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Investigation of the Associations Between Low-Dose Serum Perfluorinated Chemicals and Liver Enzymes in US Adults

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Abstract

OBJECTIVES: Perfluorinated chemicals (PFCs) have been largely used for years in a variety of products worldwide. However, the toxic effect of PFCs on exposure to the liver in the general population has not yet been determined.

METHODS: In this study, 2,216 adults (18 years of age or older) were recruited in a National Health and Nutrition Examination Survey (NHANES) in 1999–2000 and 2003–2004 to determine the relationship between serum level of PFCs and the levels of liver enzymes. The data were adjusted for all other confounding variants.

RESULTS: After performing mathematical analysis, we determined when serum log-perfluorooctanoic acid (PFOA) increases in one unit, the serum alanine aminotransferase (ALT) concentration (U/l) increases by 1.86 units (95% confidence interval (CI), 1.24–2.48; *P*=0.005), and the serum log-γ-glutamyltransferase (GGT) concentration (U/l) is 0.08 unit higher (95% CI, 0.05–0.11; *P*=0.019). The association between PFOA and liver enzymes was more evident in obese subjects, as well as subjects with insulin resistance and/or metabolic syndromes. When dividing the serum PFOA into quartiles in the fully adjusted

models in subjects with a body mass index ≥30 kg/m², the ALT level trend across the serum PFOA quartiles was significant (*P*=0.003).

CONCLUSIONS: On the basis of these data, we conclude that a higher serum concentration of PFOA may cause liver enzymes to increase abnormally in the general population, particularly in obese individuals. Further studies are warranted to clarify the casual relationship between PFCs and these liver enzymes.

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INTRODUCTION

Perfluorinated chemicals (PFCs) consist of a 4–14 carbon backbone and a charged functional moiety (primarily carboxylate, sulfonate, or phosphonate). PFCs are man-made contemporary chemicals that have only been used in the last half-century. Until recently, PFCs have been considered to be biologically inactive. Human and wildlife monitoring studies have identified PFCs worldwide. This finding led to efforts to better understand the hazards that may be inherent in these compounds, as well as the global distribution of PFCs (1).

The two most widely known PFCs are perfluorooctanoic acid (PFOA) and perfluorooctane sulfate (PFOS), which belong to the 8-carbon backbone subgroup (1). PFOA (primarily ammonium salt) can be used as a surfactant and an emulsifier in the production of polytetrafluoroethylene as well as other fluoropolymers and fluoroelastomers. N-alkyl substituted derivatives of PFOS have been used in a wide variety of industrial and consumer products including protective coatings for carpets and apparel, paper coatings, insecticide formulations, and surfactants. Other PFCs, like perfluorononanoic acid (PFNA), are used as surfactants in the production of fluoropolymer polyvinylidene fluoride. In contrast, perfluorohexane sulfonic acid (PFHxS) is mostly used in carpet-treatment applications (2). Although the major manufacturer of PFOS, 3M, has phased out of production since 2002, the potential risk of PFCs to humans still needs to be continually evaluated (3).

The possible routes of human exposure to PFCs are currently being investigated. Potential routes include contaminated drinking water, dust, food, food packaging, and cookware. Animal studies have shown that PFCs are well absorbed orally but are poorly eliminated. PFCs mainly distribute extracellularly. PFCs have a binding affinity for β-lipoproteins, as well as albumin and liver fatty acid-binding protein. PFCs are not metabolized and distributed through enterohepatic circulation to the serum and the kidney. However, PFCs are mainly distributed to the liver with concentrations being several times higher than serum concentrations (3). The half-life of serum elimination of PFCs in humans seems to be long. The longer the carbon chain length, the longer PFCs persist in the body. For example, perfluorobutane sulfonate (a 4-carbon PFC) is eliminated, on average, in a little over 1 month in humans, whereas PFOA and PFOS (8-carbon compounds, referred to as C8 compounds) are eliminated in 3.8 and 5.4 years, respectively. However, PFHxS (a 6-carbon compound) is an exception to the rule as it is eliminated in 8.5 years (4).

Exposure to PFCs at relatively high concentrations is associated with damage to liver function in animal models (5,6,7). The hepatotoxicity of PFOS and PFOA has been linked to the functions of these compounds as peroxisome proliferator-activated receptor α (PPARα) agonist and thus, their ability to alter the expression of genes involved in peroxisome proliferation, cell cycle control, and apoptosis (8,9,10). In addition, other PFCs have also been shown to act as strong peroxisomal β-oxidation inducers (11,12). In human beings, the causal biochemical mechanisms of hepatic toxicity after exposure to PFCs are not clearly defined. In occupational population, several studies have failed to establish a definite association between exposure to PFCs and adverse health effects (13,14,15,16). A few cross-sectional and longitudinal occupational studies have proposed a positive correlation among PFOA, serum lipid, and liver enzymes levels (17,18). In a non-worker population, examination of PFOA exposure through contaminated drinking water showed an insignificant correlation between abnormal clinical markers and the serum PFOA concentration (19).

The relationship between the serum PFC levels and liver enzymes in a nationally representative survey of adults has never been performed. We hypothesized that PFCs might have adverse effects on liver chemistry in the general US population according to the large scale data set of PFCs (20) and liver enzyme profiles released by US National Health and Nutrition Examination Survey (NHANES) performed between 1999–2000 and 2003–2004.

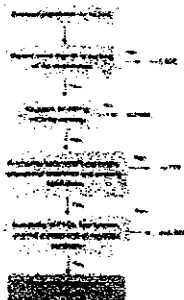
METHODS

Study design and population

The data were adopted from 1999–2000 and 2003–2004 NHANES (PFCs were not measured in 2001–2002 NHANES). NHANES is a population-based survey designed to collect information on the health and nutrition of the US household population and to obtain a representative sample of the non-institutionalized civilian US population. The survey data are published biannually. Detailed contents of the NHANES 1999–2000 and 2003–2004 are available at the NHANES website (21).

In the 1999–2000 and 2003–2004 NHANES, the participants were older than 18 years of age, were not pregnant or nursing at the time of the examination, and were randomly assigned to receive examinations (n=10,224). Individuals were excluded based on the following criteria: individuals who had fasted <6 h at the time of the examination (n=1,802); individuals that were hepatitis B virus or hepatitis C virus carriers by serology (n=168); individuals in which data were not available for body weight, body height, educational attainment, or smoking habits (n=113); and individuals without serum tests for PFCs, liver function or the five components of metabolic syndrome (n=5,925). A total of 2,216 participants were left for final analysis. A flow chart of algorithm is shown in **Figure 1**. In NHANES, a subset of the participants who received a morning fasting examination (n=1,114) had blood fasting and insulin levels measured. Insulin resistance status was determined for this subset of participants.

Figure 1.



Flow chart algorithm. HBV, hepatitis B virus; HCV, hepatitis C virus; PFCs, perfluorinated chemicals.

Full figure and legend (125K)

Potential causes of elevated liver enzymes

In accordance with earlier studies (22,23), in addition to chronic hepatitis viral infection (which was excluded from this study), we considered excessive alcohol consumption, smoking, and increased serum markers of iron stores as potential causes of elevated liver enzymes. As obesity, insulin resistance, and metabolic syndrome are strong predictors of increased liver enzyme activity (24), we also considered body mass index (BMI), insulin resistance, and metabolic syndrome as potential confounders in liver function tests.

The data were collected at all study sites by trained personnel using standardized procedures. Sociodemographic information such as age, gender, race/ethnicity, history of medication, and education level was recorded during the household interview. The education level was categorized as either above high school a diploma or high school diploma and below. The degree of alcohol intake was determined by a questionnaire and categorized into the following four categories: <12 drinks, <60 drinks, <240 drinks, and >240 drinks a year). Smoking status was subdivided into an active smoker, a former smoker, or has never smoked by serum cotinine levels and as described on the questionnaire (25). Serum iron and total iron binding capacity were measured by the Beckman/Coulter LX20 analyzer. The transferrin saturation value was calculated using the following equation: (iron/total iron binding capacity) × 100%. Weight and height were measured by standard methods and digitally recorded. The BMI was calculated as weight (in kg) divided by the square of height (in m).

The homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) index (the product of basal glucose and insulin levels divided by 22.5) is regarded as a simple, inexpensive, and reliable surrogate

measure of insulin resistance (26). The serum glucose level and the plasma insulin concentration were determined by the hexokinase enzymatical method and the immunoenzymometric assay, respectively.

Search: go

The National Cholesterol Education *Program Third Adult Treatment Panel (27) has established* guidelines for metabolic syndrome with modifications for the different sexes. People who were 18 years old and above were defined as victims of metabolic syndrome if they meet at least three of the following criteria: a waist measurement >88 cm for women and >102 cm for men; serum triglyceride ⩾1.69 mM; serum high-density lipoprotein cholesterol <1.03 mM in men and <1.29 mM in women; systolic blood pressure⩾130 mmHg or diastolic blood pressure⩾85 mmHg or self-report of anti-hypertensive medications; and fasting glucose level ⩾6.10 mM or self-report of anti-hyperglycemic medications. Three, sometimes four, blood pressure determinations were taken with a mercury sphygmomanometer by a physician using the right arm unless otherwise specified. The averaged systolic and diastolic blood pressure was obtained. The level of triglycerides was measured enzymatically. Levels of high-density lipoprotein cholesterol were measured after precipitation of other lipoproteins using a Hitachi model 704 analyzer (Roche Diagnostics, Indianapolis, IN).

Assessment of liver enzyme parameters

Total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase, γ-glutamyltransferase (GGT), and alkaline phosphatase were the liver enzymes parameters available from NHANES. Bilirubin is mostly derived from the metabolism of hemoglobin. Increases in bilirubin are highly specific for diseases of the liver or bile ducts (28). Aspartate aminotransferase and ALT are enzymes presented in liver parenchymal cells. Both of these enzymes are elevated during acute liver damage. Increased ALT activity has been used as a surrogate measure for the presence of liver disease in earlier population-based studies (22,23,24). GGT is found on the cell surface of all cells. Particularly high concentrations of GGT are found in the liver, the bile ducts, and the kidney. GGT increases occur earlier and persist longer than alkaline phosphatase in cholestatic disorders (29). In the study, we used total bilirubin, ALT, and GGT as markers of liver enzymes. Serum total bilirubin, GGT, and ALT levels were measured by enzymatic methods through automated biochemical profiling Beckman Synchron LX20). Total bilirubin was calculated in micromolar (μM) and GGT and ALT were calculated as units/litre (U/l).

Assessment of PFCs concentration

Thirteen kinds of PFCs are available in NHANES. However, in nine, over 70% of the PFCs are below the limit of detection. Therefore, we used serum samples of PFOA, PFOS, PFHxS, and PFNA for analysis in this study. A brief summary of the PFCs assessment (30) is as follows: the serum was diluted with 0.1 M formic acid without protein precipitation and a 100 μl aliquot of the serum was injected into a commercial column switching system for the determination of the concentration of the analytes on a C18 solid-phase extraction column. This column was placed automatically in front of a C8 analytical high-performance liquid chromatography column for chromatographic separation of the analytes. Detection and quantification were done by negative-ion TurboIonSpray ionization tandem mass spectrometry and isotope-labeled internal standards. The limit of detection for PFOA was 0.2 ng/ml in the NHANES 1999–2000 and 0.1 ng/ml in the NHANES 2003–2004 data sets. For PFOS, the limit of detection was 0.2 and 0.4 ng/ml in the NHANES 1999–2000 and 2003–2004, respectively. The limit of detection for PFHxS was 0.1 and 0.3 ng/ml in 1999–2000 and 2003–2004, respectively. For PFNA, the limit of detection was 0.2 ng/ml in 1999–2000 and 0.1 ng/ml in 2003–2004. For concentrations below the detection limits (0.4% for PFOA, 0.1% for PFOS, 2.3% for PFHxS, and 1.7% for PFNA), a value equal to the detection limit divided by the square root of 2 was used (20).

Statistics

PFCs concentration was expressed as the geometric mean with a 95% confidence interval (CI). Log transformation was performed for *HOMA-IR, serum GGT, and PFCs levels with significant deviation* from the normal distribution before further analyses. All the log-transformed data in the study had a normal distribution and no significant outliers were found. For linear regression models, we used an extended model approach for covariates adjustment of potential confounders. Model 1 adjusted for age, gender, and race/ethnicity. Model 2 adjusted for age, gender, race/ethnicity, life style (smoking status, drinking status, and education level), and measurement data (BMI, HOMA-IR, metabolic syndrome, and iron saturation status). To avoid "model-dependent association," the association was considered

significant only when it remained statistically significant in all models. Each PFC was modeled separately.

Sampling weights that accounted for unequal probabilities of selection, over-sampling, and non-response and variance estimation accounting for complex survey design were applied to all analyses by the Complex Sample Survey module of SPSS 13.0 for Windows XP (SPSS Inc. Chicago, IL). A mobile examination center weight variable was created by assigning half of the 2-year weight for 1999–2000 and assigning half of the 2-year weight for 2003–2004.

RESULTS

The basic demographic of the sample population is outlined in **Table 1**. The study sample consisted of 1,076 men and 1,140 women. In accordance with an earlier NHANES study (**20**), the results indicate that males have a higher average concentration of PFOS, PFOA, and PFHxS than females. Hispanic Americans have lower mean serum concentrations (ng/ml) for these three compounds than non-Hispanic whites and non-Hispanic blacks. In addition, the concentration of PFOS and PFNA was higher in the more highly educated cohort. The four PFCs were moderately correlated with one another. PFOA and PFOS were most strongly correlated, with a Spearman correlation coefficient of 0.68; PFHxS and PFNA were the least correlated at 0.24.

Table 1 - Basic demographics of the sample subjects including geometric means (s.e.) of PFC concentrations.

Full table

Unadjusted mean liver enzymes across quartiles of PFCs (ng/ml) are shown in **Table 2**. The serum ALT levels (U/l) increased across quartiles of PFOA and PFOS (*P* value <0.001 and 0.030, respectively). Similar to ALT, the serum level of GGT (U/l) also increased across quartiles of PFOA and PFOS (*P* value 0.012 and 0.010, respectively). The serum total bilirubin level (μM) increased across quartiles of PFHxS and PFNA (*P* value <0.001 and 0.014, respectively).

Table 2 - Unadjusted liver enzymes (s.e.) across quartiles of PFCs.

Full table

A summary of the association between serum concentration of log-PFCs (ng/ml) and liver enzymes after the adjustment for other potential covariates is listed in **Table 3**. When the four PFCs were entered into the full regression models separately, one unit increase in serum log-PFOA concentration was associated with a 1.86 unit (95% CI, 1.24–2.48; *P*=0.005) increase in serum ALT concentration (U/l), a 0.08 unit (95% CI, 0.05–0.11; *P*=0.019) increase in serum log-GGT concentration (U/l). PFOS associated with ALT, whereas PFNA was associated with total bilirubin with borderline statistical significance. The PFHxS

concentration was not associated with liver function tests. When the four PFCs were entered into the full regression models at the same time, one unit increase in serum log-PFOA concentration was associated with a 2.19 unit (95% CI, 1.4–2.98; P=0.009) increase in serum ALT concentration (U/l), a 0.15 unit (95% CI, 0.11–0.19; P=0.001) increase in serum log-GGT concentration (U/l). One unit increase in serum log-PFOS concentration was negatively associated with a 1.06 unit (95% CI, −1.33 to −0.79; P=0.001) decrease in serum total bilirubin concentration (μM) and was negatively associated with log-GGT concentration with borderline statistical significance. One unit increase in serum log-PFNA and log-PFHxS concentration were associated with a 0.75 unit (P=0.004 and 0.001, separately) increase in serum total bilirubin concentration (μM).

Table 3 - Linear regression coefficients (s.e.) of blood analytes with a unit increase in log-PFCs concentrations.

Full table

Linear regression coefficients (s.e.) of blood analytes (ALT and GGT) with a unit increase in log-PFOA in the different subpopulations of the sample subjects are shown in Table 4. Subjects with iron saturation above 50% were excluded because of the small sample size (N=19). The association between ALT and PFOA was significant in the following subgroups of non-Hispanic Caucasians, individuals with a lower education level, higher BMI, non-smoking, lower alcohol consumption, higher HOMA-IR, and subjects diagnosed as having metabolic syndromes. On the other hand, the association between GGT and PFOA was significant in subgroups of non-Hispanic white, higher BMI, lower alcohol consumption, and higher HOMA-IR.

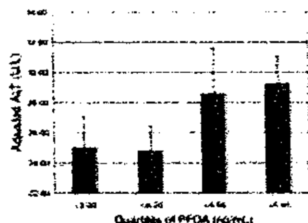
Table 4 - Linear regression coefficients (s.e.) of blood analytes with a unit increase in log-PFOA concentrations (ng/ml) in subpopulations of the sample subjects.

Full table

When dividing serum PFOA into quartiles in the fully adjusted models in subjects with BMI ⩾30 kg/m^2, the adjusted levels of ALT are shown in Figure 2. The trend in ALT levels across quartiles of serum PFOA was significant (P=0.003), whereas the trend in log-GGT was not significant.

Figure 2.

The adjusted geometric means of ALT across quartiles of the serum PFOA concentrations. The data are from the fully adjusted model (age, gender, race/ethnicity, smoking status, drinking status, education level, metabolic syndrome, and iron saturation status) in subjects with a BMI ⩾30 kg/m^2. The trends in ALT level across the quartiles of the serum PFOA were significant (P=0.003). ALT, alanine aminotransferase; BMI, body mass index; PFOA, perfluorooctanoic acid.



Full figure and legend (59K)

DISCUSSION

To our knowledge, our report is the first to link serum PFC levels to liver enzymes in a nationally representative survey. In this study, we showed that increased serum PFOA concentrations are associated with elevated serum liver markers.

PFOS and PFOA show liver toxicity in rodents and non-human primates (5,6,7). A number of short-term studies focusing on rats and mice have shown that PFOS and PFOA are capable of inducing peroxisome proliferation via activation of PPARα (8,9,10,11). There is strong evidence to support the idea that PFOA-induced liver toxicity occurs through a PPARα agonistic mode of action in rodents (8). However, adverse hepatic effects of PFOA still exist in PPAR null mice (31). These findings imply that PFOA may exert its toxic effects through both PPARα as well as other alternative pathways. As the key events of hepatic toxicity induced by PFOS are not consistent with a PPARα-agonistic model, the relevance of PPARα-induced toxicity dependent on dose–response in humans is a current scientific debate (6,32). Some studies have used other PFCs that have been conducted in mice (11,12). All of the compounds tested induced hepatomegaly and peroxisomal β-oxidase activity. The potency of PFCs to cause hepatomegaly and peroxisomal β-oxidase activity is shown as follows: PFNA>PFOA>perfluoroheptanoic acid>perfluorohexanoic acid. These results indicate that the longer the perfluoroalkyl chain of the PFC, the higher the accumulation of the compound in the mouse liver.

In some occupational epidemiology studies, the association between PFCs exposure and abnormal liver function tests could not be established (13,14,15,16). Only one cross-sectional occupational study (17) observed a positive relationship between serum PFOA and GGT. In the meantime, one longitudinal occupational study (18) revealed that serum PFOA is related to total bilirubin (0.008 mg/dl decline/1,000 ppb) and serum aspartate aminotransferase (0.35 units increase/1,000 ppb). A study was conducted to testify whether PFOA affected the non-working in a community located near a fluoropolymer production facility using either hematologic or biochemical clinical markers (19). In this non-occupational population, the median serum PFOA was 354 ng/ml (an interquartile range, 184–571 ng/ml). This serum concentration of PFOA is higher than the level in the general US population (median of 4.4 ng/ml). However, there was no significant correlation between abnormal clinical markers and serum PFOA concentration in that study. In our study, serum PFOA was associated with a change in both ALT and GGT, but not other PFCs. However, the potential biological significance between PFOA and liver enzymes is small and subclinical in this general population. As PFOA are metabolically inert, it is difficult to detect the same metabolic effect in the low exposure group of the general population and in the occupational studies presented with a high concentration level. One possible explanation is the bias of the "healthy worker effects," which states that severely ill or disabled people are more susceptible to PFOA exposure and excluded from employment. Another possible explanation is that the dose–response effects of PFOA on liver enzymes may not be a linear relationship in humans. PFOA exerts the maximal effects at a low dose already and no further consistent or potentially relevant clinical changes occur at an even higher level.

In our study, the association between PFOA and liver enzymes was more evident in subjects suffering from obesity, insulin resistance, and the metabolic syndromes. However, there was no significant difference in regards to serum PFOA concentration between these groups. Studies of gene expression profiles in rat livers treated with PFOA showed that the largest category of induced genes are those involved in metabolism and transport of lipids, particularly fatty acids (33,34). An increase in lipid

droplets due to alteration in lipoprotein metabolism after exposure to PFOA have also been observed (35). In obese individuals, a liver loaded with fat will increase liver enzymes and become insulin resistant (36). Therefore, it is possible that PFOA may further increase the free fatty acid accumulation in subjects with hepatic steatosis. Furthermore, there might be some synergistic effects on hepatotoxicity between PFOA and obesity. PFOA is primarily distributed to the liver in rats (3). In the liver, multiple proteins from the cytosol, nuclei, and mitochondria fractions are capable of specifically binding PFOA (37). Another possible explanation is that in obese subjects with hepatic steatosis, intrahepatic PFOA accumulation might be higher than non-obese subjects despite the same serum level. With the higher accumulation of PFOA in the liver, the effect of PFOA on liver is more evident.

We found that the association between PFOA and liver enzymes was more evident among non-smokers and those with lower alcohol consumption. One possible explanation is that the effect of PFOA on liver enzymes is much weaker than the effect of alcohol and tobacco smoke. When considering the hepatotoxic effect of PFOA in the smoking or higher alcohol consumption population, the trend is too small to become statistic significant. Alternatively, it is also possible that the association between PFOA and smoking tobacco or drinking alcohol is opposite to the possible synergistic effect between PFOA and obesity mentioned above.

There are several limitations of our study. First, the cross-sectional design does not permit any causal inference. Second, we did not include other environmental chemicals, which may be important covariates or explanatory variables for the outcomes of our study. Third, we did not take into account any medications that may cause elevated ALT or GGT. Fourth, a common physiology could influence both serum PFCs and liver enzymes rather than exposure affecting outcome. Finally, the status of the liver tissue was not available to determine hepatic steatosis, inflammation, or fibrosis.

In conclusion, using the NHANES data from the US adult population, we found that a higher serum concentration of PFOA was associated with elevated liver enzymes. These findings provide clues to the adverse effects of low-dose PFOA in humans. Although the potential biological significance between PFOA and liver enzymes is small and subclinical in the general US population, our data suggest that it would be prudent to monitor the liver enzymes of people with low level exposure of PFOA, particularly in subjects who are obese. Further studies are needed to confirm these findings and to clarify whether these associations are causal.

CONFLICT OF INTEREST

Guarantor of the article: Pau-Chung Chen, MD, PhD.

Specific author contributions: Designed the study, drafted the article, and interpretated the data: Chien-Yu Lin; designed the study's analytic strategy and helped conduct the literature review: Lian-Yu Lin; helped conduct the literature review: Chih-Kang Chiang, Wei-Jie Wang, and Yi-Ning Su; helped conduct the literature review, approved the analytic strategy, and approval of the final version: Kuan-Yu Hung; contributed to the study's conception, reviewed the study, and final approval of the version to be published: Pau-Chung Chen.

Financial support: This was an investigator-initiated unfunded study. All authors had access to the data and the statistical analysis report. Each author approved the final article and attested to the validity of the results.

Potential competing interests: None.

STUDY HIGHLIGHTS

partner of AGORA, HINARI, OARE, INASP, CrossRef and COUNTER

WHAT IS CURRENT KNOWLEDGE

✓ Perfluorinated chemicals (PFCs) have been largely used for years in a variety of products worldwide. Exposure to PFCs at relatively high concentrations is associated with damage to liver function in animal models. Unfortunately, the toxic effects of PFCs in the general population on exposure to the liver are still not known.

WHAT IS NEW HERE

✓ A high serum concentration of perfluorooctanoic acid causes liver enzymes to increase abnormally in the general population, especially in subjects who are obese.

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