國立臺灣大學公共衛生學院職業醫學與工業衛生研究所

博士論文

Institute of Occupational Medicine and Industrial Hygiene

College of Public Health

National Taiwan University

Doctoral Dissertation

多氯聯苯及多氯呋喃中毒者及其子代之長期健康效應研究

Long-Term Health Outcome after Exposure/Prenatal Exposure to Polychlorinated Biphenyls and Dibenzofurans

李銘杰

Li, Ming-Chieh

指導教授：郭育良 教授 陳保中 教授

Advisor: Guo Yue Leon, M.D., Ph.D.

Advisor: Chen Pau-Chung, M.D., Ph.D.

中華民國104年7月

July, 2015

國立臺灣大學博士學位論文
口試委員會審定書

多氯聯苯及多氯呋喃中毒者及其子代之長期健康效應研究

Long-term Health Outcome after Exposure/Prenatal Exposure to Polychlorinated Biphenyls and Dibenzofurans

本論文係李銘杰君（F96841022）在國立臺灣大學職業醫學與工業衛生研究所完成之博士學位論文，於民國 104 年 7 月 7 日承下列考試委員審查通過及口試及格，特此證明

口試委員：郭育良（指導教授）　陳保中（指導教授）

郭浩然

許昌奇

吳弘毅

所長 陳保中

謝　辭

我曾在無數的夜晚中想像這一天的到來。如今能從臺大畢業，獲得博士學位，直到現在我都還覺得有些不真實。在這段漫長的博士學習生涯，最想感謝的是我的指導教授郭育良老師和陳保中老師。

郭老師對於學術研究嚴謹的態度，以及其專業知識的熟悉度，一直是我學習的對象。每一篇我所發表的論文，都是和老師面對面，在電腦前一個字一個字修改後完成的，而我也在這一次又一次的修改過程中不斷進步。這是一個相當耗費時間的過程，很感謝老師能這樣帶領我成長。我是一個不務正業的博士生，想學的東西太多，總覺得學生生涯就這麼一次，一旦畢業，將很難安排時間，學我想學的一切，完成我想完成的許多事情。所以過去這幾年，我修法律學位、修生技學程、擔任許多科普專欄的編輯、寫科普書、甚至參與許多社會運動，把自己的時間塞到絲毫沒有半點空隙。而我對博士論文的投入，並沒有比任何人少過，也因為如此，我幾乎犧牲了過去數年的睡眠和假日，每天兩三點睡，每個假日都在趕進度或唸書。許多人以為我為了學業，搞得休閒活動都沒了，然而我不只是為了學業而已，而是為了許多我認為重要且有意義的事情。最近偶而會想起過去的一些日子，仍會想起那龐大的壓力，不知道自己是如何熬過來的。能挺過這一切，特別要感謝郭老師對我的包容，讓我嘗試自己的可能性。

感謝保中老師的指導和大小事情的提醒。每當我有求於老師時，例如請老師寫推薦函等，老師總是在隔天就準備好了。還記得當年，請保中老師推薦我逕讀所上博士班時，老師提醒我是否有思考清楚，例如博士畢業的就業前景，可能比碩士畢業還不好等情況，當時我回答想清楚了。但尚未經歷博士學習過程的我，說清楚了，似乎難以說服人。現在，我即將要畢業了，如果當初讓我再選一次，即使我知道博士畢業後又是一段艱苦旅程的開始，即使我知道博士的就業以及薪水可能不如碩士，我仍會選擇念博士。對我而言，以學術研究為畢生的志向，才

符合我對往後人生的期待，收入倒是其次。此時此刻我才能跟保中老師確認，我想清楚了，比當年申請逕讀博士時更清楚。

包括碩士在學期間，我在臺大已經 7 年半了。7 年半真的好長，也發生了好多事情。我和欣怡愛情長跑 9 年，在 2013 年結婚，也在 2015 年有了寶貝兒子翎希；等了 36 年，「油症患者健康照護服務條例」終於在 2015 年通過，油症患者獲得了基本的照護和補償，是近幾年來最令人欣慰的一件事；我得了一些獎，比我念博士之前獲得的獎總數還要多，如果以前有人說我能得到這些獎，我一定不信，很感謝一路上支持和幫助我的人。

這幾年也有許多令人難過和遺憾的事情發生。父母都生過大病，身體越來越不如以往；很疼我的奶奶過世了，遺憾的是，只差幾個月，奶奶就能親眼看到我畢業，以及我的兒子出生了，只能怪自己不夠努力；國中以來的好友明軒走了，還記得我們最後一次在臺北火車站相約，道別時一反往常，我們感到莫名的猶豫，那時你還說：「幹嘛把氣氛搞得好像要別離一陣子，以後再約阿。」。沒想到某日竟然接到國中同學電話，說你你搭乘客運發生意外身亡。電視新聞上反覆出現你的名字，讓我不得不相信這個殘酷的事實。你生前有留下遺書，提到要將你此生最愛的，倉木麻衣所有的專輯和單曲 CD 全留給我。那是我們從國中以來的共同最愛，收到你父母寄給我的 CD 時，我強忍的淚水終於潰堤，感謝你如此重視我。

此論文能夠完成，還要感謝我的口試委員郭浩然老師、許晃奇老師、以及吳弘斌醫師的指導，指出我的論文不清楚或是缺失處，使此論文更加完善。感謝我的爸爸媽媽、岳父岳母，以及老婆欣怡，能夠支持和包容我，讓我繼續完成我的學位，完成我的夢想。感謝過去許多學長姐、學弟妹以及研究室其他同仁的協助，由於幫助過我的人實在太多了，很抱歉無法一一列出。

最後，僅將這份論文，獻給還來不及看到我畢業的奶奶，以及我的已故好友明軒，願你們能安息。

摘　要

1979 年，約兩千人誤食遭到多氯聯苯與多氯呋喃污染的米糠油，稱做臺灣油症事件。此重大公衛議題，與 1968 年在日本發生的食用油中毒事件，無論是在毒性物質和意外發生的方式皆相當類似，又稱日本油症事件。兩起事件，官方統計受害的人數大約都快 2000 人，但真正的人數並不清楚。

我們長期追蹤這群中毒者，比較油症受害者和其性別、年齡與社經地位配對之鄰居對照組在各種死因死亡率是否有差異，以觀察油症受害者之長期健康效應；由於臺灣油症患者和日本油症患者毒物的暴露濃度類似、暴露毒物組成類似，且同為亞洲人，我們將兩個族群合併並進行統合分析，以重新評估各種死因別死亡率；多氯聯苯與多氯呋喃在人體中難以代謝，受害者體內長時間帶有高濃度的毒物，女性生產時也不例外。正因如此，油症女性受害者懷孕時，體內高濃度的多氯聯苯與多氯呋喃是否會對其子代造成影響，也是我們關注的重要議題。過去的研究認為產前暴露多氯聯苯會引發神經毒性，並傷害聽覺系統。有鑑於此，我們另外檢驗油症女性所生下的油症兒，其聽力是否受到影響。

此系列研究的重要發現如下: 1) 30 年的追蹤研究發現，油症受害者比起其鄰居對照組，其整體死亡率、肝病、循環系統疾病以及肌肉骨骼系統及結締組織疾病死亡率皆顯著增加；男性油症受害者在胃癌以及淋巴及造血組織癌症之死亡率顯著上升。2) 臺灣與日本油症的統合分析結果發現，全體油症受害者的整體死亡率明顯上升；全體男性油症受害者在總癌症死亡率、肺癌、心臟疾病以及肝疾病的死亡率明顯上升；此外，全體女性油症受害者其肝癌死亡率亦顯著上升，這是第一次發現女性油症受害者之肝癌死亡率也有上升。3) 油症兒在產前暴露多氯聯苯與多氯呋喃，成年後會有聽力損失問題。且聽力損失的程度，與油症兒出生時，其母親體內推估的多氯呋喃濃度呈現正相關。

根據上述的研究結果，本文建議實施油症患者健康照護政策時，應盡可能增

加各種癌症疾病的篩檢項目，特別是肝癌、肺癌、胃癌以及淋巴及造血組織癌症等，但不應僅限於上述列舉的癌症項目。此外，油症兒亦有許多健康上的損害，除了本文所發現的聽力損失問題，過去亦曾發現許多疾病與產前暴露多氯聯苯/多氯呋喃有關，其健康損害的程度並不亞於第一代油症患者。目前油症兒的健康問題，受到關注的程度仍比不上第一代，建議未來油症兒的照護政策，應盡可能比照第一代。

關鍵字：多氯聯苯、多氯呋喃、油症、死因、聽力損失、產前暴露。

Abstract

In 1979, there was an outbreak of severe acne, skin pigmentation, and conjunctivitis in central Taiwan. Most of the cases had consumed the same brand of cooking oil, bought at the same stores. The illness, and its relation to cooking oil consumption, resembled a form of polychlorinated biphenyls (PCBs) and dibenzofurans (PCDFs) poisoning (called "Yusho," oil disease in Japanese) that had occurred in western Japan in 1968, and oil and blood samples sent to Tokyo for analysis had high concentrations of PCBs and PCDFs. Yucheng ("oil disease" in Chinese) thus became the second recorded disease outbreak due to rice bran cooking oil contaminated by PCBs/PCDFs during manufacture. Although about 2000 persons registered with health agencies as being exposed after each episode, the exact number of victims is unknown.

We followed the exposed persons and compared their cause-specific mortality with that of neighborhood referents 30 years after the accident. Furthermore, we conducted a meta-analysis of Yucheng and Yusho cohorts to reevaluate the effects of PCBs and PCDFs on major causes of mortalities. PCBs have been suggested as neurotoxicants especially when exposed during prenatal and early postnatal periods, and known to cause neurological effects including auditory impairments. Thus we conducted a follow-up study to examine the association between gestational PCBs/PCDFs exposure and

auditory function in Yucheng children's early adulthood.

The main findings of current studies were as follows: 1) 30 year follow-up of mortality in the Yucheng cohort as compared to a neighborhood reference group found increased deaths from liver diseases, cardiovascular diseases, systemic lupus erythematosus, and neoplasms including stomach cancer and lymphatic and hematopoietic tissue cancer. 2) A meta-analysis of Yucheng and Yusho cohorts showed similar elevation from all cancer, lung cancer, heart disease, and hepatic disease mortalities in exposed men. Furthermore, a new finding of elevated liver cancer mortality in exposed women was identified. 3) Gestational exposure to PCDFs caused adverse asymmetrical hearing effects detectable even in early adulthood.

Our studies suggest that the health care policy for Yucheng victims should include, but not limited to, stomach, liver, lung, and lymphatic and hematopoietic tissue cancer screening as part of the regular health examination. Besides, we suggest that Yucheng children should receive as much health care as first-generation Yucheng victims.

Key words: Polychlorinated Biphenyls, Polychlorinated Dibenzofurans, Yucheng, Mortality, Hearing Loss, Prenatal, Gestational.

Table of content

List of figures

List of tables

Chapter I. 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; Patterson et al. 2009; Wong et al. 2008). Due to the world-wide ubiquitous background exposure, PCDDs, PCDFs, and PCBs are still a concern to human health.

PCBs, PCDFs, and dioxin-like chemicals are ubiquitous food contaminants in developed countries around the world. However, only two major events of food contamination by PCBs and PCDFs have occurred, 1968 in Japan, and 1979 in Taiwan. In Japan, Yusho (oil-syndrome in Japanese) accident, involving more than 1800 people, was caused by the use of Kanemi brand rice oil contaminated by Kanechlor-400, a Japanese commercial brand of PCB mixture. In addition, the repeated heating partially degraded the PCBs into PCDFs and polychlorinated terphenyls and quarterphenyls (PCTs and PCQs) (Masuda et al., 1986). In 146 Yusho patients, the average amount of Kanechlor 400 ingested was estimated to be about 2 g, with a minimum of 0.5 g

(Kuratsune et al., 1972). Another study of 141 Yusho patients estimated the average intake of PCBs, PCDFs and PCQs per patient to be 633, 3.4, and 596 mg, respectively (Hayabuchi et al., 1979). In the Yusho victims, exposure levels have been studied in the biological samples. PCB concentrations in the adipose tissue of Yusho patients were estimated to have reached 46–76 ppm (wet weight basis; concentration of the analytes reported based on the sample's wet weight) soon after the incident (Masuda et al., 1996). The concentrations of non-ortho and mono-ortho PCBs in the blood of Yusho patients about 34 years after the outbreak were 320 ± 187 (mean, standard deviation) and 75651 ± 58264 pg/g lipid, respectively (Todaka et al., 2007). The concentrations of residual PCDFs in the blood and adipose tissue of Yusho patients 20 years after exposure remained 3-fold to 64-fold greater than those of the general population (Masuda et al., 1997).

In Taiwan, an outbreak of severe acne, skin pigmentation, and conjunctivitis in central Taiwan, and was later called Yucheng (oil-syndrome in Chinese). Most of the victims consumed the same brand of cooking oil obtained from the same store (Hsu et al., 1985). The illness, and its relation to cooking oil consumption, resembled Yusho. Approximately 2000 persons registered with health agencies as being exposed. The Yucheng rice oil was contaminated with PCBs (Kanechlor-500), and their pyrolytic products PCDFs and PCQs (Hsu et al., 1985). Interview was carried out with 98

Yucheng patients and each patient was estimated to consume an average of about 1 g (range = 0.7–1.4) of PCBs and 3.8 mg (range = 1.8–5.6) of PCDFs (Lan et al., 1981). Another estimation of the intakes of PCBs, PCDFs, and PCQs by Yucheng patients were 973, 3.8, and 490 mg, respectively.1 The concentrations of residual PCDFs in the blood of Yucheng victims 14 years after exposure remained one to two orders of magnitude higher than controls (Guo et al., 1997).

In Yucheng cohorts, for example, the concentrations of the PCBs ranged from 3 ppb to 1156 ppb,7 with about 28% below 50 ppb, much above the 1-3 ppb tolerable daily intake set in Germany (van Leeuwen et al., 2000), but still within the range of dioxin-like PCB congeners reported in 187 studies regarding 29,687 subjects of 26 countries world wide (Consonni et al., 2012). However, the initial call of these two events as PCBs intoxication was overly simplified. Due to repeated heating of the rice oil, pyrolytic products PCDFs became present, especially 2,3,4,7,8-penta-CDF and 1,2,3,4,7,8-hexa-CDF.(Guo et al., 1997; Masuda et la., 1979) The PCDFs contributed to much higher levels of the toxic equivalencies (TEQs) than did PCBs.

The Yucheng and Yusho victims were exposed to comparable amount of PCBs and PCDFs. In Yusho, the oil was estimated to be contaminated by 1000-3000 ppm of PCBs and 5 ppm of PCDFs, and the victims were exposed for 1-2 months. On the other hand in Yucheng, the oil was contaminated by 67 to 99 ppm of PCBs and 0.21 to 0.40 ppm of

PCDFs, and the victims were exposed for 9-10 months (Guo et al., 2003; Masuda et al., 2003).

Unlike the occupational cohorts, many of the victims of the Asian outbreaks were symptomatic, and so it seemed likely that the doses to which they were exposed could produce a detectable cancer excess. By 1998, although mortality studies of the Yusho and Yucheng cohorts both showed excess mortality for non-malignant liver disease, only the Yusho cohort showed an excess of liver cancer (Ikeda et al., 1987; Yu et al., 1997). We anticipated that the discrepancy in findings between Yusho and Yucheng would resolve with further follow-up. However, when we updated our report in 2007, we did not observe any increase in liver cancer, but did see an unanticipated excess of deaths from systemic lupus erythematosis (Tsai et al., 2007). These studies used the Taiwan population as the referents, and we were concerned that regional or socioeconomic variation might have biased the findings.

The statistical power for each cohort has been limited by the number of exposed people. Here we conducted a meta-analysis of two cohorts to reevaluate the effects of PCBs and PCDFs on major causes of mortalities.

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 2006; Schantz et al. 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 S, 1996; Lin et al., 2008). 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. Table 1 shows the whole picture of current studies.

Therefore, the aim for this study were:

1. To examine the overall and cause-specific mortalities in Yucheng subjects as compared to their age and gender matched neighborhood referents 30 years after PCBs/PCDFs exposure.
2. To conducted a meta-analysis of two cohorts to reevaluate the effects of PCBs /PCDFs on major causes of mortalities.
3. To examine the association between gestational PCBs/PCDFS exposure and auditory function in Yucheng children's early adulthood.

Chapter II. Literature review

2.1 Polychlorinated biphenyls, dibenzofurans and mortalities

In human epidemiological studies, multitude of health outcomes have been found in people exposed to dioxins occupationally and environmentally. The majority of epidemiological studies focused on TCDD and PCBs induced health outcomes. For TCDD, acute and chronic effects were reported include chloracne, porphyria, transient hepatotoxicity, and peripheral ,central neurotoxicity, atherosclerosis, hypertension, diabetes, vascular ocular changes, and signs of neural system damage (Pelclová et al., 2006). For PCBs, health effects were documented including recurrent infections, neurobehavioral effects, hypothyroidism, infertility and reproductive system disorders, cardiovascular disease, hypertension, diabetes, liver disease, asthma, arthritis, and low birth weight (Carpenter et al., 2006).

Carcinogenicity has been an important outcome of PCBs and dioxin-like chemicals. In animal studies, lymphomas, leukemia and neoplasms in liver, lung, adrenal cortex, nasal turbinate/hard palate, thyroid, thymus, skin/subcutaneous tissue, tongue, and stomach have been documented (Teeguarden et al., 2005). In workers exposed to PCBs, elevated mortality rates were found for malignant melanoma (Sinks et al., 1992; Kimbrough et al., 2003; Ruder et al., 2006), brain cancer (Sinks et al., 1992; Kimbrough

et al., 2003; Ruder et al., 2006), gastrointestinal cancer (Kimbrough et al., 2003; Bertazzi et al., 1987; Tironi et al., 1996; Prince et al., 2006), cancer of the biliary tract, liver, and gallbladder (Kimbrough et al., 2003; Prince et al., 2006; Brown et al., 1981; Brown et al., 1987; Gustavsson et al., 1986; Gustavsson et al., 1997), cancer of the hematopoietic system (Kimbrough et al., 2003; Bertazzi et al., 1987; Gustavsson et al., 1986; Gustavsson et al., 1997); stomach cancer (Mallin et al., 2004), thyroid cancer (Mallin et al., 2004), and prostate cancer (Prince et al., 2006; Charles et al., 2003). In addition, workers exposed to PCDDs/PCDFs were found to have increased cancer mortality for rectum cancer (Flesch-Janys et al., 1998), laryngeal cancer (Steenland et al., 1999), bladder cancer (Steenland et al., 1999), lung cancer (Fingerhut et al., 1991; Flesch-Janys et al., 1998; Hooiveld et al., 1998; Ott et al., 1996), soft tissue sarcoma (Fingerhut et al., 1991; Saracci et al., 1991), and lymphatic and hematopoietic cancer (Steenland et al., 1999; Flesch-Janys et al., 1998).

Among people exposed to dioxins, the Seveso cohort consisted of people lived in a densely populated area accidentally exposed to TCDD through a contaminated chemical cloud released from a chemical plant. Follow-up studies in Seveso found increased mortality of lymphatic and hematopoietic cancer, diabetes and chronic obstructive pulmonary disease in the highly contaminated zones A and B, as compared to the non-

contaminated municipalities (Bertazzi et al., 2001, Consonni et al., 2008). The Ranch Hand Cohort of the US consisted of veterans exposed to Agent Orange contaminated with TCDD during Vietnam War. Mortality of circulatory diseases was increased in the Ranch Hand Cohort (Ketchum et al., 2005). Yusho victims of Japan were accidentally exposed to PCBs/PCDFs through the ingestion of contaminated rice oil. In Yusho males, increased mortality of total neoplasms, liver cancer, and lung cancer were found compared to general population (Ikeda et al., 1996; Ikeda et al., 1987; Onozuka et al., 2008). However, such increase was not found for Yusho females.

2.2 Mortalities among Yucheng and Yusho victims

In 2009, a 40-year mortality study of Yusho cohort found elevated all cancer, lung cancer, and liver cancer in males.15 Similarly, in 2013, a 30-year mortality study of Yucheng cohort found a trend of excess all neoplasms (standardized mortality ratio (SMR) =1.3, 95% confidence interval (CI) = 0.9–1.7), and elevated stomach and lymphatic and haematopoietic tissue cancer in males. Besides, increased mortalities from chronic liver diseases, liver cancer, cardiovascular diseases, and systemic lupus erythematosus were identified in male and/or female Yucheng in subjects.16 Both episodes found higher risk of dying from cancer only in males after exposure to high dose of PCBs/PCDFs. Among Yucheng and Yusho females, however, no significant elevation of cancer mortality was found. The statistical power for each cohort has been limited by the number of exposed people. Here we conducted a meta-analysis of two cohorts to reevaluate the effects of PCBs and PCDFs on major causes of mortalities.

2.3 Gestational exposure to polychlorinated biphenyls and hearing loss

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; Powers et al. 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 et al. 2000).

Chapter III. Material and methods

3.1 Polychlorinated biphenyls, dibenzofurans and mortalities

The follow-up study of mortality status has been approved by the Institutional Review Board of the National Taiwan University Medical Center. We began with the Yucheng Registry (Hsu et al., 1985) and the list of neighborhood referents that was described previously (Yu et al., 1997; Guo et al., 1999). When the PCB poisoning was discovered in 1979, a registry of subjects was set up by the Taiwan Provincial Department of Health. The criteria used to identify subjects included consumption of brands of rice oil produced in the factory known as the source of the contamination, and the development of skin, nail, eye, and other symptoms from January to October 1979. About 10% of persons in the registry gave a history of PCB exposure and had elevated serum PCB concentrations but were asymptomatic (Hsu et al., 1985).

A total of 2,061 subjects were included in the Yucheng registry by 1983, including 70 children born to exposed mothers. Among the 1,991 in the list who were directly exposed, 154 did not have an address, and thus could not be traced further. These individuals were excluded from the first study of mortality in 1992 (Yu et al., 1997). Each person in Taiwan is assigned a national identification number when registering their first permanent address. We had the national identification number for all participants. A typical national identification number has 1 English letter and 9 digits. The last digit of the national identification number is a check digit, which is generated from the letter and the other digits based on a formula. The check digit helps identify legitimate national identification numbers. Among the national identification numbers listed for the Yucheng subjects, 34 had check digits that were inconsistent with the rest

of the number and were excluded. We thus had 1,803 exposed Yucheng subjects for this study.

The neighborhood referents were recorded as residents, in 1979, of the same community (usually on the same street), had the same gender, had birthdays within 3 years of the Yucheng subjects' birthday, and were not themselves in the registry. We attempted to identify three referents for each Yucheng subject, and found 5,519 eligible persons. Among them, 8 had no date of birth recorded, and 98 were born after June 30, 1978, during or after the incident, and so had been selected in error and were excluded. An additional 243 had national identification numbers with an inconsistent check digit, and they were excluded, leaving 5,170 neighborhood referents. The final ratio of Yucheng subjects to neighborhood referents was 1: 2.9. We previously reported that these referents were of similar education, occupation, and socioeconomic status as the Yucheng subjects (Guo et al., 1999).

We compared the national identification numbers of these two groups with the national mortality registry to determine vital status, and, if deceased, date of death and cause of death. In Taiwan, it is mandatory to report deaths within 1 month to the local registration office responsible for the area in which the deceased resided. These reports are believed to be complete. The cause of death was coded according to the ninth revision of the International Classification of Diseases (ICD-9). Unfortunately, the national mortality registry did not contain national identification numbers until 1985. To address this issue, we used another mortality registry to obtain identification numbers. The Taiwan Ministry of the Interior had established a separate death registry based on death certificates. This registry had complete identification numbers, but lacked the ICD-9 codes. We submitted the identification numbers to the Ministry of Interior's

registry to determine fact and date of death, and then, using them plus the date of birth and area code of the decedents, matched to the national mortality registry for ICD-9 cause of death. We only accepted exact matches. This yielded a valid match for 89% of all decedents from 1980-84.

Among the 1,803 Yucheng subjects and 5,170 neighborhood referents, 295 and 757 had died between January 1, 1980 and December 31, 2008, respectively. The overall and cause-specific mortality of the Yucheng subjects were compared to neighborhood referents. Each study subject contributed observed person-time from January 1, 1980 to the date of the end of follow-up (December 31, 2008) or through their date of death.

We used an age-stratified method to calculate standardized mortality ratio (SMR). The person-years at risk for all subjects were combined into gender, 5-year age, and 1-year calendar time-specific groups. The accumulated person-years were then multiplied by the gender, age, calendar time, and cause-specific neighborhood referents' mortality rates to yield the expected numbers of cause-specific deaths. The observed number of cause-specific deaths was then divided by the expected number of cause-specific deaths to yield the SMR. The 95% confidence intervals around the SMRs were estimated based on the Fisher mid-P exact confidence intervals. Mortality data also were analyzed separately by gender. For those national identification numbers that appeared in the mortality database, but lacked an ICD-9 code, the person-time of observation was still included when calculating SMRs.

3.2 Mortalities among Yucheng and Yusho victims

Data extraction

The articles and the extracted data were reviewed independently by two investigators (Ming-Chieh Li and Yue-Liang Leon Guo). The following information was extracted from the two studies: first author, year of publication, country, cohort size, follow-up period, person-year of follow-up, and SMRs and 95% CI for cancer or non-cancer diseases. The cause of death was coded according to the ninth revision of the International Classification of Diseases (ICD-9). Information on chemical contaminants in the oils were extracted from Masuda et al., 1986.[1] Exposure levels were extracted from Guo et al., 1997[9], Lambert et al., 2006,[17] Tanabe et al.,[18] 1989, and Masuda et al., 1998.[19]

Statistical analysis

Log-transformed 95% CIs were calculated for estimating the standard errors (SEs) for the ln(SMR) by the formula: SE=[ln(upper limit)-ln(lower limit)]÷(2×1.96).[20] For diseases in which there was no death (0) observed, we elected not to calculate the combined SMRs.

Overall pooled SMRs and 95% CIs were obtained using random-effects methods.[21] Heterogeneity of effects across studies was assessed by the Cochran's Q statistic and was deemed significant when *p*-Value < 0.10. To evaluate the percentage of variation attributable to heterogeneity, we calculated the I^2 statistics.[22] Substantial heterogeneity was defined at I^2 > 50% and/or *p*-Value <0.10 by the Q test. For those diseases with significant heterogeneity, summary mortality was not calculated, and only results from individual cohorts were shown. Statistical analyses were conducted using STATA 12.0 (Stata Corp, College Station, TX), notably the metan commands. Statistical significance of pooled SMRs was defined as a *p*-Value of lower than 0.05.

3.3 Gestational exposure to polychlorinated biphenyls and hearing loss

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.

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.

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.

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 (ER2; Etymotic Research, 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 (ER10B+; Etymotic Research), 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.

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 ℃, 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.

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. <=20) at different frequencies as dependent variables, and exposure

status (Yucheng vs. referent) 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).

Chapter IV. Results

4.1 Polychlorinated biphenyls, dibenzofurans and mortalities

A total of 1,803 Yucheng subjects with 48,751 person-years and 5,170 neighborhood referents with 141,774 were at risk from January 1, 1980 to the dates of death or December 31, 2008. A total of 295 Yucheng subjects and 757 neighborhood referents died during that time. Table 1 shows that there was a similar age and gender distribution for Yucheng subjects and neighborhood referents.

Table 2 shows results for all-cause and cause-specific mortality. The *all-cause* standardized mortality ratio was elevated for all Yucheng subjects and for males specifically. Elevations occurred among all Yucheng subjects for *diseases of the circulatory system* (SMR=1.3, 95% CI: 1.0–1.6). In *diseases of the circulatory system*, the SMRs for *acute myocardial infarction* (SMR=2.0, 95% CI: 1.0–3.4), *other forms of heart disease* (SMR=2.3, 95% CI: 1.4–3.5), *cardiac dysrhythmias* (SMR=5.8, 95% CI: 1.8–13.9), and *late effects of cerebrovascular disease* (SMR=2.9, 95% CI: 1.3–5.7) were increased. The SMR for *diseases of the musculoskeletal system* and *connective tissue* (SMR=6.4, 95% CI: 2.8–12.7) was much increased due to *systemic lupus erythematosus* mortality (1 male and 5 females in Yucheng subjects, 0 in neighborhood referents).

Among Yucheng males, the SMRs for *diseases of the digestive system* (SMR=1.9, 95% CI: 1.2–2.8), and *injury and poisoning* (SMR=1.5, 95% CI: 1.0–2.1) were increased. In *diseases of the digestive system*, the SMR for *chronic liver disease and cirrhosis* (SMR=2.5, 95% CI: 1.5–3.9) was increased. Although the SMR for *disease of the circulatory system* was not increased, the SMRs for *acute myocardial infarction*

(SMR=3.3, 95% CI: 1.6–6.4) and *other forms of heart disease* (SMR=2.2, 95% CI: 1.2–3.8) were increased. Although the SMR for all neoplasms was not increased, the SMRs for *malignant neoplasm of stomach* (SMR=3.5, 95% CI: 1.5–7.0) and *malignant neoplasm of lymphatic and haematopoietic tissue* (SMR=3.0, 95% CI: 1.1–6.6) were increased. The SMR for *diabetes mellitus* was decreased (SMR=0.3, 95% CI 0.1–0.9).

Among Yucheng females, the SMRs for *diseases of the circulatory system* (SMR=1.5, 95% CI: 1.0–2.1) and *musculoskeletal system and connective tissue* (SMR=16.5, 95% CI: 6.7–34.3) were increased. In *disease of the circulatory system*, the SMRs for *other forms of heart disease* (SMR=2.4, 95% CI: 1.2–4.5), *cardiac dysrhythmias* (SMR=9.6, 95% CI: 2.4–26.0), and *late effects of cerebrovascular disease* (SMR=5.4, 95% CI: 1.7–13.1) were increased. In *disease of musculoskeletal system and connective tissue*, the relative mortality from systemic lupus erythematosus was very high (5 in Yucheng females, 0 in neighborhood referents).

Compared with our previous study (Tsai, et al., 2007), new findings here are increased mortality from all causes, malignant neoplasms, and diseases of the circulatory system (Table 3).

4.2 Mortalities among Yucheng and Yusho victims

Table 4 summarizes the characteristics of Yucheng and Yusho cohorts. A total of 1,803 Yucheng subjects (Male, N=830; Female, N=973) with 48,751 person-years of follow-up and 1,664 Yusho subjects with 50,773 person-years are included. A total of 295 Yucheng subjects and 441 Yusho subjects died during the follow-up period.

Table 5 showed the cause specific mortalities from the individual studies, as well as the pooled mortalities. An increase in all-cause mortality was found in pooled subjects (pooled SMR=1.1, 95% CI: 1.1–1.2, I^2=28.6%), notably among pooled males (pooled SMR=1.2, 95% CI: 1.1–1.3, I^2=0.0%). Pooled male and pooled female subjects had different findings in regard to all cancer mortality. The SMR for all cancer was increased only in pooled males (pooled SMR=1.3, 95% CI: 1.1–1.6, I^2=0.0%). Despite that liver cancer was not elevated in pooled subjects (pooled SMR=1.5, 95% CI: 0.9–2.7, I^2=50.1%), significant elevation was found in pooled females (pooled SMR=2.0, 95% CI: 1.1–3.6, I^2=0.0%). Elevation was found for lung cancer (pooled SMR=1.5, 95% CI: 1.1–2.1, I^2=0.0%) among pooled subjects, notably among pooled males (pooled SMR=1.7, 95% CI: 1.2–2.3, I^2=0.0%).

Elevations occurred in pooled subjects for heart disease (pooled SMR=1.3, 95% CI: 1.0–1.7, I^2=43.4%). Increased hepatic disease mortality was found in pooled subjects

(pooled SMR=1.5, 95% CI: 1.0–2.4, I^2=27.7%), notably among pooled males (pooled SMR=1.9, 95% CI: 1.3–2.8, I^2=0.0%).

4.3 Gestational exposure to polychlorinated biphenyls and hearing loss

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 6). Among Yucheng children, non-participants had average age of 21.3 ± 3.8, 51.0% males. Among referents, non-participants had average age of 21.3 ± 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 7.

Table 8 showed results of logistic regression using elevated pure tone auditory thresholds (>20 vs. <=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 9 showed 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 10 showed 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).

Chapter V. Discussion

5.1 Polychlorinated biphenyls, dibenzofurans and mortalities

We did a follow-up study comparing the mortality experience of persons with high exposures to PCBs and PCDFs 30 years previously with that of a neighborhood referent group. We found increased all-cause mortality, and specific increases in mortality from *malignant neoplasms of the stomach*, and of *lymphatic and haematopoietic tissue*; *diseases of the circulatory system*, *diseases of the digestive system*, and *diseases of the musculoskeletal system and connective tissue*. In Taiwan in the 1980s, much of the population resided in the 2 largest cities – Taipei in the north and Kaohsiung in the south. Yucheng occurred in central Taiwan, in relatively rural Taichung and Changhua counties. Thus the national mortality rates, dominated by the experience of the cities, were not reflective of the demographic characteristics of the Yucheng subjects. It has always been desirable to have a local referent for mortality, but, until recently, there were too few deaths to allow stable comparisons.

This is the first time the Yucheng follow-up has showed elevated mortality due to malignant neoplasms. They occur mostly in males, which is also true in the 40 year follow-up from Yusho in Japan (Onozuka et al., 2009). The predominant excesses in Japan are in liver and lung cancer, with a small increase in stomach cancer, whereas we see excesses in stomach and haematopoietic malignancies, and no liver cancer excess. It may be worth noting that, throughout follow-up, there has been a larger excess of non-malignant liver disease mortality, but not liver cancer mortality, among Yucheng subjects compared with Yusho subjects from Japan. The differences might be due to the differences in the degree and character of the contaminants in the rice oil (Masuda et al.,

1985), or to the different prevalence of some other etiologic factor, such as aflatoxin (Montesano, et al., 1997), or hepatitis virus (Centers for Disease Control and prevention, 2008) between Japan and Taiwan. However, the mechanisms underlying both the difference in cancer sites and the much later appearance of malignancy in Taiwan are still unclear.

Several cohorts with exposure to high levels of dioxin-like chemicals show elevated risks of cancer of the lymphatic and hematopoietic system (Steenland et al., 1999; Flesch-Janys et al., 1998; Bertazzi et al., 2001; Bertazzi et al., 1989; Consonni et al., 2008; Kimbrough et al., 2003; Gustavsson et al., 1986; Gustavsson et al., 1997). For stomach cancer, a mortality study of capacitor manufacturing workers found elevated risk in male workers (Mallin et al., 2004). Incidence of stomach cancer was increased in the highly exposed residents living around a former PCB production site (Pavuk et al., 2004).

We also found excess mortality from circulatory diseases, specifically acute myocardial infarction and other forms of heart disease, but not cerebrovascular disease. Among other forms of heart diseases, death from cardiac dysrhythmias was elevated in Yucheng subjects. A systematic review suggested an association between dioxin exposure and mortality from ischemic heart disease, and possibly all cardiovascular disease (Humblet et al., 2008). People living in areas contaminated with persistent organic pollutants, including PCBs and dioxins/furans, had elevated rates of hospital discharge for coronary heart disease and acute myocardial infarction compared to those living in non-contaminated areas (Sergeev and Carpenter, 2005). In the Ranch Hand cohort, exposed to Agent Orange contaminated with TCDD, increased mortality from circulatory diseases was found at 20 years of follow-up (Ketchum and Michalek, 2005).

In Yusho subjects exposed to PCBs/PCDFs in Japan, elevated mortality from heart disease was found among females in the period 25–29 years after the incident, but not for other periods (Onozuka et al., 2009). Another study of Yusho (Kashima et al., 2011) reported an increased SMR for cardiovascular disease shortly after the exposure. Our findings of increased mortality from circulatory diseases support the association of exposure to dioxin-like chemicals with cardiovascular mortality.

Among Yucheng subjects, the SMR for systemic lupus erythematosus was quite increased, with one among Yucheng males, five among Yucheng females; and zero among the neighborhood referents. This finding was consistent with the previous study using the general population as reference group (Tsai et al., 2007). In the Yusho cohort, no mortality due to systemic lupus erythematosus was reported. However, Shimizu reported higher nitrotyrosine in the serum of Yusho subjects (Shimizu et al., 2008). Nitrotyrosine is a marker of protein oxidation in sera and is associated with disease severity in patients with lupus (Morgan et al., 2005). Further study is warranted to determine whether nitrotyrosine was elevated in Yucheng subjects, which might have contributed to the development of systemic lupus erythematosus.

Diabetes has higher prevalence among Yucheng females, but not males (Wang et al., 2008). However, diabetes mortality was not higher in females and lower in males. Possible causes of these observations include the low case-fatality rate for diabetes, making estimates of the SMR unstable, and assigning diabetes-related cardiovascular disease to the cardiovascular disease category.

There are strengths in this investigation. The establishment of a registry soon after the exposure allowed for relatively complete and unbiased ascertainment of exposed

subjects for mortality studies. The use of neighborhood referents limited bias due to socioeconomic or geographic factors. There are also limitations in this study. First, in the national mortality registry of 1980-84, only 89% of all decedents had complete national identification numbers and ICD-9 codes. Thus, some deceased subjects could have been misclassified as being alive. This would affect both Yucheng subjects and referents, and should cause underestimation of deaths in both groups. Therefore, it is unlikely to produce high SMRs in the Yucheng group. Second, some subjects were excluded due to wrong or missing national identification numbers. This might have caused underestimation of deaths in both groups. Third, although using neighborhood referents may minimize some bias due to socioeconomic or geographic factors, confounding due to other factors such as medical history, smoking status, alcohol drinking, and physical activity could not be controlled. Fourth, selection bias cannot be ruled out, because the selection processes of Yucheng subjects and their neighborhood referents were different. Since one of the selection criteria for the Yucheng subjects was presence of symptoms related to PCB exposure, it is possible that those included in the registry were at higher risk of having some illnesses. However, the most prevalent symptoms among the Yucheng subjects in the registry were skin (chloracne and hyperkeratosis), nail (discoloration), and eye symptoms (discharge and eyelid swelling). These were more likely directly related to PCB poisoning, and less likely early signs of other important illnesses but unrelated to PCBs. We cannot exclude the possibility that persons with exposure and symptoms were more likely to be registered than those without. There was, however, much local publicity at the time about the etiology of the illness and the specific sites where the contaminated oil was sold or used. About 10% of those registered had a history of consuming the oil and/or elevated serum levels of PCBs. We do not believe there were many people with high PCB exposure and no

symptoms; if there were, our estimates of the SMRs are too high. Finally, some of the referents may have been exposed to the contaminated oil without their knowledge. We believe this to be unlikely. The provincial health department announced the etiology of the episode through mass media and local health units in October, 1979, and offered analysis of serum for PCBs to anyone who thought they had been exposed (Hsu et al., 1985). In 1992, pooled neighborhood blood samples from 56 women were analyzed for PCBs and PCDFs, which showed background exposure only (Guo et al., 1997). If there were many people with exposure who did not participate in the registry but suffered ill effects from their exposure, then our estimates of the SMRs are too low.

5.2 Mortalities among Yucheng and Yusho victims

This is the first study examining overall mortality in the two largest exposed populations to PCBs and PCDFs in the world. Our results suggested elevated mortality from all-cause, lung cancer, heart disease, and hepatic disease among pooled subjects. In addition, we found increased all-cause, all cancer, lung cancer, and hepatic disease among pooled males, and increased liver cancer among pooled females.

Compared to individual mortality studies (Onozuka et al., 2009; Li et al., 2013), this study's new finding included elevated mortality from liver cancer in pooled females. In individual studies, significant excess of liver cancer was shown only among Yusho males (Onozuka et al., 2009). Combining two cohorts increased statistical power and female liver cancer was found elevated. The literature about PCBs and liver cancer has been inconclusive. A recent study carried out among subjects with hepatocellular carcinoma (HCC) living in a highly polluted area by PCBs did not find substantial differences in total PCB mean and median values with respect to the general population, and no variation in total PCB serum levels according to HCC etiology (viral vs non-viral vs unknown) (Zani et al., 2013a). Furthermore, liver cancer mortality among cohorts occupationally exposed to PCBs has been inconsistent, as summarized in a recent systematic review (Zani et al., 2013b). Among several follow-up studies of

occupational cohorts exposed to PCBs, only one reported significantly elevated mortality for liver cancer in female (Mallin et al., 2004), but not the others (DeGuire et al., 1992; Pesatori et al., 2013; Ruder et al., 2014; Kimbrough et al., 2014). A possible explanation for those findings could be the healthy worker effect, which rendered a reduced overall mortality and thus non-significant mortality of individual conditions with moderate elevation. Besides, Yucheng and Yusho cohorts were both exposed to high dose of PCDFs, which were chemically and toxicologically similar to 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD), in addition to PCBs. PCDFs or the combined effects of PCBs and PCDFs induced the observed results.

Hepatitis B virus (HBV) is one of the major causes of liver cirrhosis and hepatocellular carcinoma. If Yucheng or Yusho group lived in the area with high prevalence rate of HBV, selection of referent groups from areas with low prevalence rates of HBV would have resulted in bias. In Taiwan, the carrier rate of hepatitis B surface antigen in the general population was as high as 15-20 percent (Chien et al., 2006). However, in Yucheng mortality study, referents were selected from the neighborhood (Li et al., 2013). Therefore, biased results due to discrepancy of HBV carrier rates in Yucheng and reference groups were unlikely. In Japan, referents were background population of the country. However, only approximately 1.5 million people

were infected with HBV, accounting for only 1-2% in Japan general population (Yokosuka et al., 2009). Due to the low prevalence rate of HBV, the likelihood of bias induced by HBV is not large. Japan and Taiwan cannot be considered overlapping as regards HCC epidemiology, as HBV infection has been the main cause of liver disease in the former and hepatitis C virus in the latter, in the last decades (Kim et al., 2013). The discrepancies between the two cohorts may also be explained by the different age at the beginning of the viral hepatitis infection.

Although TCDD and PCBs were both classified as human carcinogens by International Agency for Research on Cancer (International Agency for Research on Cancer, 1997; Lauby-Secretan et al., 2013), human studies showed limited information on specific sites of cancer. Current study provided evidence for reconsideration of human carcinogenesis in lung or liver.

Several discrepancies in SMR were found between Yucheng and Yusho. Comparing to their own control population, Yucheng had elevated heart disease mortality, but Yusho did not. Causes for such observed difference include several possibilities. Japanese people had lower standardized mortality rate for heart diseases as compared to Taiwanese people (Department of Budget, Accounting and Statistics, Taipei City Government, 2008). Even after 40 years of follow-up, exposure to PCBs and PCDFs did

not affect the Yusho victims' heart mortality significantly. On the other hand, heart diseases were increased in Yucheng, likely as a results of accelerated atherosclerosis, as reviewed by Humblet et al (Humblet et al., 2008). The finding of elevated heart mortality in Yucheng is comparable to people highly exposed to Agent Orange (Ketchum et al., 2005). It is also possible that misclassification in ICD-9 coding occurred in Japan caused inability to detect elevated heart diseases in Yusho victims (Onozuka et al., 2009).

The other discrepancy in mortality was elevated liver cancer in Yusho men, but not in Yucheng men. This might have to do with the observed increased mortality due to cirrhosis and chronic liver disease occurring early in Yucheng men (Tsai et al., 2007). Acute insult might have caused deterioration in susceptible Yucheng men, who deceased from cirrhosis or chronic liver disease, rendering lower number of susceptible victims who would have develop liver cancer in later years as observed in Yusho men.

The discrepancies in mortality between Yusho and Yucheng study might be caused due to several reasons. First, in Yucheng study, the rice oil was contaminated by Kanechlor 500 and their pyrolytic products PCDFs and PCQs, whereas in Yusho study, Kanechlor 400 was the major contaminant. However, previous studies showed that Yusho and Yucheng victims had similar level of dioxin-TEQ (Lan et al., 1981; Lambert

et al., 2006; Tanabe et al., 1989; Masuda et al., 1998), with an average concentration of 2300 ppt-TEQ in Yucheng victims, and 2630 ppt-TEQ in Yusho victims. Thus combining two cohorts is reasonable. Second, the different follow-up period between two cohorts would be an issue. Since the majority of cancers and chronic diseases appear in older people, the shorter follow-up period in Yucheng study might cause underestimations when calculating meta-SMR. However we still found some cancers increased significantly. Finally, although the median exposure levels were close, Yusho event was caused by higher levels of PCBs and PCDFs in the contaminated oil, and a shorter period of exposure. It is possible that shorter exposure to higher levels of toxins might have caused heterogeneity in the outcomes.

This meta-analysis offers some advantages over previously reported studies. 1) Yucheng and Yusho subjects belong to longitudinal follow-up cohorts, providing better inference in causal relationship. 2) To our best knowledge, there have been only two events of this magnitude and severity in the world. Both Yucheng and Yusho victims were Asian people, and were exposed to similar high dose of PCBs/PCDFs. Thus, combining two cohorts is reasonable and allows us to detect the mortalities rates more accurately and powerfully. 3) Many follow-up studies on mortality among people exposed to PCBs and/or PCDFs were occupational groups, and potentially subject to

healthy worker effect. Both Yucheng and Yusho cohorts were not occupational cohorts, and less likely affected by this effect.

However, there are limitations in this meta-analysis. 1) A shorter follow-up period (30 years) in Yucheng cohort, as compared to 40 years in Yusho, might not be sufficient to allow for chronic diseases to develop, even if there was truly effects. Thus, the risk of mortality of chronic diseases might be underestimated. 2) Despite pooling of the follow-up person-years, a total of 99,524 person-years still did not provide sufficient statistical power to detect diseases with medium to low occurrence. 3) Comparing the age-standardized mortality rates using the 2000 World Heath Organization standard population as the standard, Yucheng (9442×10^{-5}) had higher rates than Yusho (6987×10^{-5}) people (data not shown). However, SMR is a relative measurement. When calculating SMR, the reference group provided information to compute the expected death in the exposed group. Therefore different overall mortality rates do not bias the results when combining two SMR values.

5.3 Gestational exposure to polychlorinated biphenyls and hearing loss

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. 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; Potter et al. 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.

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 12000, 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 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.

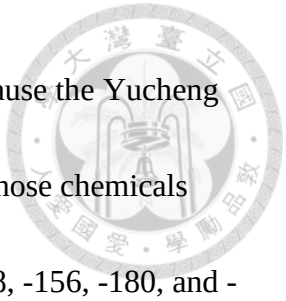
In this study, we did not examine effects of postnatal exposure due to breast-feeding

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, 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 & 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 Chao et al. (1997), 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.

Chapter VI. Conclusions and suggestions

6.1 Conclusion and suggestions for future studies

The main findings of these studies were as follows: 1) 30 year follow-up of mortality in the Yucheng cohort as compared to a neighborhood reference group found increased deaths from liver diseases, cardiovascular diseases, systemic lupus erythematosus, and neoplasms including stomach cancer and lymphatic and hematopoietic tissue cancer. Additional follow up is necessary to confirm the present findings. 2) The meta-analysis of Yucheng and Yusho cohorts reevaluated the effects of PCBs and PCDFs on major causes of mortalities. Mortalities from all-cause, all cancer, lung cancer, and hepatic disease in exposed men were similarly elevated. Furthermore, a new finding of elevated liver cancer mortality in exposed women was identified. 3) A follow-up study of Yucheng children gestational exposure to PCBs/PCDFs found increased prevalence of mild asymmetric 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. Further studies are warranted to identify the mechanism on how gestational exposure to PCDFs induces asymmetric hearing loss.

6.2 Suggestions for health care policy of Yucheng victims

According to the results of current studies, we suggest that the health care policy for Yucheng victims should include, but not limited to, stomach, liver, lung, and lymphatic and hematopoietic tissue cancer screening as part of the regular health examination. Besides, current health care policy pay insufficient attention to Yucheng children. We suggest that Yucheng children should receive as much health care as first-generation Yucheng victims.

Reference

Adcock IM, Brown CR, Kwon O, et al. Oxidative stress Induces NFκB DNA binding and inducible NOS mRNA in human epithelial cells. Biochemical and Biophysical Research Communications 1994;199:1518-24.

Sergeev AV and Carpenter DO. Hospitalization rates for coronary heart disease in relation to residence near areas contaminated with persistent organic pollutants and other pollutants. Environ Health Perspect 2005;113:756-61.

Anderson HA. General population exposure to environmental concentration of halogenated biphenyls. In: Kimbrough RD, Hansen AA, editors. Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxinx and Related Products. Amsterdam: Elsevier; 1989:325-44.

Bastomsky CH. Enhanced thyroxine metabolism and high uptake goiters in rats after a single dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Endocrinology 1977;101:292-6.

Bertazzi PA, Riboldi L, Pesatori A, et al. Cancer mortality of capacitor manufacturing workers. Am J Ind Med 1987;11:165-76.

Bertazzi PA, Consonni D, Bachetti S, et al. Health effects of dioxin exposure: a 20-year mortality study. Am J Epidemiol 2001;153:1031-44.

Bertazzi PA, Zocchetti C, Pesatori AC, Guercilena S, Sanarico M, Radice L. Ten-year mortality study of the population involved in the Seveso incident in 1976. Am J

Epidemiol 1989;129:1187-200.

Boucher O, Bastien CH, Saint-Amour D, et al. Prenatal exposure to methylmercury and PCBs affects distinct stages of information processing: an event-related potential study with Inuit children. Neurotoxicology 2010;31:373-84.

Bradburn MJ. Oxford: Centre for Statistics in Medicine. Updated and New Commands for Meta-analysis in STATA. Cancer Research UK Medical Statistics Group, 2004.

Brown DP, Jones M. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Arch Environ Health 1981;36:120-129.

Brown DP. Mortality of workers exposed to polychlorinated biphenyls—an update. Arch Environ Health 1987;42:333-9.

Casoli P, Tumiati B, La Sala G. Fatal exacerbation of systemic lupus erythematosus after induction of ovulation. J Rheumatol 1997;24:1639-40.

Centers for Disease Control and prevention (CDC). Travelers' health; yellow book. Atlanta, GA: US Department of Health and Human Services. Available at http://wwwn.cdc.gov/travel/yellowbookch4-HepB.aspx (accessed September 4, 2012).

Chao WY, Hsu CC, Guo YL. Middle-ear disease in children exposed prenatally to polychlorinated biphenyls and polychlorinated dibenzofurans. Arch Environ Health 1997;52:257-62.

Charles LE, Loomis D, Shy CM, et al. Electromagnetic fields, polychlorinated biphenyls, and prostate cancer mortality in electric utility workers. Am J Epidemiol 2003;157:683-91.

Chau JK, Lin JR, Atashband S, Irvine RA, Westerberg BD. Systematic review of the evidence for the etiology of adult sudden sensorineural hearing loss. Laryngoscope 2010;120:1011-21.

Chen YC, Guo YL, Hsu CC, Rogan WJ. Cognitive development of Yu-Cheng ('oil-disease') children prenatally exposed to heat-degraded PCBs. JAMA 1992;268:3213-18.

Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. Epidemiol Rev 2006;28:126-35.

Consonni D, Pesatori AC, Zocchetti C, et al. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. Am J Epidemiol 2008;167:847-58.

Consonni D, Sindaco R, Bertazzi PA. Blood levels of dioxins, furans, dioxin-like PCBs, and TEQs in general populations: a review, 1989-2010. Environ Int 2012;44:151-62.

Consonni D, Pesatori AC, Zocchetti C, Sindaco R, D'Oro LC, Rubagotti M. Mortality in

a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. Am J Epidemiol 2008;167:847-58.

Crofton KM, Ding D, Padich R, Taylor M, Henderson D. Hearing loss following exposure during development to polychlorinated biphenyls: a cochlear site of action. Hear Res 2000;144:196-204.

Curhan SG, Eavey R, Wang M, Stampfer MJ, Curhan GC. Body mass index, waist circumference, physical activity, and risk of hearing loss in women. Am J Med 2013;126:1142.e1-8.

D Onozuka, T Yoshimura, S Kaneko ,M Furue. Mortality after exposure to polychlorinated biphenyls and polychlorinated dibenzofurans: a 40-year follow-up study of Yusho patients. Am J Epidemiol 2009;169:86-95

Dalton TP, Kerzee JK, Wang B, et al. Dioxin exposure is an environmental risk factor for ischemic heart disease. Cardiovasc Toxicol 2001;1:285-98.

Daniel V, Huber W, Bauer K, Suesal C, Conradt C, Opelz G. Associations of blood levels of PCB, HCHS, and HCB with numbers of lymphocyte subpopulations, in vitro lymphocyte response, plasma cytokine levels, and immunoglobulin. Environ Health Perspect 2001;109:173-8.

Dasmahapatra AK, Wimpee BA, Trewin AL, Hutz RJ. 2,3,7,8- Tetrachlorodibenzo-p-dioxin increases steady-state estrogen receptor-beta mRNA levels after CYP1A1

and CYP1B1 induction in rat granulosa cells in vitro. Mol Cell Endocrinol 2001;182:39-48.

DeGuire L, Cyr D, Thériault G, Provencher S, Iturra H, Case BW. Malignant melanoma of the skin among workers in a telecommunications industry: mortality study 1976-83. Br J Ind Med 1992;49:728-31.

Department of Budget, Accounting and Statistics, Taipei City Government. The leading causes of death and life expectancy of Taipei citizens. 2008.

DO Carpenter. Polychlorinated biphenyls (PCBs): routes of exposure and effects on human health. Rev Environ Health 2006;21:1-23

dos Santos Silva I. Principles and methods. In: dos Santos Silva I, editor. Cancer Epidemiology. Lyon, France: IARC; 1999. p 260.

Fingerhut MA, Halperin WE, Marlow DA, et al. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzop- dioxin. N Engl J Med 1991;324:212-8.

Flesch-Janys D, Steindorf K, Gurn P, et al. Estimation of the cumulated exposure to polychlorinated dibenzo-p-dioxins/ furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. Environ Health Perspect 1998;106(suppl 2):655-62.

Flesch-Janys D, Steindorf K, Gurn P, Becher H. Estimation of the cumulated exposure to polychlorinated dibenzo-p-dioxins/ furans and standardized mortality ratio

analysis of cancer mortality by dose in an occupationally exposed cohort. Environ. Health Perspect 1998;106:655-62.

GH Lambert, LL Needham, W Turner et al. Induced CYP1A2 activity as a phenotypic biomarker in humans highly exposed to certain PCBs/PCDFs. Environ Sci Technol 2006;40:6176-80

Goldey ES, Crofton KM. Thyroxine replacement attenuates hypothyroxinemia, hearing loss, and motor deficits following developmental exposure to Aroclor 1254 in rats. Toxicol Sci 1998;45:94-105.

Goldey ES, Kehn LS, Lau C, Rehnberg GL, Crofton KM. Developmental exposure to polychlorinated biphenyls (Aroclor 1254) reduces circulating thyroid hormone concentrations and causes hearing deficits in rats. Toxicol Appl Pharmacol 1995;135:77-88.

Gorski JR, Rozman K. Dose-response and time course of hypothyroxinemia and hypo-insulinemia and characterization of insulin hypersensitivity in 2,3,7,8-tetrachloro-dibenzo-p-dioxin(TCDD)-treated rats. Toxicology 1987;44:297-307.

Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. Lancet 2006;368:2167-78.

Grandjean P, Weihe P, Burse VW, Needham LL, Storr-Hansen E, Heinzow B, et al. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally

exposed to seafood neurotoxicants. Neurotoxicol Teratol 2001;23:305-17.

Grimvall E, Rylander L, Nilsson-Ehle P, et al. Monitoring of polychlorinated biphenyls in human blood plasma: methodological developments and influence of age, lactation, and fish consumption. Arch Environ Contam Toxicol 1997;32:329-36.

Grune T, Reinheckel T, Davies KJ. Degradation of oxidized proteins in mammalian cells. FASEB J 1997;11:526-34.

Guo Y, Hendrickx AG, Overstreet JW, et al. Endocrine biomarkers of early fetal loss in cynomolgus macaques (Macaca fascicularis) following exposure to dioxin. Biol Reprod 1999;60:707-13.

Guo YL, Chen YC, Yu ML, Hsu CC. Early development of Yu-Cheng children born seven to twelve years after the Taiwan PCB outbreak. Chemosphere 1994;29:2395-404.

Guo YL, Ryan JJ, Lau BP, Yu ML, Hsu CC. Blood serum levels of PCBs and PCDFs in Yucheng women 14 years after exposure to a toxic rice oil. Arch Environ Contam Toxicol 1997;33:104-8.

Guo YL, Yu ML, Hsu CC, Rogan WJ. Chloracne, goiter, arthritis, and anemia after polychlorinated biphenyl poisoning: 14-year follow-Up of the Taiwan Yucheng cohort. Environ Health Perspect 1999;107:715-9.

Guo YL, Yu ML, Hsu CC. The Yucheng Rice Oil Poisoning Incident. In Schecter A,

Gasiewicz TA, eds. Dioxins and Health. John Wiley and Sons, Inc., Hoboken, New Jersey, USA, 2003.

Guo YL, Ryan JJ, Lau BPY, Yu ML, Hsu CC. Serum levels of PCB/PCDFcongeners 14 years after accidental exposure to contaminated rice oil. Arch Environ Contam. Toxicol 1997;33:104-8.

Guo YL, Lin CJ, Yao WJ, Ryan JJ, Hsu CC. Musculoskeletal changes in children prenatally exposed to polychlorinated biphenyls and related compounds (Yu-Cheng children). J Toxicol. Environ. Health. 1994;41:83-93.

Guo YL, Yu ML, Hsu CC, Rogan WJ. Chloracne, goiter, arthritis, and anemia after polychlorinated biphenyl poisoning: 14-year follow-up of the Taiwan Yucheng cohort. Environ. Health Perspect 1999;107:715-9.

Gustavsson P, Hogstedt C, Rappe C. Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med 1986;10:341-4.

Gustavsson P, Hogstedt C. A cohort study of Swedish capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med 1997;32:234-9.

Gustavsson P, Hogstedt C, Rappe C. Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med 1986;10:341-4.

Hayabuchi H, Yoshimura T, Kuratsune M. Consumption of toxic rice oil by 'yusho' patients and its relation to the clinical response and latent period. Food Cosmet Toxicol 1979;17:455-61.

Herr DW, Goldey ES, Crofton KM. Developmental exposure to Aroclor 1254 produces low-frequency alterations in adult rat brainstem auditory evoked responses. Fundam Appl Toxicol 1996;33:120-8.

Hooiveld M, Heederik DJ, Kogevinas M, et al. Second followup of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. Am J Epidemiol 1998;147:891-901.

Hsu ST, Ma CI, Hsu SK, Hsu NH, Yeh CC, Wu SB. Discovery and epidemiology of PCB poisoning in Taiwan: a four-year follow up. Environ Health Perspect 1985;59:5-10.

Hsu ST, Ma CI, Hsu SK, et al. Discovery and epidemiology of PCB poisoning in Taiwan: a four-year follow up. Environ Health Perspect 1985;59:5-10.

Hsu ST, Ma CI, Hsu SKH, et al. Discovery and epidemiology of PCB poisoning in Taiwan: a four-year followup. Environ Health Perspect 1985;59:5-10.

Humblet O, Birnbaum L, Rimm E, Mittleman MA, Hauser R. Dioxins and Cardiovascular Disease Mortality. Environ Health Perspect 2008;116:1443-8.

International Agency for Research on Cancer (IARC). Polychlorinated dibenzo-para-

dioxins and polychlorinated dibenzofurans. IARC Monogr Eval Carcinog Risks Hum 69, 1997.

Ikeda M, Kuratsune M, Nakamura Y, et al. A cohort study on mortality of Yusho patients—a preliminary report. Fukuoka Igaku Zasshi 1987;78:297-300.

Ikeda M, Yoshimura T. Survival of patients. In: Kuratsune M, Yoshimura H, Hori Y, et al, eds. YUSHO: A Human Disaster Caused by PCBs and Related Compounds. Fukuoka, Japan: Kyushu University Press 1996:315-23.

Ikeda M, Kuratsune M, Nakamura Y, Hirohata T. A cohort study on mortality of Yusho patients - a preliminary report. Fukuoka Acta Med 1987;78:297-300.

Inouye K, Ito T, Fujimaki H, et al. Suppressive effects of 2,3,7,8-tetrachlorodibenzop-dioxin (TCDD) on the high-affinity antibody response in C57BL/6 mice. Toxicol Sci 2003;74:315-24.

International agency for research on cancer (IARC). Monographs in PDF–Volume 100-A Review of Human Carcinogens. Part F-Chemical Agents and Related Occupations. Lyon, 2012. Available at http://monographs.iarc.fr/ (accessed June 19, 2012).

Jacobson J and Jacobson S. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 1996;335:783-9.

Jacobson SW, Fein GG, Jacobson JL, Schwartz PM, Dowler JK. The effect of

intrauterine PCB exposure on visual recognition memory. Child Dev. 1985;56:853-60.

Jensen AA. Chemical contaminants in human milk. Residue Rev 1983;89:1-128.

Jokinen MP, Walker NJ, Brix AE, Sells DM, Haseman JK, Nyska A. Increase in cardiovascular pathology in female Sprague-Dawley rats following chronic treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin and 3,3',4,4',5-pentachlorobiphenyl. Cardiovasc Toxicol 2003;3:299-310.

K Mallin, K McCann, A D'Aloisio et al. Cohort mortality study of capacitor manufacturing workers, 1944-2000. J Occup Environ Med 2004;46:565-76.

K Shimizu, F Ogawa, JJ Thiele et al. Increased levels of urinary nitrite and nitrotyrosine in Yusho victims 40 years after accidental poisoning with polychlorinated biphenyls in Nagasaki, Japan. J Appl Toxicol 2008;28:1040-4.

Kashimaa S, Yorifujib T, Tsudad T. Acute non-cancer mortality excess after polychlorinated biphenyls and polychlorinated dibenzofurans mixed exposure from contaminated rice oil: Yusho. Sci Tot Environ 2011;409:3288-94.

Ketchum NS, Michalek JE. Postservice mortality of Air Force veterans occupationally exposed to herbicides during the Vietnam War: 20-year follow-up results. Mil Med 2005;170:406-13.

Ketchum NS, Michalek JE. Postservice mortality of Air Force veterans occupationally

exposed to herbicides during the Vietnam War: 20-year follow-up results. Mil Med 2005;170:406–413.

Kim MN, Kim BK, Han KH. Hepatocellular carcinoma in patients with chronic hepatitis C virus infection in the Asia-Pacific region. J Gastroenterol 2013;48:681-8.

Kimbrough RD, Doemland ML, Mandel JS. A mortality update of male and female capacitor workers exposed to polychlorinated biphenyls. J Occup Environ Med. 2003;45:271-82.

Kimbrough RD, Krouskas CA, Xu W, Shields PG. Mortality among capacitor workers exposed to polychlorinated biphenyls (PCBs), a long-term update. Int Arch Occup Environ Health. 2014. http://link.springer.com/article/10.1007%2Fs00420-014-0940-y Accessed October 12, 2014.

KJ Rothman, JJD Boice. Epidemiologic Analysis with a Programmable Calculator. Washington, DC: USDHEW, NIH; 1979.

Kopf PG, Huwe JK, Walker MK. Hypertension, cardiac hypertrophy, and impaired vascular relaxation induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin are associated with increased superoxide. Cardiovasc Toxicol 2008;8:181-93

Kuratsune M, Yoshimura T, Matsuzaka J, Yamaguchi A. Epidemiologic study on Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand

of polychlorinated biphenyls. Environ Health Perspect 1972;1:119-28.

Lambert GH, Needham LL, Turner W, Lai TJ, Patterson DG Jr, Guo YL. Induced CYP1A2 activity as a phenotypic biomarker in humans highly exposed to certain PCBs/PCDFs. Environ Sci Technol 2006;40:6176-80.

Lan CF, Chen PH, Shieh LL, Chen YH. An epidemiological study on polychlorinated biphenyls poisoning in Taichung area. Clin Med 1981;7:96-100 (In Chinese).

Lans MC, Brouwer A, Koppe JG, Van den Berg M. Enzyme induction and alterations in thyroid hormone, vitamin A and K levels by TCDD in neonatal and maternal rats. Chemosphere 1990;20:1129-34.

Lasky RE, Widholm JJ, Crofton KM, Schantz SL. Perinatal exposure to Aroclor 1254 impairs distortion product otoacoustic emissions (DPOAEs) in rats. Toxicol Sci 2002;68:458-64.

Lauby-Secretan B, Loomis D, El Ghissassi F, et al. Carcinogenicity of polychlorinated and polybromiated biphenyls. Lancet Oncology 2013;14:287-8.

Li MC, Tsai PC, Chen PC, Hsieh CJ, Leon Guo YL, Rogan WJ. Mortality after exposure to polychlorinated biphenyls and polychlorinated dibenzofurans. Environ Res 2013;120:71-5.

Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. Statistics in medicine 2002;21:1525-37.

Lilienthal H, Heikkinen P, Andersson PL, van der Ven LT, Viluksela M. Auditory effects of developmental exposure to purity-controlled polychlorinated biphenyls (PCB52 and PCB180) in rats. Toxicol Sci 2011;122:100-11.

Lin KC, Guo NW, Tsai PC, Yang CY, Guo YL. Neurocognitive changes among elderly exposed to PCBs/PCDFs in Taiwan. Environ Health Perspect 2008;116:184-9.

Lind PM, Orberg J, Edlund UB, Sjoblom L, Lind L. The dioxin-like pollutant PCB 126 (3,3',4,4',5-pentachlorobiphenyl) affects risk factors for cardiovascular disease in female rats. Toxicol Lett 2004;150:293-9.

Longnecker MP, Hoffman HJ, Klebanoff MA, et al. In utero exposure to polychlorinated biphenyls and sensorineural hearing loss in 8-year-old children. Neurotoxicol Teratol 2004;26:629-37.

M Pavuk, JR Cerhan, CF Lynch et al. Environmental exposure to PCBs and cancer incidence in eastern Slovakia. Chemosphere 2004; 54:1509-20.

Mallin K, McCann K, D'Aloisio A, et al. Cohort mortality study of capacitor manufacturing workers, 1944-2000. J Occup Environ Med 2004;46:565-76.

Martinez JM, DeVito MJ, Birnbaum LS, et al. Toxicology of dioxins and dioxinlike compounds. In: Schecter A, Gasiewicz TA, eds. Dioxins and health. 2nd ed. Hoboken, NJ: Wiley 2003:137-57.

Masuda Y, Kuratsune M. Toxic compounds in the rice oil which caused Yusho. Fukuoka

Igaku Zasshi 1979;70:229-37 (In Japanese).

Masuda Y, Kuroki H, Haraguchi K, et al. The condition of PCBs and PCDFs in the blood of Yusho patients 20 years after the onset. Fukuoka Igaku Zasshi 1997;88:149-56 (In Japanese).

Masuda Y, Schecter A, P€apke O. Concentrations of PCBs, PCDFs and PCDDs in the blood of Yusho patients and their toxic equivalent contribution. Chemosphere 1998;37:1773-80.

Masuda Y. Causal agents of Yusho. In: Kuratsune M, Yoshimura H, Hori Y, et al, eds. YUSHO: A Human Disaster Caused by PCBs and Related Compounds. Fukuoka, Japan: Kyushu University Press 1996:47-80.

Masuda Y, Kuroki H, Haraguchi K, Nagayama J. PCDFs and related compounds in humans from Yusho and Yu-Cheng incidents. Chemosphere 1986;15:1621-8.

Masuda Y. The Yusho rice oil poisoning incident. In Schecter A, Gasiewicz TA, eds. Dioxins and Health. John Wiley and Sons, Inc., Hoboken, New Jersey, USA, 2003.

Masuda Y, Kuroki H, Haraguchi K, Nagayama J. PCB and PCDF congeners in the blood and tissues of Yusho and Yu-cheng patients. Environ Health Perspect 1985;59:53-8.

Mc Kinney JD, Fawkes J, Jordan S, et al. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) as a potent and persistent thyroxine agonist: a mechanistic model for toxicity based

on molecular reactivity. Environ Health Perspect 1985;61:41-53.

Montesano R, Hainaut P, Wild CP. Hepatocellular carcinoma: from gene to public health. J Natl Cancer Inst 1997;89:1844-51.

Morgan PE, Dean RT, Davies MJ. Protective mechanisms against peptide and protein peroxides generated by singlet oxygen. Free Radic Biol Med 2004;36:484-96.

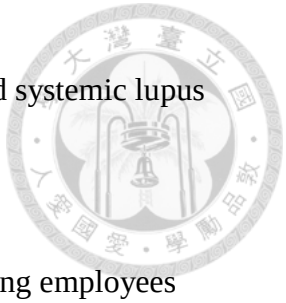
Morgan PE, Sturgess AD, Davies MJ. Increased levels of serum protein oxidation and correlation with disease activity in systemic lupus erythematosus. Arthritis Rheum 2005;52:2069-79.

Morse DC, Wehler EK, Wesseling W, Koeman JH, Brouwer A. Alterations in rat brain thyroid hormone status following pre- and postnatal exposure to polychlorinated biphenyls (Aroclor 1254). Toxicol Appl Pharmacol 1996;136:269-79.

Oakley GG, Devanaboyina U, Robertson LW, Gupta RC. Oxidative DNA damage induced by activation of polychlorinated biphenyls (PCBs): implications for PCB-induced oxidative stress in breast cancer. Chem Res Toxicol 1996;9:1285-92.

Ogura I. Half-life of each dioxin and PCB congener in the human body. Organohalogen Compounds 2004;66:3329-37.

Onozuka D, Yoshimura T, Kaneko S, Furue M. Mortality after exposure to polychlorinated biphenyls and polychlorinated dibenzofurans: a 40-year follow-up study of Yusho patients. Am J Epidemiol 2009;169:86-95.



Ostensen M. Sex hormones and pregnancy in rheumatoid arthritis and systemic lupus erythematosus. Ann N YAcad Sci 1999;876:131–43.

Ott MG, Zober A. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. Occup Environ Med 1996;53:606-12.

PA Bertazzi, C Zocchetti, AC Pesatori, et al. Ten-year mortality study of the population involved in the Seveso incident in 1976. Am J Epidemiol 1989;129:1187-200.

Patterson DG Jr, Hampton L, Lapeza CR Jr, et al. High-resolution gas chromatographic/high-resolution mass spectrometric analysis of human serum on a whole-weight and lipid basis for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Anal Chem 1987;59:2000-5.

Patterson DG Jr, Turner WE, Caudill SP, Needham LL. Total TEQ reference range (PCDDs, PCDFs, cPCBs, mono-PCBs) for the US population 2001-2002. Chemosphere 2008;73(Suppl. 1):S261-S277.

Patterson DG Jr, Wong LY, Turner WE, et al. Levels in the U.S. population of those persistent organic pollutants (2003-2004) included in the Stockholm Convention or in other long-range transboundary air pollution agreements. Environ Sci Technol 2009;43:1211-8.

Pavuk M, Cerhan JR, Lynch CF, et al. Environmental exposure to PCBs and cancer

incidence in eastern Slovakia. Chemosphere 2004;54:09-1520.

PE Morgan, AD Sturgess, MJ Davies. Increased levels of serum protein oxidation and correlation with disease activity in systemic lupus erythematosus. Arthritis Rheum 2005;52:2069-79.

Pelclová D, Urban P, Preiss J, et al. Adverse health effects in humans exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Rev Environ Health 2006;21:119-38.

Pesatori AC, Grillo P, Consonni D, et al. Update of the mortality study of workers exposed to polychlorinated biphenyls (Pcbs) in two Italian capacitor manufacturing plants. Med Lav 2013;104:107-14.

Petitti DB. Meta-analysis, decision analysis, and cost-effectiveness analysis: methods for quantitative synthesis in medicine. Oxford University Press, 1999.

Phillips DL, Pirkle JL, Burse VW, Bernert JT Jr, Henderson LO, Needham LL. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch Environ Contam Toxicol 1989;18:495-500.

Poon E, Powers BE, McAlonan RM, Ferguson DC, Schantz SL. Effects of developmental exposure to polychlorinated biphenyls and/or polybrominated diphenyl ethers on cochlear function. Toxicol Sci 2011;124:161-8.

Potter CL, Moore RW, Inhorn SL, Hagen TC, Peterson RE. Thyroid status and thermogenesis in rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol

Appl Pharmacol 1986;84:45-55.

Potter CL, Sipes IG, Haddock-Russell D. Hypothyroxinemia and hypothermia in rat in response to 2,3,7,8-tetrachlorodibenzo-p-dioxin administration. Toxicol Appl Pharmacol 1983;69:89-95.

Powers BE, Poon E, Sable HJ, Schantz SL. Developmental exposure to PCBs, MeHg, or both: long-term effects on auditory function. Environ. Health Perspect 2009;117:1101-7.

Powers BE, Widholm JJ, Lasky RE, Schantz SL. Auditory deficits in rats exposed to an environmental PCB mixture during development. Toxicol Sci 2006;89:415-22.

Prince MM, Ruder AM, Hein MJ, et al. Mortality and exposure response among 14,458 electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Environ Health Perspect 2006;114:1508-14.

Roth W, Voorman R, Aust SD. Activity of thyroid hormone-inducible enzymes following treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol Appl Pharmacol 1988;92:65-74.

Ruder AM, Hein MJ, Hopf NB, Waters MA. Mortality among 24,865 workers exposed to polychlorinated biphenyls (PCBs) in three electrical capacitor manufacturing plants: a ten-year update. Int J Hyg Environ Health 2014;217:176-87.

Ryan JJ, Hsu CC, Boyle MJ, Guo YL. Blood serum levels of PCDFs and PCBs in Yu-

Cheng children perinatally exposed to a toxic rice oil. Chemosphere 1994;29:1263-78.

Rylander L, Dyremark E, Stromberg U, stm man C, Hagmar L. The impact of age, lactation and dietary habits on PCB in plasma in Swedish women. Sci Total Environ 1997;207:55-61.

Rylander L, Hagmar L. Medical and psychometric examinations of conscripts born to mothers with a high intake of fish contaminated with persistent organochlorines. Scand J Work Environ Health 2000;26:207-12.

Safe SH. Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. Critical Reviews in Toxicology 1994;24:87-149.

Saracci R, Kogevinas M, Bertazzi PA, et al. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. Lancet 1991;338:1027-32.

Schantz SL, Widholm JJ. Rice DC. Effects of PCBS exposure on neuropsychological function in children. Environ Health Perspect 2003;11:357-76.

Schantz SL. Developmental neurotoxicity of PCBs in humans: what do we know and where do we go from here. Neurotoxicol Teratol 1996;18:217-27.

Sergeev AV, Carpenter DO. Hospitalization rates for coronary heart disease in relation to residence near areas contaminated with persistent organic pollutants and other

pollutants. Environ. Health Perspect 2005;113:756-61.

Shimizu K, Ogawa F, Thiele JJ, Lee JB, Bae S, Sato S. Increased levels of urinary nitrite and nitrotyrosine in Yusho victims 40 years after accidental poisoning with polychlorinated biphenyls in Nagasaki, Japan. J Appl Toxicol 2008;28:1040-4.

Sinks T, Steele G, Smith AB, et al. Mortality among workers exposed to polychlorinated biphenyls. Am J Epidemiol 1992;136:389-98.

SL Wang, PC Tsai, CY Yang, et al. Increased risk of diabetes and polychlorinated biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort. Diabetes Care 2008;31:1574-9.

Steenland K, Piacitelli L, Deddens J, et al. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo- p-dioxin. J Natl Cancer Inst 1999;91:779-86.

Tanabe S, Kannan N, Wakimoto T, Tatsukawa R, Okamoto T, Masuda Y. Isomer-specific determination and toxic evaluation of potentially hazardous coplanar PCBs, dibenzofurans and dioxins in the tissues of "Yusho" PCB poisoning victim and in the causal oil. Toxicol Environ Chem 1989;24:215-31.

Teeguarden JG and Walker NJ. Experimental Toxicology: Carcinogenesis, in Dioxins and Health, Second Edition (eds A. Schecter and T. A. Gasiewicz), John Wiley & Sons, Inc., Hoboken, NJ, USA. doi: 10.1002/0471722014.ch11, 2005.

Tilson HA, Kodavanti PR, Mundy WR, Bushnell PJ. Neurotoxicity of environmental chemicals and their mechanism of action. Toxicol Lett 1998;102-3:631-5.

Tironi A, Pesatori A, Consonni D, et al. The mortality of female workers exposed to PCBs. Epidemiol Prev 1996;20:200-2.

Todaka T, Hirakawa H, Hori T, Tobiishi K, Iida T, Furue M. Concentrations of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and non-ortho and mono-ortho polychlorinated biphenyls in blood of Yusho patients. Chemosphere 2007;66:1983-9.

Tsai PC, Ko YC, Huang W, Liu HS, Guo YL. Increased liver and lupus mortalities in 24-year follow-up of the Taiwanese people highly exposed to polychlorinated biphenyls and dibenzofurans. Sci Total Environ 2007;374:216-22.

Uziel A. Periods of sensitivity to thyroid hormone during the development of the organ of Corti. Acta Otolaryngol Suppl 1986;429:23-7.

van den Berg M, Birnbaum LS, Denison M, et al. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci 2006;93:223-41.

van Leeuwen FX, Feeley M, Schrenk D, Larsen JC, Farland W, Younes M. Dioxins: WHO's tolerable daily intake (TDI) revisited. Chemosphere 2000;40:1095-101.

Vorderstrasse BA, Bohn AA, Lawrence BP. Examining the relationship between

impaired host resistance and altered immune function in mice treated with TCDD. Toxicology 2003;188:15-28.

Wang SL, Tsai PC, Yang CY, Guo YL. Increased risk of diabetes and polychlorinated biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort. Diabetes Care 2008;31:1574-9.

Wong LE, Millette MD, Uddin MS, et al. Serum dioxin levels in residents of Calcasieu and Lafayette parishes, Louisiana with comparison to the US population. J Expo Sci Environ Epidemiol 2008;18:252-61.

Yokosuka O, Kurosaki M, Imazeki F, et al. Management of hepatitis B: Consensus of the Japan Society of Hepatology 2009. Hepatol Res 2011;41:1-21.

Yu ML, Guo YL, Hsu CC, Rogan WJ. Increased mortality from chronic liver disease and cirrhosis 13 years after the Taiwan“Yucheng” (“oil disease”) incident. Am J Ind Med 1997;31:172-5.

Yu ML, Guo YL, Hsu CC, Rogan WJ. Increased mortality from chronic liver disease and cirrhosis 13 years after the Taiwan "Yucheng" ("oil disease") incident. Am J Ind Med 1997;31:172-5.

Zani C, Gelatti U, Donato F, et al. Polychlorinated biphenyls in serum, liver and adipose tissue of subjects with hepatocellular carcinoma living in a highly polluted area. Chemosphere 2013;91:194-9.

Zani C, Toninelli G, Filisetti B, Donato F. Polychlorinated Biphenyls and Cancer: An Epidemiological Assessment. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2013;31:99-144.

Figures

Figure 1. The whole picture of current studies

To examine the long-term health outcomes of Yucheng victims	
For Yucheng victims themselves	**For Yucheng victims' children**
What is of concern? ● The health effects after long-term exposure to high dose of PCBs/PCDFs. **What is already known?** ● Yucheng victims had increased liver and lupus mortalities. **What does this study examine?** ● To examine the mortality status in Yucheng victims using neighborhood referents as reference group ● To reevaluate the effects of PCBs /PCDFs on major causes of mortalities by a combination analysis of Yucheng and Yusho victims.	**What is of concern?** ● The neurological effects after prenatal exposure to PCBs/PCDFs. **What is already known?** ● Yucheng children had poorer cognitive development and a higher incidence of otitis media. No auditory assessment was performed. **What does this study examine?** ● To examine whether gestational exposure to PCBs/PCDFs caused adverse hearing effects.

Tables

Table 1 Demographic description in 1980 of Yucheng subjects and neighborhood referents.

Types	Status of January 1, 1980	
	Yucheng subjects (N=1,803)	**Neighborhood referents (N=5,170)**
Age		
0-19	792 (44%)	2,173 (42%)
20-39	603 (33%)	1,828 (35%)
40-59	343 (19%)	980 (19%)
60+	65 (4%)	189 (4%)
Gender		
Male	830 (46%)	2,369 (46%)
Female	973 (54%)	2,801 (54%)
Person-year	48,751	141,774
Deceased	295	757

N: Number

Table 2. Observed and expected numbers of deaths and standardized mortality ratio (SMR) for overall and cause-specific deaths among 1,803 Yucheng subjects, from January 1, 1980 to December 31, 2008.

Cause of death (ICD 9)	**Males**			**Females**			**Total**		
	O	**E**	**SMR (95% CI)**	**O**	**E**	**SMR (95% CI)**	**O**	**E**	**SMR (95% CI)**
All causes (001-999)	178	143.9	**1.2 (1.2-1.4)**	117	105.4	1.1 (0.9-1.3)	295	248.9	**1.2 (1.1-1.3)**
Infectious and parasitic diseases (001-139)	9	6.0	1.5 (0.7-2.8)	2	3.5	0.6 (0.1-1.9)	11	9.4	1.2 (0.6-2.0)
Neoplasms (140-239)	46	36.4	1.3 (0.9-1.7)	21	26.4	0.8 (0.5-1.2)	67	62.6	1.1 (0.8-1.4)
Malignant neoplasm of liver and intrahepatic bile ducts(155)	4	9.0	0.4 (0.1-1.1)	6	2.8	2.1 (0.9-4.5)	10	11.7	0.9 (0.4-1.5)
Malignant neoplasm of trachea, bronchus and lung (162)	10	6.5	1.5 (0.8-2.7)	1	2.8	0.4 (0.0-1.7)	11	10.2	1.1 (0.6-1.9)
Malignant neoplasm of stomach (151)	7	2.0	**3.5 (1.5-7.0)**	1	2.0	0.5 (0-2.5)	8	4.0	2.0 (0.9-3.8)
Malignant neoplasm of lymphatic and haematopoietic tissue (200-208)	5	1.7	**3.0 (1.1-6.6)**	0	1.6	--	5	3.3	1.5 (0.6-3.4))
Malignant neoplasm of thyroid gland (193)	0	0	--	2	1.0	2.0 (0.3-6.7)	2	0.9	2.2 (0.4-7.2)
Malignant neoplasm of female breast (174)	0	0	--	4	3.6	1.1 (0.4-2.7)	--	--	--
Endocrine, nutritional, and metabolic diseases and immunity disorders (240-279)	7	10.3	0.7 (0.3-1.3)	11	9.7	1.1 (0.6-2.0)	18	20.0	0.9 (0.5-1.4)
Diabetes mellitus (250)	3	9.4	**0.3 (0.1-0.9)**	9	9.5	1.0 (0.5-1.7)	12	19.0	0.6 (0.3-1.1)
Mental disorders (290-319)	0	1.3	--	0	0.3	--	0	1.3	--
Diseases of the nervous	1	1.9	0.5 (0.0-	1	1.6	0.6 (0.0-3.2)	2	3.5	0.6 (0.1-

system and sense organs (320-389)			2.6)						1.9)
Disease of the circulatory system (390-459)	38	32.0	1.2 (0.9-1.6)	33	22.2	**1.5 (1.0-2.1)**	71	54.5	**1.3 (1.0-1.6)**
Acute myocardial infarction (410)	8	2.4	**3.3 (1.6-6.4)**	3	3.2	0.9 (0.2-2.5)	11	5.6	**2.0 (1.0-3.4)**
Other forms of heart disease (420-429)	11	5.0	**2.2 (1.2-3.8)**	9	3.7	**2.4 (1.2-4.5)**	20	8.7	**2.3 (1.4-3.5)**
Cardiac dysrhythmias (427)	1	0.3	3.0 (0.1-14.4)	3	0.3	**9.6 (2.4-26.0)**	4	0.7	**5.8 (1.8-13.9)**
Late effects of cerebrovascular disease (438)	3	1.8	1.7 (0.4-4.5)	4	0.7	**5.4 (1.7-13.1)**	7	2.4	**2.9 (1.3-5.7)**
Diseases of the respiratory system (460-519)	7	9.7	0.7 (0.3-1.4)	7	7.2	1.0 (0.4-1.9)	14	16.7	0.8 (0.5-1.4)
Disease of the digestive system (520-579)	23	12.1	**1.9 (1.2-2.8)**	9	11.8	0.8 (0.4-1.4)	32	24.1	1.4 (0.9-1.9)
Chronic liver disease and cirrhosis (571)	16	6.5	**2.5 (1.5-3.9)**	3	5.9	0.5 (0.1-1.4)	19	12.4	1.5 (1.0-2.3)
Disease of the genitourinary system (580-629)	6	3.7	1.6 (0.7-3.4)	6	6.2	1.0 (0.4-2.0)	12	9.9	1.2 (0.7-2.1)
Diseases of the skin and subcutaneous tissue (680-709)	1	0.3	3.1 (0.2-15.4)	0	0.9	--	1	1.2	0.8 (0.0-4.2)
Diseases of the musculoskeletal system and connective tissue (710-739)	1	0.7	1.4 (0.1-6.7)	6	0.4	**16.5 (6.7-34.3)**	7	1.1	**6.4 (2.8-12.7)**
Systemic lupus erythematosus (710)	1	0	--	5	0	--	6	0	--
Symptoms, signs, and ill-defined conditions (780-799)	8	8.6	1.0 (0.4-1.8)	7	4.9	1.4 (0.6-2.8)	15	13.2	1.1 (0.7-1.8)
Injury and poisoning (800-999)	27	18.5	**1.5 (1.0-2.1)**	12	9.0	1.3 (0.7-2.3)	39	27.3	**1.4 (1.0-1.9)**

ICD-9: International Classification of Diseases, ninth revision; **O**: Observed numbers; **E**: Expected numbers **95% CI**=95% confidence interval calculated based on Mid-P tests; **Bolded text**: The ratio of Yucheng observed number of deaths over expected number of deaths is significant.

Table 3. The differences in results using the different reference populations.

Types of mortality	Reference population	
	Neighborhood referents	**Taiwan general population**
All causes	Increase in all Yucheng subjects and Yucheng males	Not different
Malignant neoplasms	*Malignant neoplasm of stomach* and *Malignant neoplasm of lymphatic and hematopoietic tissue* were increased in Yucheng males	*Malignant neoplasm of lymphatic and hematopoietic tissue* was slightly increased in Yucheng males, but did not reach statistical significant.
Disease of the circulatory system	Increase in all Yucheng subjects and Yucheng females	Slightly increase in Yucheng females, but did not reach statistical significant.
Disease of the digestive system	Increase in Yucheng males, especially for *chronic liver disease and cirrhosis*	Increase in all Yucheng subjects and Yucheng males, especially for *chronic liver disease and cirrhosis*
Diseases of the musculoskeletal system and connective tissue	Increase in all Yucheng subjects and Yucheng females, especially for *systemic lupus erythematosus*	Increase in all Yucheng subjects and Yucheng females, especially for *systemic lupus erythematosus*

Table 4. Summary of the characteristics of Yucheng and Yusho cohorts

Author, year	**Event year**	**Country, (area of residence)**	**Sample size of the cohort**	**mean age, range at enrollment**	**Follow-up period**	**Chemical Exposure[c]**	**Exposure level[d]**	**Person-year of follow-up**	**Subjects dead during follow period**
Li et al., 2013 (Yucheng)	1979	Taiwan, Taichung, Changhua, Miaoli	Male, N=830 Female, N=973	26.7, 0 to 68	30 years	PCBs[a] PCDFs PCQs	PCBs: 540 ppt TEQ PCDFs: 1760 ppt TEQ Total: 2300 ppt TEQ	48,751	295
Onozuka et al., 2009 (Yusho)	1968	Japan, western Japan, Fukuoka Nagasaki	Male, N=860 Female, N=804	30.3, 0 to 85	40 years	PCBs[b] PCDFs PCQs	PCBs: 230 ppt TEQ PCDFs: 2400 ppt TEQ Total: 2630 ppt TEQ	50,773	441

PCBs: polychlorinated biphenyls; PCDFs: polychlorinated dibenzofurans; PCQs: polychlorinated quarterphenyls; N: number.

[a]: Kanechlor-400 (a commercial brand of PCB mixture); [b]: Kanechlor-500 (a commercial brand of PCB mixture).

[c]: Chemical Exposure data were extracted from Hsu et al., 1985 (Yucheng) and Kuratsune et al., 1972 (Yusho), respectively.

[d]: Exposure levels were extracted from Guo et al, 1997; Lambert et al, 2006; Tanabe et al., 1989; Masuda et al., 1998.

Table 5. Cause specific mortalities from the individual studies, as well as the pooled mortalities.

Cause of Death (ICD-9 Codes)	YUCHENG		YUSHO		POOLED		
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Total**
	Observed/Expected	**Observed/Expected**	**Observed/Expected**	**Observed/Expected**	**SMR (95% CI)**	**SMR (95% CI)**	**SMR (95% CI)**
All-cause (001-999)	178/143.9	117/105.4	269/238.3	172/170.8	**1.2 (1.1-1.3)** I^2=0.0%	1.1 (0.9-1.2) I^2=0.0%	**1.1 (1.1-1.2)** I^2=28.6%
All cancer (140-208)[b]	44/35.9	22/25.2	100/73.1	33/44.3	**1.3 (1.1-1.6)** I^2=0.0%	0.8 (0.5-1.3) I^2=0.0%	— I^2=72.0%[a]
Stomach (151)	7/2.0	1/2.0	20/17.1	2/8.9	— I^2=82.5%[a]	0.3 (0.1-1.1) I^2=0.0%	— I^2=74.0%[a]
Rectum (154)[b]	0/1.1	1/0.7	2/3.1	1/1.8	—	1.0 (0.2-5.8) I^2=0.0%	—
Liver (155)	4/9.0	6/2.8	17/9.4	7/3.6	— I^2=80.8%[a]	**2.0 (1.1-3.6)** I^2=0.0%	— I^2=50.1%
Pancreas (157)[b]	0/0	1/0.7	6/4.0	3/2.9	—	1.1 (0.4-3.7) I^2=0.0%	—
Lung (162)	10/6.5	1/2.8	26/14.8	4/4.9	**1.7 (1.2-2.3)** I^2=0.0%	0.7 (0.3-1.9) I^2=0.0%	**1.5 (1.1-2.1)** I^2=0.0%
Female breast (174)	—	4/3.6	—	3/3.2	—	1.1 (0.4-2.9) I^2=0.0%	—
Uterus (179-182)[b]	—	1/1.0	—	3/2.6	—	1.1 (0.4-3.4) I^2=0.0%	—

Leukemia (204-208)[b]	2/0.7	0/0.3	2/1.7	0/1.1	2.0 (0.6-6.0) I^2=0.0%	—	—
Hypertension (401-405)[b]	5/2.9	4/2.0	2/2.2	1/2.7	1.5 (0.7-3.4) I^2=0.0%	1.4 (0.3-5.6) I^2=26.7%	1.6 (0.9-2.9) I^2=0.0%
Heart disease (393-398, 410-429)[b]	21/12.1	17/9.7	38/36.0	34/30.0	— I^2=68.7%[a]	— I^2=51.7%	**1.3 (1.0-1.7)** I^2=43.4%
Cerebrovascular disease (430-438)[b]	11/16.5	12/9.6	34/36.3	32/31.8	0.9 (0.6-1.2) I^2=0.0%	1.1 (0.8-1.5) I^2=0.0%	1.0 (0.8-1.2) I^2=0.0%
Hepatic disease (570-573)[b]	16/7.6	5/6.8	11/6.7	4/2.8	**1.9 (1.3-2.8)** I^2=0.0%	1.0 (0.5-1.9) I^2=0.0%	**1.5 (1.0-2.4)** I^2=27.7%

SMR: standardized mortality ratio; Observed/Expected: Observed and Expected number; CI=confidence interval; I^2: Statistically significant heterogeneity was considered present at $I^2 > 50\%$. [a]: P-value of heterogeneity tests <0.1; [b]: Although data were not present in our published Yucheng mortality paper, we recalculated SMR and 95% CI from the original data. The horizontal line in the table indicated that data were not available or no observed case. Weights were from random effects analysis.

Table 6. Characteristics in Yucheng children and their neighborhood referents at time of study.

	Yucheng children		**Referent children**		
Demographic variable	***N*=86**		***N*=97**		***P*-value**
Age (years)*					
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
≤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*					
>21.25	43	50.0 %	47	48.5 %	0.83
≤21.25	43	50.0 %	50	51.5 %	
Total cholesterol (mg/dL)*					
>163	44	51.2 %	49	50.5 %	0.93
≤163	42	48.8 %	48	49.5 %	
Triglyceride (mg/dL)*					
>71	48	55.8 %	44	45.4 %	0.16
≤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

*divided by median level of all subjects; dB: decibel;

Table 7. 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 8. 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

Table 9. Effects of maternal serum level of PCBs/PCDFs (ppt lipid base, log-transformed) on hearing threshold (log-transformed) by linear regression (*N*=53)

Right ear							
Hearing level (dB)	**250 Hz**	**500 Hz**	**1000 Hz**	**2000 Hz**	**4000 Hz**	**8000 Hz**	**Average threshold level**
Congeners							
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							
Hearing level (dB)	**250 Hz**	**500 Hz**	**1000 Hz**	**2000 Hz**	**4000 Hz**	**8000 Hz**	**Average threshold level**
Congeners							
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

Table 10. Effects of maternal serum level of PCBs/PCDFs (ppt lipid base, log-transformed) on DPOAEs (log-transformed) by linear regression (*N*=53)

Right ear							
Hearing level (dB)	**1.5 kHz**	**2 kHz**	**3 kHz**	**4 kHz**	**5 kHz**	**6 kHz**	**Average threshold level**
Congeners							
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							
Hearing level (dB)	**1.5 kHz**	**2 kHz**	**3 kHz**	**4 kHz**	**5 kHz**	**6 kHz**	**Average threshold level**
Congeners							
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

Publication list

Refereed papers

1. **Ming-Chieh Li**, Pau-Chung Chen, Pei-Chien Tsai, Masutaka Furue, Daisuke Onozuka, Akihito Hagihara, Hiroshi Uchi, Takesumi Yoshimura, Yue Leon Guo*. Mortality after exposure to polychlorinated biphenyls and polychlorinated dibenzofurans: a meta-analysis of two highly exposed cohorts. **International Journal of Cancer** doi: 10.1002/ijc.29504
2. **Ming-Chieh Li**, Hung-Pin Wu, Chiu-Yueh Yang, Pau-Chung Chen, George H. Lambert, Yue Leon Guo*. Gestational exposure to polychlorinated biphenyls and dibenzofurans induced asymmetric hearing loss: Yucheng children study. **Environmental Research** 2015:137;65-71
3. **Ming Chieh Li**, Pei Chien Tsai, Pau-Chung Chen, Chia Jung Hsieh, Yue-Liang Leon Guo*, Walter J. Rogan. Mortality after exposure to polychlorinated biphenyls and dibenzofurans: 30 years after the "Yucheng Accident". **Environmental Research**2013;120;71-75

Conference papers

1. **Ming-Chieh Li**, Hung-Pin Wu, Chiu-Yueh Yang, Pau-Chung Chen, George H. Lambert, Yue Leon Guo*. Gestational Exposure to Polychlorinated Biphenyls and Dibenzofurans Induced Asymmetric Hearing Loss: Yucheng Children Study. 26th Annual International Society for Environmental Epidemiology Conference (ISEE). Seattle, Washington, USA on August 24-28th, 2014. (**Poster presentation**)
2. **Ming-Chieh Li**, Pei-Chien Tsai, Pau-Chung Chen, Chia-Jung Hsieh, Yue Leon Guo*. Mortality in a Population Highly Exposed to Polychlorinated Biphenyls and Polychlorinated Dibenzofurans: 30 Years after Yucheng Accident. Occupational and Environmental Medicine 2011 Sep; 68(Supple 1): A83. (doi:10.1136/oemed-2011-100382.273) The 22nd International Conference on Epidemiology in Occupational Health (EPICOH), Oxford, United Kingdom, September 7-9, 2011. (**Poster discussion**)
3. **Ming-Chieh Li**, Yue Leon Guo*. Chronic effects of Taiwanese People Highly Exposed to Polychlorinated Biphenyls and Dibenzofurans (PCBs/PCDFs) -A Mortality Analysis of Yucheng Subjects. Epidemiology: January 2011 - Volume 22 - Issue 1 - p S56 (doi: 10.1097/01.ede.0000391833.42084.5c) International Society of Exposure Sciences-International Society of Environmental Epidemiology (ISES-ISEE) 22nd Annual Conference, Seoul, Korea, 28 August-1 September 2010: Chemicals and Environmental Health Issues: Persistent Organic Chemicals. (**Oral presentation**)
4. **Ming-Chieh Li**, Pau-Chung Chen, Yue Leon Guo*. People Highly Exposed to Polychlorinated Biphenyls and Dibenzofurans (PCBs/PCDFs) Have Lower Glucose Levels Compared with Unexposed Group. Occupational and Environmental Medicine 2010 Sep; 60(Suppl 1): A7. (doi: 10.1136/oem.2010.60608.21) 1st

International Symposium of Reproductive Hazards in the Workplace and Environment (RHICOH 2010), Taipei, Taiwan, April 20-21, 2010. (**Oral presentation**)

5. **Ming-Chieh Li**, Pau-Chung Chen, Yue Leon Guo*. Increased Kidney and Heart Disease Mortalities in 6-28 Years Follow-Up of the Taiwanese People Highly Exposed to Polychlorinated Biphenyls and Dibenzofurans (PCBs/PCDFs). The 41st Asia-Pacific Academic Consortium for Public Health (APACPH) Conference, Taipei, Taiwan, December 3-6, 2009. (**Poster presentation**)