The Relationship Between Anthropometry, Liver Enzymes, and Serum Concentrations of PCDD/Fs

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RUNNING TITLE: PCDD/F exposure and liver function

KEY WORDS: PCDD/Fs, abdominal obesity, liver function, serum aminotransferases, waist-to-hip ratio

ABBREVIATIONS:

albumin (ALB), abdominal obesity (AO), adjusted odds ratio (AOR), alkaline phosphatase (ALP), cholesterol (CHOL), diastolic blood pressure (Dia BP), glutamate oxaloacetate transaminase (GOT), glutamic pyruvic transaminase (GPT), γ-glutamyltransferase (GGT), homeostasis model assessment for insulin resistance (HOMA-IR), liver function tests (LFTs), nonalcoholic steatohepatitis (NASH), National Health and Nutrition Examination Survey (NHANES), systolic blood pressure (Sys BP), tetrachlorodibenzo-para-dioxin (TCDD), total bilirubin (TBIL), triglycerides (TG), total protein (TP), polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs), pentachlorophenol (PCP), pentachlorodibenzo-p-dioxin (PeCDF), persistent organic pollutants (POPs), waist circumference (WC), waist-to-hip ratio (WHR)
ABSTRACT

BACKGROUND: Obesity has been identified as an important contributing factor to raised serum levels of hepatic enzymes. Liver damage can be observed in human occupationally and accidentally exposure to high levels of PCDD/Fs.

OBJECTIVES: To investigate and clarify the effect of moderate-to-high PCDD/F exposure and abdominal obesity on liver function.

METHODS: This cross-sectional study recruited 2028 healthy participants living near a deserted pentachlorophenol factory. We measured seventeen 2,3,7,8-substituted PCDD/Fs, then examined associations between the main predictor variable, serum TEQ_{DF-1998}, and dependent variables, liver function tests (LFTs) including the serum aminotransferases, alkaline phosphatase, bilirubin, and albumin.

RESULTS: Serum ln-GOT (waist-to-hip ratio (WHR): β = 0.429, p < 0.001; ln-TEQ_{DF-1998}: β = 0.036, p = 0.005), ln-GPT (WHR: β = 1.776, p < 0.001; ln-TEQ_{DF-1998}: β = 0.047, p = 0.035), and ln-GGT (WHR: β = 2.042, p < 0.001; ln-TEQ_{DF-1998}: β = 0.057, p = 0.022) levels were significantly increased with WHR and serum ln-TEQ_{DF-1998} levels, respectively. Moreover, we observed a significant interaction between ln-TEQ_{DF-1998} and WHR in association with ln-GOT, ln-GPT, and ln-GGT levels (All P for interaction < 0.05). We further found higher abnormality of GOT and GGT were associated with increased levels of 2,3,7,8-TCDF (all Ptrend < 0.001) and higher abnormality of GOT, GGT, and GPT (all Ptrend < 0.01) were associated with increased levels of 1,2,3,7,8-PeCDF.

After we had adjusted for confounding factors, we found that participants with higher serum ln-TEQ_{DF-1998} levels or abdominal obesity were at a significantly increasing risk for abnormality of GGT (Ptrend < 0.001). The joint highest tertile of serum ln-TEQ_{DF-1998} levels and abdominal obesity was associated with elevated GGT at 7.9 times the odds of the joint lowest tertile (AOR 7.91, 95% CI: 3.92, 15.97).

CONCLUSIONS: We hypothesize that serum TEQ_{DF-1998} and abdominal obesity would affect the association with GGT level simultaneously in general populations.
Introduction

According to the statistics data from Department of Health, Executive Yuan, the ten leading causes of death in Taiwan in 2010 were: Malignant tumors, cardiovascular disease, cerebrovascular disease, pneumonia, diabetes, injuries from accidents, chronic lower respiratory diseases, chronic liver diseases and cirrhosis, and nephritis. The death rate of chronic liver diseases and cirrhosis in 2010 is 3.4%. Liver function tests (LFTs) are commonly used in clinical practice to screen for liver disease, monitor the progression of known disease, and monitor the effects of potentially hepatotoxic drugs. The most common LFTs include the serum aminotransferases, alkaline phosphatase, bilirubin, and albumin. Aminotransferases, such as glutamic pyruvic transaminase (GPT) and glutamate oxaloacetate transaminase (GOT), measure the concentration of intracellular hepatic enzymes that have leaked into the circulation and serve as a marker of hepatocyte injury. Alkaline phosphatase (AP), γ-glutamyl transpeptidase (GGT), and total bilirubin (TBIL) act as markers of biliary function and cholestasis. Albumin (ALB) reflect liver synthetic function.

Until recently, calculation of the body-mass index (BMI) has been the method of choice for the classification of obesity. Body mass index (BMI), despite its limitations, is the true reflection of visceral body weight and obesity (Gallagher et al. 2000). Waist circumference (WC) gives information about abdominal adipose tissue. Liver is profoundly affected by obesity where it may be associated with hepatomegaly, increased liver biochemistry values and alterations in liver histology like macrovesicular steatosis, steatohepatitis, fibrosis and cirrhosis (Mokdad et al. 2003). Besides its well-known association with chronic diseases of lifestyle (Bray 2003; Ali AT, 2005), obesity has been identified as an important contributing factor to raised serum levels of hepatic enzymes (Galambos and Wills 1978; Adler and Schaffner 1979; Yu and Keeffe 2002). It is thought that this relationship is due to the high release of free fatty acids from the visceral fat depot into the portal circulation, leading to nonalcoholic steatohepatitis (NASH) (Marchesini et al. 2001; Browning and Horton 2004). However, previous studies reported inconsistent results about the association between dioxins exposures and changes in hepatic function. Some studies found that PCDD/Fs and 2,3,7,8-tetrachlorodibeno-para-dioxin (2,3,7,8-TCDD) exposures were significantly associated with elevated GPT (Triebig et al. 1998; Michalek et al. 2001), GOT (Triebig et al. 1998), and γ-glutamyltransferase (GGT) (Sweeney et al. 1997; Kitamura et al. 2000). By contrast, some studies showed that 2,3,7,8-TCDD exposures were not associated with serum GPT, GOT, or total bilirubin (Calvert et al. 1992).

A now-deserted pentachlorophenol factory, in the northwest of Tainan City in southern Taiwan, produced sodium pentachlorophenate (Na-PCP), a pesticide widely
used in the 1960s. After the factory closed, approximately 5000 kilograms of Na-PCP was improperly stored at the original site. However, at the time, the government did not prevent the storage of the Na-PCP or the pollution it caused. The PCDD/F levels of fish caught from the nearby aqua farms and reservoir were almost over the World Health Organization (WHO) safety level for human consumption (Lee et al. 2006). The regression analysis of PCDD/F content in sediment and fish was 0.82 ($R^2$), which indicated a positive correlation between exposure to PCDD/Fs in sediment and fish (HJ Chang et al. 2010). The measured data provided evidence that the PCDD/Fs and untreated wastewater from the factory might have spread via the wastewater and soil into the sea reservoir and the surrounding aquaculture area. For decades, residents have been depending on catching and selling seafood grown in reservoirs, fish farms, and ponds nearby. Unfortunately, they were never informed of the danger of eating those products. We hypothesized that the residents had a high risk of exposure to PCDD/Fs. Therefore, the aim of this work was to study the association between exposure to PCDD/Fs and Liver function tests (LFTs), and to examine whether the abnormality of liver function would be greater when abdominal obesity (AO) and serum PCDD/Fs exposure coexist.

**Materials and Methods**

*Participants and procedures.* This cross-sectional study was done from July 2005 through May 2010 in a district health center near the deserted PCP factory (JW Chang et al. 2010a; JW Chang et al. 2010b). Because the factory was only 1-2 km from a major residential area, the residents had a high risk of being exposed to PCDD/Fs from eating contaminated seafood from that reservoir. The exposure area was defined as Hsien-Gong, Lu-Erh, and Ssu-Tsao Li, three of the municipal administrative divisions in the study district. The primary recruitment criterion, in addition to age and an agreement to provide the amount of blood required for the study, was that the participant had to reside in the exposure area. The 3128 participants consisted of approximately 85% of all invited residents over 17 years old in the exposure area. We had incorrect addresses for 145 (26.3%) of the 552 non-participants, and 67 (12.1%) were either too ill to participate or else deceased. We received no response to our mailed invitation from the remaining 340 (61.6%), most of whom did not work locally and had changed their permanent address. Information about the history of major systemic diseases included questions about prior diagnoses by a physician, and their current use of related drugs. To remove bias, subjects with known cardiovascular disease (myocardial infarction, stroke, peripheral arterial disease), liver disease (hepatitis B or C, liver cirrhosis, fatty liver, hepatolithiasis), diabetes mellitus, renal disease (nephritis, nephrotic syndrome, and nephropathy), etc. were excluded from the
study. Of the initial 3128 study participants, we excluded 960 who had at least one of following diseases: diabetes mellitus (n = 483, 50.3%), renal disease (n = 212, 22.1%), cardiovascular disease (n = 75, 7.8%), and liver disease (n = 376, 39.2%). We also exclude 140 who did not have one of waist or hip circumference. Finally, only 2028 participants met the inclusion criteria. Anthropometrical measurements including height, weight, bodyfat, waist and hip circumference were recorded according to standard procedures. The waist-to-hip ratio (WHR) was measured by taking waist circumference as the midpoint between the lower rib margin and the iliac crest and hip circumference as the widest circumference of the buttock. Waist circumference (WC) cut-offs were taken as 90 cms for males and 80 cms for females to define abdominal obesity using South Asia Pacific Guidelines (Webb 2002).

Participants were asked to fast the night before 80-mL samples of venous blood were drawn. Information obtained from the questionnaire included personal characteristics (age, gender, medical history of major systemic diseases, etc.), and current lifestyle habits (alcohol intake, tobacco use, eating habits, etc.). The quantity of dietary intake for the previous 1 year was based on a semiquantitative dietary questionnaire, which was also used in our previous study (Chang et al. 2008). We also used a bodyfat analyzer (HBF-352; Omron, Tokyo, Japan) to measure bodyfat percentage and body weight.

Laboratory procedures. Blood samples were drawn into chemically cleaned tubes without anticoagulants. The samples were then stored at −70°C until they were analyzed. We used isotope dilution high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS), as previously described (JW Chang et al. 2010a; JW Chang et al. 2010b), to measure seventeen 2,3,7,8-substituted PCDD/Fs in serum samples. All PCDD/Fs were adjusted to the lipid content analyzed from the corresponding samples. Quality assurance/quality control (QA/QC) protocols followed USEPA Method 1613 to ensure positive identification and the quality of the measurements. Serum total cholesterol, triglycerides, and liver function tests including albumin, GOT, GPT, GGT, total bilirubin, and Alkaline phosphatase were determined in the central laboratory of National Cheng Kung University Hospital with an auto analyzer Hitachi 747E. Blood glucose was measured by a hexokinase method (Roche Diagnostic GmbH, Mannheim, Germany) with an auto analyzer Hitachi 747E. The reference values of the National Cheng Kung University Hospital were used to define the clinically abnormal outcomes of biochemical parameters, which were: GOT 40 U/L, GPT 55 U/L, GGT 80 U/L, and total bilirubin 1.4 mg/dL.
Data processing and statistical analysis. PCDD/F concentration is expressed in picograms (pg = 10^{-12} gram) WHO_{1998}-TEQ_{DF}/g lipid. The Shapiro-Wilk normality test was used to determine whether or not the levels of TEQ_{DF-1998} followed a normal distribution. Because there was substantial skewing of serum TEQ_{DF-1998}, the natural logarithmic transformation was used to subordinate the skew of these values for the analysis. The natural logarithmically transformed serum TEQ_{DF-1998} improved the normality (checked using Q-Q plots) and homogeneity of variance, and the statistical analysis was done using the ln-transformed data. All values under the detection limit were treated as half of this limit (EPA 1989). All statistical analysis was performed using JMP 5.0 (SAS Institute, Cary, NC). Unless indicated otherwise, data are expressed as mean values ± standard deviation. Comparison of categorical variables was performed by the chi-square or Fisher’s exact test. And comparison of continuous variables was performed by the Wilcoxon rank-sum test. Correlations between anthropology measurement, biochemistry examination, and serum TEQ_{DF-1998} were tested by linear regression and expressed by Pearson’s correlation coefficient. All statistical tests were two-tailed and a value of \( p < 0.05 \) was considered statistically significant. Multiple linear regression models were applied to assess the associations between serum TEQ_{DF-1998} and LFTs of outcomes, controlling for potential confounders. If necessary, natural logarithm (ln) transformation was used to enhance normality for outcomes with skewed distribution. Total protein, albumin, GOT, GPT, GGT, total bilirubin, and ALP were ln-transformed for the linear regression analysis. In both multiple linear and logistic regression analyses, the potential confounders to be included in the models were age (years), sex, cigarette smoking history (ever/never), and alcohol drinking history (yes/no). Potential interaction of serum TEQ_{DF-1998} and WHR was evaluated by adding an interaction term of “ln- TEQ_{DF-1998} \times WHR” into the multiple linear regression model. We also considered the interaction term to be significant at P values less than 0.05. In addition, we used multiple logistic regression to assess the association between serum TEQ_{DF-1998} and abnormality of liver function tests (LFTs). The subjects were split into 6 groups according to tertile of serum TEQ_{DF-1998} and abdominal obesity (AO). The adjusted odds ratios (AORs) were calculated using the lowest quartile of serum TEQ_{DF-1998} and non-AO as the reference group.

Results

The average age of the participants (1191 non abdominal obesity (AO); 837 AO) was 43.4 years old (non-AO: 37.6 ± 14.2; AO: 51.7 ± 17.2; \( p < 0.001 \)) (Table 1). In general, AO had higher anthropometrical measurements including BMI, bodyfat, waist and hip circumference, and blood pressure (All \( p < 0.001 \)). In addition, AO had
higher cholesterol (AO: 201.2 ± 42.1; non-AO: 185.6 ± 40.1 mg/dL; \( p < 0.001 \)),
triglycerides (AO: 141.7 ± 128.7; non-AO: 99.2 ± 86.8 mg/dL; \( p < 0.001 \)),
GOT (AO: 27.3 ± 15.6; non-AO: 23.6 ± 13.2 U/L; \( p < 0.001 \)),
GPT (AO: 29.6 ± 24.5; non-AO: 22.5 ± 20.7 U/L; \( p < 0.001 \)),
GGT (AO: 41.2 ± 78.6; non-AO: 27.6 ± 79.8 U/L; \( p < 0.001 \))
and ALP (AO: 69.8 ± 21.6; non-AO: 64.9 ± 21.3 U/L; \( p < 0.001 \)).
In addition, the mean serum TEQDF-1998 level was 25.8 pg WHO\textsubscript{1998}-TEQDF/g lipid (range: 3.5-514.0 pg WHO\textsubscript{1998}-TEQDF/g lipid).
The serum TEQDF-1998 was significantly lower in non-AO than in AO (non-AO: 20.7 ± 30.0; AO : 33.1 ± 36.5 pg WHO\textsubscript{1998}-TEQDF/g lipid; \( p < 0.001 \)). In respect to LFTs, Pearson correlation showed that WHR were significantly associated with GGT (\( r = 0.396, p < 0.001 \)) and moderately-to-strongly associated with GPT (\( r = 0.354, p < 0.001 \)),
GOT (\( r = 0.274, p < 0.001 \)), ALP (\( r = 0.225, p < 0.001 \)),
and ALB (\( r = -0.060, p < 0.001 \)). Moreover, serum ln-TEQDF-1998 levels were also significantly associated with GOT (\( r = 0.164, p < 0.001 \)),
ALB (\( r = -0.155, p < 0.001 \)), ALP (\( r = 0.086, p < 0.001 \)),
GGT (\( r = 0.083, p < 0.001 \)), and GPT (\( r = 0.073, p < 0.001 \)) (Supplemental Table). Table 2 demonstrated that ln-GOT
(WHR; \( \beta = 0.429, p < 0.001 \); ln-TEQDF\textsubscript{1998}; \( \beta = 0.036, p = 0.005 \)),
ln-GPT (WHR; \( \beta = 1.776, p < 0.001 \); ln-TEQDF\textsubscript{1998}; \( \beta = 0.047, p = 0.035 \)),
and ln-GGT (WHR; \( \beta = 2.042, p < 0.001 \); ln-TEQDF\textsubscript{1998}; \( \beta = 0.057, p = 0.022 \)) levels were significantly increased
with WHR and serum ln-TEQDF-1998 levels. None of the other liver enzyme, TP,
albumin, TBIL, or ALP serum levels showed significant correlations with serum
ln-TEQDF\textsubscript{1998} levels. Moreover, we observed a significant interaction between
ln-TEQDF\textsubscript{1998} and WHR in association with ln-GOT, ln-GPT, and ln-GGT levels (All \( P \) for interaction < 0.05).
We further explored the relationship between abnormality of all LFTs and quintiles of each of the 17 congeners levels
in multiple logistic regression models. The results showed that higher abnormality of GOT and GGT (all \( P_{\text{trend}} < 0.001 \))
were associated with increased levels of 2,3,7,8-TCDF. In addition, the results also showed that higher abnormality of GOT, GGT and GPT (all \( P_{\text{trend}} < 0.01 \))
were associated with increased levels of 1,2,3,7,8-PeCDF (Figure 1).
After we had adjusted for confounding factors, we found that participants with higher
serum TEQDF\textsubscript{1998} levels or abdominal obesity were at a significantly increasing risk
for abnormality of GGT (\( P_{\text{trend}} < 0.001 \)) (Table 3). The joint highest tertile of serum
TEQDF\textsubscript{1998} levels and abdominal obesity was associated with elevated GGT at 7.9
times the odds of the joint lowest tertile (AOR 7.91, 95% CI: 3.92, 15.97).
These data show that serum TEQDF\textsubscript{1998} and abdominal obesity affected the association with GGT.
Therefore, we observed a integrated risk of co-existence to both serum TEQDF\textsubscript{1998}
and abdominal obesity, even in healthy participants.

**Discussion**
In this study, GOT, GGT and ALP was more strongly correlated with WHR than with BMI or bodyfat, although without significant difference in correlations. In one study of Third National Health and Nutrition Examination Survey (NHANES III), using the WHR as a measure of central adiposity, was found to be more strongly associated with elevated GPT concentration than BMI (Ruhl and Everhart 2003). Nonetheless, growing evidence suggests that the body fat distribution may be even more important than the grade of obesity as determined by the BMI in the relationship between body weight and potential liver damage (Ruhl and Everhart 2003; Vanbarneveld et al. 1989; Hollmann et al. 1997). Van Barneveld et al. (Vanbarneveld et al. 1989) found a strong linear association between GGT and WHR as an indicator of fat distribution in a randomly selected group (n=69) of 38-year-old Dutch men from the city of Ede, Netherlands. In a study of premenopausal obese women with menstrual irregularity (n= 58), women characterized by upper body segment obesity (android type), as assessed by WHR>0.85, showed stronger correlations with metabolic abnormalities, including triglycerides, GOT, and GPT compared to women with lower body fat localization (gynoid obesity) (Hollmann et al. 1997). In a very recent analysis on data from NHANES III, WHR was found to be more strongly associated with elevated GPT activity, defined as an GPT>43 U/L for both sexes, than BMI (Ruhl and Everhart 2003).

From our results, abdominal adiposity, simply measured by WHR, appears to be a slightly but consistently stronger predictor of hepatic enzymes (GOT and GGT) and, consequently, potential liver injury, than the grade of relative weight as determined by the BMI. However, it is important to note that these two measures were very highly correlated. These findings are consistent with the current knowledge on the independent role of body fat distribution in predicting the risk of related diseases (Kissebah et al. 1982; Bouchard et al. 1990). To the best of our knowledge, this is the first study to evaluate the association between PCDD/Fs and LFTs in a large and population-based sample of people exposed to a wide range of PCDD/Fs. Liver damage can be observed in human occupationally and accidentally exposure to high levels of PCDD/Fs (WHO 1989). However, in the case of low PCDD/F exposure, relevant effects on liver function are uncertain. We still found that PCDD/Fs are associated with decreased liver function, and that serum TEQ_{DF-1998} is an important determinant of serum GOT, GPT and GGT level independent of age, sex, smoking and alcohol drinking. In several studies hepatotoxicity in PCDD/F-exposed workers was addressed with inconsistent results. Only a few studies found statistically significant associations between TCDD exposure and liver parameters (GGT, GOT, GPT). In addition, hepatotoxic effects, such as elevated GGT levels have sometimes been observed in humans following exposure to high 2,3,7,8-TCDD levels. In general,
the effects are mild and in some cases appear to have been transient (Mocarelli et al. 1986; Roegner et al. 1991) or not exist (Calvert et al. 1992; Ott et al. 1994). In a group of 138 former chemical workers with high TCDD exposure, none of the liver function indicators (GGT, GOT, GPT) were significantly correlated with current TCDD concentration. Only one indicator, alkaline phosphatase, was positively correlated with back-calculated TCDD concentration (Ott et al. 1994). Both the Vietnam Experience Study and the U.S. Air Force Ranch Hand Study found statistically significant elevations in GGT levels (Centers for Disease Control Vietnam Experience Study 1988; Roegner et al. 1991). In Army Vietnam veterans, mean GGT levels were 43.2 U/L compared with 41.1 U/L in non-Vietnam veterans (OR for out-of-range value = 1.3, 95% CI:1.0, 1.8) (Centers for Disease Control Vietnam Experience Study 1988). In the 1987 follow-up study, the comparison of the adjusted mean GGT level in the comparison group and in each of the three Ranch Hand groups defined by 2,3,7,8-TCDD level found statistically significant increases in the Ranch Hand population (≤10 pg/g 2,3,7,8-TCDD, \( p < 0.017 \); 15- ≤33.3 pg/g 2,3,7,8-TCDD, \( p<0.043 \); >33.3 pg/g 2,3,7,8-TCDD, \( p < 0.001 \)) (Roegner et al. 1991). A medical survey of 281 former workers employed in the manufacture of sodium trichlorophenol and its derivatives at two chemical plants more than 15 years earlier found no evidence of an elevated risk for clinical hepatic disease. However, multivariate regression analysis showed a statistically significant interaction between 2,3,7,8-TCDD exposure and lifetime alcohol consumption, indicating that the elevated risk for an out-of-range GGT (OR 2.27, 95% CI: 1.17, 4.39) was confined to persons with a history of significant alcohol consumption (Calvert et al. 1992). GGT was found to be elevated among one TCP production plant workers exposed to 2,3,7,8-TCDD following an industrial accident in Great Britain (May 1982). In a larger study, Mocarelli et al. (1986) tested liver enzyme levels yearly from 1977 to 1982 in male and female children from Seveso and from the unexposed surrounding area (Mocarelli et al. 1986). A slight increase in GGT and GPT occurred in the highest exposure group (based on zone of residences) compared to controls, but the values declined to normal levels within 3 years of the initial exposure. 2,3,7,8-TCDD blood levels have been more recently analyzed in about 30 of the subjects (Mocarelli et al. 1991). However, almost all clinical laboratory tests on these individuals were normal; any abnormal test result was only transitory in nature.

Similarly altered biochemical values (mainly increased serum GPT and GGT) were reported much earlier in individuals residing in an area of Seveso with average soil 2,3,7,8-TCDD concentrations of 580.4 \( \mu \)g/m² (Pocchiari et al. 1979). A study of clinical chemistry parameters and urinary porphyrins in Missouri residents living in a 2,3,7,8-TCDD-contaminated area did not show a significant association between liver
enzymes and TCDD tissue levels in 51 persons (high-risk, based on soil levels of
dioxins) exposed for up to 11 years (Webb et al. 1989).

Our study is not without limitations. First of all, the cross-sectional design does
not allow us to make any conclusive statement about the temporality of the observed
associations. In addition, we cannot rule out the presence of additional unknown
confounding variables that we were unable to control in our analyses. Moreover, we
were not able to exclude other risk factors for liver function, such as drug use, past
blood transfusions, or high-risk sexual activity. It is the first large, population-based
investigation to do so, and the findings seem to support a role of abdominal obesity
and serum PCDD/Fs level independent of overall adiposity in predicting increased
liver enzymes and potential liver damage. We conclude that in populations with a
wide range of exposure to environmental PCDD/Fs, serum TEQ_{DF-1998} is an important
independent determinant of LFTs. Serum PCDD/F and abdominal obesity would
affected the association with GGT level simultaneously. Our results support efforts to
reduce potential sources of environmental exposure to PCDD/Fs and to offer
possibilities for decreasing the abnormality of liver function.
Reference

Lee CC, Lin WT, Liao PC, Su HJ, Chen HL. 2006. High average daily intake of PCDD/Fs and serum levels in residents living near a deserted factory producing pentachlorophenol (PCP) in Taiwan: influence of contaminated fish consumption. Environ Pollut 141(2): 381-386.


Hollmann M, Runnebaum B, Gerhard I. 1997. Impact of waist-hip-ratio and


Webb KB, Evans RG, Knutsen AP, Roodman ST, Roberts DW, Schramm WF, et al. 1989. Medical evaluation of subjects with known body levels of
Figure Legend

**FIGURE 1.** Adjusted odds ratios (filled circles) and 95% CIs (vertical bars) for GOT, GPT, and GGT according to quintiles of serum 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF levels (pg/g lipid):

Serum 2,3,7,8-TCDF level indicate:

1st quintile: < 0.5 pg/g lipid;
2nd quintile: 0.5 ≤ serum 2,3,7,8-TCDF level < 0.6 pg/g lipid;
3rd quintile: 0.6 ≤ serum 2,3,7,8-TCDF level < 0.8 pg/g lipid;
4th quintile: 0.8 ≤ serum 2,3,7,8-TCDF level < 1.1 pg/g lipid;
5th quintile: 1.1 pg/g lipid ≤ serum 2,3,7,8-TCDF level

Serum 1,2,3,7,8-PeCDF levels indicate:

1st quintile: < 0.45 pg/g lipid;
2nd quintile: 0.45 ≤ serum 1,2,3,7,8-PeCDF level < 0.65 pg/g lipid;
3rd quintile: 0.65 ≤ serum 1,2,3,7,8-PeCDF level < 0.85 pg/g lipid;
4th quintile: 0.85 ≤ serum 1,2,3,7,8-PeCDF levels < 1.2 pg/g lipid;
5th quintile: 1.2 pg/g lipid ≤ serum 1,2,3,7,8-PeCDF level

The odds ratios are adjusted for age, sex, WHR, cigarette smoking history, and alcohol drinking history.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>non-AO (n = 1191)</th>
<th>AO (n = 837)</th>
<th>All (N = 2028)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.6 ± 14.2 (17.0-87.9)</td>
<td>51.7 ± 17.2 (17.0-92.0)</td>
<td>43.4± 17.0 (17.0- 92.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>576 (48.4%)</td>
<td>485 (58.0%)</td>
<td>1061 (52.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.4 ± 3.3 (11.5- 37.6)</td>
<td>26.1 ± 4.1 (16.8- 53.4)</td>
<td>23.9± 4.1 (11.5- 53.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bodyfat (%)</td>
<td>24.7± 6.3 (6.0-48.7)</td>
<td>31.7± 5.6 (10.0- 49.9)</td>
<td>27.6± 7.0 (6.0- 49.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>75.4± 8.8 (48.0-109.0)</td>
<td>89.3± 10.1 (59.0-130.0)</td>
<td>81.1± 11.6 (48.0-130.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>95.0± 7.0 (77.0-144.5)</td>
<td>99.2± 8.8 (50.0-133.0)</td>
<td>96.7± 8.0 (50.0-144.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>350 (29.4%)</td>
<td>246 (29.4%)</td>
<td>596 (29.4%)</td>
<td>0.995</td>
</tr>
<tr>
<td>Drinking (%)</td>
<td>137 (11.5%)</td>
<td>128 (15.3%)</td>
<td>265 (13.1%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>115.1 ± 17.2 (82.0-218.0)</td>
<td>129.3 ± 23.2 (70.0-218.0)</td>
<td>121.0± 21.1 (70.0- 218.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>70.9± 10.7 (40.0-120.0)</td>
<td>77.0 ± 11.9 (44.0-120.0)</td>
<td>73.4± 11.6 (40.0- 120.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>7.6 ± 0.7 (4.6- 10.6)</td>
<td>7.5 ± 0.7 (4.4- 10.4)</td>
<td>7.6± 0.7 (4.4- 10.6)</td>
<td>0.379</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.6± 0.4 (2.7- 6.5)</td>
<td>4.5± 0.4 (2.9- 6.5)</td>
<td>4.6± 0.4 (2.7- 6.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

(Continued on next page.)
Table 1 (cont.). Demographic characteristics of all study participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD (Range) or Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>non-AO (n = 1191)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>185.6± 40.1 (82.0-334.0)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>99.2± 86.8 (25.0-1666.0)</td>
</tr>
<tr>
<td>GOT (U/L)</td>
<td>23.6± 13.2 (7.0-262.0)</td>
</tr>
<tr>
<td>GPT (U/L)</td>
<td>22.5± 20.7 (4.0-384.0)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>27.6± 79.8 (4.0-1974.0)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.6± 0.3 (0.1-2.6)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>64.9± 21.3 (7.6-189.0)</td>
</tr>
<tr>
<td>Serum TEQDF-1998 (pg WHO1998-TEQDF/g lipid)</td>
<td>20.7± 30.0 (3.5-514.0)</td>
</tr>
</tbody>
</table>

Abbreviations: AO = abdominally obese; BP = blood pressure; TEQDF-1998 = toxic equivalency of PCDDs (D) and PCDFs (F), and 1998 indicates the World Health Organization 1998 toxic equivalency factors.

p-Value: indicates whether demographic characteristics and serum PCDD/Fs differ by AO (Wilcoxon Rank-Sum test for continuous variables and χ² test for categorical variables).
<table>
<thead>
<tr>
<th>Dependable Variable</th>
<th>WHR</th>
<th>ln-TEQ&lt;sub&gt;DF-1998&lt;/sub&gt;</th>
<th>WHR</th>
<th>ln-TEQ&lt;sub&gt;DF-1998&lt;/sub&gt;</th>
<th>β (SE)</th>
<th>p-Value</th>
<th>p for interaction&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln-TP</td>
<td>-0.010 (0.032)</td>
<td>-0.001 (0.004)</td>
<td>0.759</td>
<td>0.877</td>
<td>-</td>
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<tr>
<td>ln-ALB</td>
<td>-0.066 (0.030)</td>
<td>-0.001 (0.004)</td>
<td>0.028</td>
<td>0.746</td>
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</tr>
<tr>
<td>ln-GOT</td>
<td>0.429 (0.107)</td>
<td>0.036 (0.013)</td>
<td>&lt;0.001</td>
<td>0.005</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>ln-GPT</td>
<td>1.776 (0.184)</td>
<td>0.047 (0.022)</td>
<td>&lt;0.001</td>
<td>0.035</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>ln-GGT</td>
<td>2.042 (0.207)</td>
<td>0.057 (0.025)</td>
<td>&lt;0.001</td>
<td>0.022</td>
<td>0.005</td>
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</tr>
<tr>
<td>ln-TBIL</td>
<td>-0.548 (0.140)</td>
<td>0.032 (0.017)</td>
<td>&lt;0.001</td>
<td>0.060</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln-ALP</td>
<td>0.314 (0.098)</td>
<td>0.015 (0.012)</td>
<td>0.001</td>
<td>0.206</td>
<td>-</td>
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</tr>
</tbody>
</table>

Abbreviations: TP = total protein; ALB = albumin; GOT = glutamate oxaloacetate transaminase; GPT = Glutamic Pyruvic Transaminase; GGT= γ-Glutamyltransferase; TBIL= Total bilirubin; ALP= Alkaline phosphatase; SE= standard error

Adjusted for age, sex, cigarette smoking history, and alcohol drinking history.

<sup>†</sup>Interaction were derived from t test statistic of the interaction term included in the model.
### Table 3 Association among serum TEQDF, abdominal obesity and the abnormality of hepatic enzymes

<table>
<thead>
<tr>
<th>Categories</th>
<th>GOT</th>
<th></th>
<th></th>
<th>GGT</th>
<th></th>
<th></th>
<th>GPT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>No. (%)</td>
<td>OR (95% CI)</td>
<td>No. (%)</td>
<td>OR (95% CI)</td>
<td>No. (%)</td>
<td>OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Abdominal obesity†/serum TEQDF-1998‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-AO /1st tertile</td>
<td>510</td>
<td>20 (3.9%)</td>
<td>1</td>
<td>18 (3.5%)</td>
<td>26 (5.1%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>non-AO /2nd tertile</td>
<td>411</td>
<td>10 (2.4%)</td>
<td>0.72 (0.33-1.58)</td>
<td>12 (2.9%)</td>
<td>1.03 (0.48-2.22)</td>
<td>15 (3.7%)</td>
<td>0.94 (0.48-1.83)</td>
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</tr>
<tr>
<td>non-AO /3rd tertile</td>
<td>270</td>
<td>23 (8.5%)</td>
<td>3.14 (1.56-6.30)</td>
<td>18 (6.7%)</td>
<td>3.00 (1.42-6.32)</td>
<td>17 (6.3%)</td>
<td>2.33 (1.15-4.73)</td>
<td></td>
</tr>
<tr>
<td>AO /1st tertile</td>
<td>162</td>
<td>15 (9.3%)</td>
<td>2.98 (1.47-6.08)</td>
<td>14 (8.6%)</td>
<td>3.08 (1.45-6.53)</td>
<td>20 (12.4%)</td>
<td>3.69 (1.95-6.97)</td>
<td></td>
</tr>
<tr>
<td>AO / 2nd tertile</td>
<td>273</td>
<td>29 (10.6%)</td>
<td>3.55 (1.84-6.85)</td>
<td>39 (14.3%)</td>
<td>6.44 (3.36-12.33)</td>
<td>30 (11.0%)</td>
<td>3.61 (1.94-6.72)</td>
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<tr>
<td>AO / 3rd tertile</td>
<td>402</td>
<td>36 (9.0%)</td>
<td>3.62 (1.77-7.43)</td>
<td>53 (13.2%)</td>
<td>7.91 (3.92-15.97)</td>
<td>33 (8.2%)</td>
<td>3.84 (1.92-7.68)</td>
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</tbody>
</table>

†Abdominal obesity indicate: waist: hip ratio (WHR) was defined as >0.9 in males and >0.8 in females
‡Serum TEQDF-1998 indicate: 1st tertile: < 11.7 pg WHO98-TEQDF/g lipid; 2nd tertile: 11.7 ≤ serum TEQDF-1998 < 23.1 pg WHO98-TEQDF/g lipid; 3rd tertile: 23.1 pg WHO98-TEQDF/g lipid ≤ serum TEQDF-1998

Abbreviations: AO = abdominal obesity; OR = Odds Ratio; CI = Confidence Interval

Adjusted for age, sex, cigarette smoking history, and alcohol drinking history.
The graph shows the odds ratio of Quintiles of 2,3,7,8-TCDFs for GOT, GGT, and GPT. The y-axis represents the odds ratio ranging from 0 to 8, while the x-axis represents the quintiles from 1st to 5th.
Quintiles of 1,2,3,7,8-PeCDF

GOT

GGT

GPT

odds ratio
### Supplemental Table
Pearson correlation coefficients among hepatic enzymes, anthropometry and serum TEQ<sub>DF-1998</sub> (N= 2028).

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>BMI</th>
<th>Bodyfat</th>
<th>WHR</th>
<th>Sys BP</th>
<th>Dia BP</th>
<th>Pulse BP</th>
<th>ln-TP</th>
<th>ln-ALB</th>
<th>ln-GOT</th>
<th>ln-GPT</th>
<th>ln-GGT</th>
<th>ln-TBIL</th>
<th>ln-ALP</th>
<th>ln-TG</th>
<th>ln-CHOL</th>
<th>IR</th>
<th>ln-TEQ&lt;sub&gt;DF-1998&lt;/sub&gt;</th>
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<td>BMI</td>
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<td>Sys BP</td>
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<tr>
<td>Dia BP</td>
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<tr>
<td>Pulse BP</td>
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<tr>
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<td>ln-GPT</td>
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<td>0.168**</td>
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<tr>
<td>ln-TBIL</td>
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<td>ln-ALP</td>
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<td>ln-CHOL</td>
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<tr>
<td>ln-TEQ&lt;sub&gt;DF-1998&lt;/sub&gt;</td>
<td>0.648**</td>
<td>0.083**</td>
<td>0.369**</td>
<td>0.220**</td>
<td>0.358**</td>
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<td>-0.155**</td>
<td>0.164**</td>
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<td>-0.021</td>
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<td>0.047**</td>
<td>0.194**</td>
<td>0.023</td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: Waist=waist circumference; WHR=waist-to-hip ratio; Sys BP=systolic blood pressure; DiaBP=diastolic blood pressure; TP = total protein; ALB = albumin; GOT = glutamate oxaloacetate transaminase; GPT = Glutamic Pyruvic Transaminase; GGT=γ-Glutamyltransferase; TBIL= Total bilirubin; ALP= Alkaline phosphatase; CHOL= cholesterol; TG=triglycerides; IR=HOMA; TEQ<sub>DF-1998</sub> = toxic equivalency of PCDDs (D) and PCDFs (F), and 1998 indicates the World Health Organization 1998 toxic equivalency factors.

*<sup>p</sup> < 0.05 (two-tailed test). **<sup>p</sup> < 0.01 (two-tailed test). ***<sup>p</sup> < 0.001 (two-tailed test).