205.83(8.31–585.80) |
| Sum of six PCBs | 1237.76(76.23–3856.52) |
| **PCDFs (pg/g lipid)** | |
| 23478-PCDF | 1298.72(903.04–2044.90) |
| 123478-PCDF | 2998.95(1499.94–4690.79) |

**Table 3**
Odds ratio of abnormal hearing threshold (hearing threshold level $>20$ dB) in children prenatally exposed to PCBs/PCDFs as compared to referents by logistic regression.

| Hearing threshold level | OR | 95% CI |
|---|---|---|
| **Right ear** | | |
| 250 Hz | **3.42*** | 1.20–11.32 |
| 500 Hz | **3.40*** | 1.10–12.77 |
| 1000 Hz | 1.41 | 0.58–3.53 |
| 2000 Hz | **6.35*** | 1.97–28.45 |
| 4000 Hz | 1.54 | 0.63–3.87 |
| 8000 Hz | 2.18 | 0.88–5.77 |
| Average threshold level | 2.15 | 0.86–5.72 |
| **Left ear** | | |
| 250 Hz | 0.93 | 0.30–2.76 |
| 500 Hz | 1.11 | 0.36–3.42 |
| 1000 Hz | 1.66 | 0.63–4.52 |
| 2000 Hz | 0.90 | 0.34–2.29 |
| 4000 Hz | 1.05 | 0.46–2.39 |
| 8000 Hz | 1.00 | 0.36–2.78 |
| Average threshold level | 1.36 | 0.53–3.61 |

OR: odd ratio; CI: confidence interval.
All models were adjusted for sex, age, body mass index, triglyceride, total cholesterol
* $p$-Value $<0.05$.

Gestational exposure to PCBs has been associated with asymmetric hearing loss in human studies, but the findings were inconsistent. One study in Faroe Islands found that gestational exposure to wet-weight PCB concentrations was associated with hearing thresholds at frequencies 250 and 12,000, but only on the left side (Grandjean et al., 2001). A study in 8-year-old children showed that higher maternal serum PCB concentrations were associated with increased hearing thresholds at 2000 Hz in the left ear, and 4000 Hz in the right ear (Longnecker et al., 2004). In this study, we found increased hearing threshold more prominently in the right ear in PCB/PCDF-exposed children, as well as clearer association of maternal 2,3,4,7,8-pnCDF with right ear threshold than with left ear threshold. The mechanism of this kind of asymmetric hearing loss has not been identified.

Most toxic effects of 2,3,7,8-substituted PCDFs and non-ortho-substituted PCBs are mediated through the aryl hydrocarbon receptor (AhR), a cytosolic receptor protein present in most vertebrate tissues (Van den Berg et al., 2006). The most potent

**Table 4**
Effects of maternal serum level of PCBs/PCDFs (ppt lipid base, log-transformed) on hearing threshold (log-transformed) by linear regression ($N=53$).

| Congeners | Hearing level (dB) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 250 Hz | 500 Hz | 1000 Hz | 2000 Hz | 4000 Hz | 8000 Hz | Average threshold level |
| **Right ear** | | | | | | | |
| **PCB-118** | −0.79/069 | −1.78/0.39 | −2.14/0.31 | −1.33/0.55 | −2.99/0.34 | −1.72/0.58 | −2.07/0.35 |
| **PCB-153** | 0.79/0.65 | −0.16/0.93 | −0.34/0.85 | 0.39/0.84 | −0.72/0.79 | −0.99/0.72 | −0.21/0.91 |
| **PCB-138** | 1.62/0.37 | 0.59/0.76 | 0.40/0.83 | 1.15/0.56 | 0.25/0.93 | −0.13/0.96 | 0.60/0.76 |
| **PCB-156** | 1.15/0.49 | 0.17/0.92 | −0.02/0.99 | 0.73/0.69 | 0.13/0.96 | −0.26/0.92 | 0.26/0.89 |
| **PCB-180** | 0.77/0.65 | −0.20/0.91 | −0.48/0.79 | 0.41/0.83 | −0.43/0.87 | −0.68/0.80 | −0.17/0.93 |
| **PCB-170** | 1.10/0.52 | 0.13/0.94 | −0.11/0.95 | 0.72/0.71 | 0.01/1.00 | −0.43/0.87 | 0.19/0.92 |
| **Sum of six PCBs** | 1.14/0.53 | 0.14/0.94 | −0.12/0.94 | 0.76/0.70 | −0.16/0.96 | −0.47/0.87 | 0.16/0.94 |
| **23478-PCDF** | ***7.55/0.02*** | ***7.50/0.03*** | ***7.11/0.04*** | 6.45/0.08 | 10.16/0.05 | 8.46/0.11 | ***7.83/0.03*** |
| **123478-PCDF** | 3.97/0.07 | 3.67/0.12 | 3.74/0.11 | 3.23/0.20 | 5.51/0.12 | 3.79/0.28 | 4.06/0.10 |
| **Left ear** | | | | | | | |
| **PCB-118** | −0.37/0.82 | −0.73/0.65 | −0.95/0.62 | −1.35/0.52 | −2.72/0.28 | −2.45/0.39 | −1.43/0.45 |
| **PCB-153** | 0.43/0.76 | 0.67/0.63 | 0.69/0.68 | 0.28/0.88 | −0.12/0.96 | −0.34/0.89 | 0.38/0.82 |
| **PCB-138** | 0.85/0.55 | 1.12/0.43 | 1.27/0.46 | 0.92/0.63 | 0.76/0.74 | 0.41/0.87 | 1.02/0.55 |
| **PCB-156** | 0.48/0.71 | 0.90/0.49 | 0.97/0.54 | 0.54/0.76 | 0.56/0.79 | 0.22/0.93 | 0.74/0.63 |
| **PCB-180** | 0.40/0.77 | 0.66/0.62 | 0.64/0.69 | 0.25/0.89 | −0.12/0.96 | −0.25/0.92 | 0.36/0.82 |
| **PCB-170** | 0.52/0.70 | 0.91/0.50 | 0.96/0.56 | 0.55/0.76 | 0.40/0.85 | 0.05/0.99 | 0.71/0.66 |
| **Sum of six PCBs** | 0.51/0.72 | 0.75/0.60 | 0.93/0.59 | 0.55/0.77 | 0.23/0.92 | −0.11/0.96 | 0.62/0.72 |
| **23478-PCDF** | 3.22/0.23 | ***5.23/0.05*** | 5.44/0.09 | 4.85/0.17 | ***10.09/0.01*** | 8.40/0.08 | ***6.40/0.04*** |
| **123478-PCDF** | 1.24/0.49 | 2.76/0.12 | 3.04/0.16 | 2.07/0.38 | ***5.72/0.04*** | 3.90/0.22 | 3.40/0.11 |

Data were represented as beta value/$p$-Value; $p$-Value $< 0.05$ was considered significant (values in bold and italics).

ligand for AhR is 2,3,7,8-TCDD. In environmental and biological media, mixtures of these compounds are frequently seen. To summarize the overall toxicity in mixtures, toxic equivalency (TEQ) of these compounds has been applied, which is operationally defined by the sum of the products of the concentration of each compound multiplied by its toxic equivalent factor (TEF) value, the latter being the relative effect potency of each compound as compared to that of 2,3,7,8-TCDD. In the blood of the mothers in this study, the TEQ were mostly contributed by 2,3,4,7,8-pnCDF, followed by 1,2,3,4,7,8-hxCDF. The TEQ of PCB congeners were rather low. Therefore, it is not surprising to find strongest relationship between hearing deficits and 2,3,4,7,8-pnCDF, but not other compounds. This finding implies that the hearing effects of these compounds in Yucheng children were mediated by AhR.

In this study, we did not examine effects of postnatal exposure due to breast-feeding in Yucheng children. After the intoxication event, breast-feeding among exposed people was discouraged by the Health Authority in Taiwan. Therefore, effects caused by breast-feeding could have been much smaller as compared to transplacental exposure. Among Yucheng children who were previously examined, a large percentage did not have detectable congeners,

**Table 5**
Effects of maternal serum level of PCBs/PCDFs (ppt lipid base, log-transformed) on DPOAEs (log-transformed) by linear regression ($N=53$).

| Congeners | Hearing level (dB) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1.5 kHz | 2 kHz | 3 kHz | 4 kHz | 5 kHz | 6 kHz | Average threshold level |
| **Right ear** | | | | | | | |
| **PCB-118** | 0.29/0.79 | −0.40/0.72 | 1.06/0.33 | −0.61/0.64 | 0.53/0.70 | −0.54/0.73 | 0.05/0.96 |
| **PCB-153** | −0.51/0.58 | −0.89/0.36 | 0.20/0.83 | −1.24/0.28 | −0.62/0.60 | −1.49/0.28 | −0.76/0.38 |
| **PCB-138** | −0.96/0.31 | −1.39/0.16 | −0.11/0.91 | −1.55/0.18 | −0.97/0.43 | −1.89/0.18 | −1.15/0.20 |
| **PCB-156** | −0.53/0.55 | −0.82/0.37 | 0.04/0.97 | −1.24/0.25 | −0.83/0.46 | −1.52/0.24 | −0.82/0.32 |
| **PCB-180** | −0.36/0.67 | −0.66/0.49 | 0.32/0.73 | −1.00/0.36 | −0.46/0.69 | −1.17/0.38 | −0.56/0.51 |
| **PCB-170** | −0.48/0.60 | −0.81/0.40 | 0.17/0.85 | −1.14/0.31 | −0.63/0.59 | −1.36/0.32 | −0.71/0.41 |
| **Sum of six PCBs** | −0.71/0.44 | −0.99/0.31 | 0.10/0.92 | −1.42/0.22 | −0.87/0.46 | −1.57/0.27 | −0.91/0.30 |
| **23478-PCDF** | ***−4.06/0.02*** | ***−3.93/0.03*** | −3.26/0.08 | −3.81/0.08 | −4.19/0.07 | −4.21/0.11 | ***−3.91/0.02*** |
| **123478-PCDF** | −1.50/0.25 | −1.40/0.32 | −1.39/0.36 | −1.35/0.30 | −1.95/0.16 | −2.57/0.13 | −2.09/0.06 |
| **Left ear** | | | | | | | |
| **PCB-118** | −0.35/0.77 | 0.06/0.96 | −0.96/0.47 | −0.68/0.56 | 0.58/0.64 | 0.04/0.98 | −0.22/0.83 |
| **PCB-153** | −1.13/0.26 | −1.10/0.31 | −1.60/0.16 | −1.45/0.15 | −0.27/0.80 | −0.43/0.74 | −1.00/0.27 |
| **PCB-138** | −1.65/0.11 | −1.66/0.13 | −2.12/0.07 | −1.78/0.09 | −0.65/0.55 | −0.89/0.51 | −1.46/0.11 |
| **PCB-156** | −1.15/0.23 | −1.09/0.29 | −1.55/0.15 | −1.41/0.14 | −0.29/0.78 | −0.50/0.69 | −1.00/0.24 |
| **PCB-180** | −1.00/0.31 | −0.91/0.39 | −1.42/0.21 | −1.20/0.22 | −0.02/0.98 | −0.20/0.87 | −0.79/0.37 |
| **PCB-170** | −1.16/0.25 | −1.06/0.32 | −1.56/0.17 | −1.34/0.18 | −0.14/0.90 | −0.34/0.79 | −0.93/0.29 |
| **Sum of six PCBs** | −1.33/0.17 | −1.25/0.23 | −1.84/0.11 | −1.60/0.12 | −0.34/0.72 | −0.54/0.69 | −0.15/0.19 |
| **23478-PCDF** | −3.40/0.08 | −3.42/0.10 | −3.16/0.16 | −2.97/0.13 | −3.91/0.06 | −4.26/0.09 | ***−3.51/0.04*** |
| **123478-PCDF** | −1.63/0.17 | −1.59/0.21 | −2.18/0.07 | −1.80/0.22 | −2.55/0.09 | −2.77/0.12 | −1.69/0.15 |

Data were represented as beta value/$p$-Value; $p$-Value $< 0.05$ was considered significant (values in bold and italics).

and even with detectable concentrations, the ratio between serum concentrations in Yucheng and control children were not as large as that between mothers (Ryan et al., 1994). Since maternal serum concentrations of 2,3,4,7,8-pnCDF was correlated with children's hearing loss, the effects may well be explained by transplacental exposure. Even if the effects of breast-feeding cannot be completely ruled-out, they were likely much smaller than transplacental exposure. Findings from previous studies also support the inference that prenatal rather than postnatal PCB exposure was harmful to the children's central nervous system function (Jacobson et al., 1985; Jacobson and Jacobson, 1996).

Our study offers some advantages over previously reported studies. (1) The study participants belong to a longitudinal follow-up cohort, providing better causal relationship. (2) The Yucheng children were compared to their closely controlled referent children, with similar socioeconomic background, and general living environment. (3) Hearing threshold was further confirmed by an objective measurement of hearing functioning, the DPOAE. (4) In a portion of participants, maternal serum concentrations were available and gestational exposure could be estimated. This allowed for a dose–response analysis.

However, there are some limitations in this study. (1) Due to widely dispersed geographic distribution of current residences of the exposed population, the participation was limited. This study could not be conducted in the field as the hearing testing required a silent background, and had to be set up only in the selected locations. However, we do not believe this biased the study finding. When contacted, the candidates of the study were invited to a general physical examination. Although hearing was mentioned in the invitation, it belonged to more than 10 items of mentioned examinations and was not the highlight of the examination. Thus the participation was very likely unrelated to the candidates' hearing status. In addition, the participants and non-participants had similar distributions of age and gender. Despite that we did not have information on other health indices, we did not believe that participation introduced selection bias strong enough to bias the study results. (2) Yucheng children's gestational exposure of PCBs/PCDFs was back-extrapolated, and it might have introduced variation in the exposure dose assessment. However, because the half-lives used in present study were based on published data derived from studies on Yucheng population, uncertainty of back extrapolation was minimized. (3) Because the Yucheng children were prenatally exposed to a mixture of PCBs/PCDFs, and those chemicals were highly correlated with each other (Among PCBs-118, −153, −138, −156, −180, and −170; 2,3,4,7,8-pnCDF, and 1,2,3,4,7,8-hxCDF, correlation coefficients ranged from 0.81 to 0.99; all $p$-values $< 0.001$), it was hard to tell which chemical (s) were the actually causal agent(s). The best association between hearing threshold and maternal chemicals was found for 2,3,4,7,8-pnCDF. However, the possibility could not be totally excluded that other PCB or PCDF congeners played a role or that PCBs interacted with PCDFs to result in the observed associations. (4) A higher proportion of otitis media in early childhood among exposed children was one possible cause of increased hearing threshold. However, 29 among our participants were previously examined by , and those with previous otitis media (a total of 15) did not have different hearing thresholds from those without (a total of 14). Therefore a history of otitis media does not appear to play a role in causing our observed hearing deficits in this study. (5) In the back-extrapolation of the serum concentrations in mothers, changes in body mass index (BMI) were not taken into account. Similar approach in serum concentrations back-extrapolation has been taken before without BMI adjustment (Chao et al., 1997) On the other hand, it is possible that among those with large weight gain, back-extrapolation without considering BMI change may under-estimate serum concentrations in previous times.

In conclusion, a follow-up study of Yucheng children gestational exposure to PCBs/PCDFs found increased prevalence of mild hearing loss in early adulthood, as compared to their neighborhood referent children. Such damage was related to gestational exposure to 2,3,4,7,8-pnCDF.

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