Science of the Total Environment 512–513 (2015) 364–370

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Association of polyfluoroalkyl chemical exposure with serum lipids in children

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HIGHLIGHTS

- The association between serum PFASs and lipids was evaluated in Taiwanese children.
- Eight out of ten particular PFAS chemicals were detected in most participants (>94%).
- PFOS, PFOA and PFNA were positively associated with total cholesterol, LDL and TG.

ARTICLE INFO

Article history:
Received 16 September 2014
Received in revised form 16 January 2015
Accepted 17 January 2015
Available online 30 January 2015

Editor: Adrian Covaci

Keywords:
Polyfluoroalkyl substances
Polyfluoroalkyl compounds
Serum lipids
Children

ABSTRACT

Perfluoroalkyl and polyfluoroalkyl substances (PFASs), as well as polymers of PFASs, have been widely used in commercial applications and have been detected in humans and the environment. Previous epidemiological studies have shown associations between particular PFAS chemicals and serum lipid concentrations in adults, particularly perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). There exists, however, limited information concerning the effect of PFASs have on serum lipids among children. In the present cross-sectional study, 225 Taiwanese children (12–15 years of age) were recruited to determine the relationship between serum level PFASs and lipid concentration. Results showed that eight out of ten particular PFASs were detected in the serum of >94% of the participants. Serum PFOS and perfluorotetradecanoic acid (PFTA) levels were at an order of magnitude higher than the other PFASs, with arithmetical means of 32.4 and 30.7 ng/ml in boys and 34.2 and 27.4 ng/ml in girls, respectively. However, the variation in serum PFTA concentration was quite large. Following covariate adjustment, linear regression models revealed that PFOS, PFOA, and perfluorononanoic acid (PFNA) were positively associated with total cholesterol (TC), low-density lipoprotein (LDL) and triglycerides (TG), particularly for PFOS and PFTA. Quartile analysis, with the lowest exposure quartile as a reference, yielded associations between serum PFTA and elevations in TC ($p = 0.002$) and LDL ($p = 0.004$). Though not statistically significant, high-density lipoprotein (HDL) appeared to decrease linearly across quartiles for PFOS and PFOA exposure. In conclusion, a significant association was observed between serum PFASs and lipid level in Taiwanese children. These findings for PFTA are novel, and emphasize the need to investigate the exposure route and toxicological evidence of PFASs beyond PFOS and PFOA.

1. Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are a diverse class of compounds that have an aliphatic carbon backbone in which the hydrogen atoms have substituted with fluorine. These perfluorinated chemicals include perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorinated sulfonates such as perfluorooctane sulfonic acid (PFOS) and perfluorohexane sulfonic acid (PFHxS). PFASs and

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http://dx.doi.org/10.1016/j.scitotenv.2015.01.042
0048-9697/

polymers made with the aid of PFASs have been widely used in manufactured products and are ubiquitously present in both the environment and the human body (Buck et al., 2011; Kissa, 2001). Uptake of PFASs occurs via direct exposure through diet, drinking water, and inhalation of household dust, or via indirect exposure such as PFAS contamination resulting from contact with food packaging (D'eon and Mabury, 2011). Elimination of PFASs occurs slowly without biotransformation. The estimated geometric mean half-lives of PFOA, PFOS, and PFHxS in human serum have been reported to be 3.5 years (95% CI, 3.0–4.1), 4.8 years (95% CI, 4.0–5.8), and 7.3 years (95% CI, 5.8–9.2), respectively (Olsen et al., 2007a). Two typical PFASs, PFOA and PFOS, belong to the 8-carbon backbone subgroup and have been studied more extensively than other PFASs. By virtue of its ability to bioaccumulate, its potential for long-range environmental transport, and its chemical stability and toxicity, PFOS and its salts have been added to Annex B of the Stockholm Convention of persistent organic pollutants in 2009. Additionally, PFOA, has been classified as a Group 2B carcinogen by the International Agency for Research on Cancer (IARC, 2012).

Animal studies have demonstrated that high level exposure to PFOS and PFOA could induce adverse outcomes, including hepatotoxicity (Qazi et al., 2010), developmental neurotoxicity (Mariussen, 2012; Zeng et al., 2011), and carcinogenicity (Biegel et al., 2001; Butenhoff et al., 2012a,b). Although the specific mechanism of action for PFASs remains to be elucidated, peroxisome proliferator-activated receptor-α (PPARα) has been considered to play an important factor in mediating PFAS effects (Abbott et al., 2007; Wolf et al., 2012). PPARα falls within a class of ligand-activated transcription factors of the steroid/thyroid nuclear hormone receptor superfamily, and plays a role in lipid homeostasis, energy metabolism, and cell differentiation (Peraza et al., 2006). PFASs could activate PPARα with varying potencies (Buhrke et al., 2013; Wolf et al., 2008). Several studies have shown that PFOA could induce hypolipidemic effects in rodents (Loveless et al., 2006; Wang et al., 2013). However, the majority of human epidemiological studies have not reported complimentary hypolipidemic results.

Epidemiological studies have suggested that exposure to PFOA and PFOS may be associated with serum lipid levels in PFAS-expose populations, though the findings are inconsistent. Positive associations have been found in adult populations exposed to relatively high levels of PFASs. An association between serum PFOA and total cholesterol was observed in two occupational populations (Costa et al., 2009; Sakr et al., 2007) and a community in a PFOA-contaminated water district (Steenland et al., 2009). However, no associations were reported in a third occupational population (Olsen and Zobel, 2007) and a separate PFOA-contaminated community cohort (Emmett et al., 2006). The association of lipids and PFOS is similar in magnitude to those with PFOA. Cross-sectional studies of the general population have found positive serum lipid associations with PFASs. Analysis of the National Health and Nutrition Examination Survey (NHANES) of the American general population noted a positive association between PFOS and PFOA and cholesterol (Nelson et al., 2010). A similar analysis of the Canadian Health Measures Survey (CHMS), Cycle 1, found only weak associations between PFOS and PFOA and serum lipids, but did observe significant associations with the PFHxS and cholesterol outcomes (Fisher et al., 2013). These observed inconsistencies in associations between PFASs and lipids may be due to differences in age and gender distributions of the participants across studies, differences in size of the study populations, or variation in PFAS exposure across study populations (Starling et al., 2014).

Despite several investigations of PFASs' impact on adults, there have been relatively few studies focused on the association between PFAS exposure and lipid concentrations in children and adolescents. Studies by Frisbee et al. (2010) and Geiger et al. (2014) have found that PFOA and PFOS were significantly associated with increased total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) in children. However, the association between PFASs and lipids has been inconsistent. While Frisbee et al. (2010) reported a positive association between PFOS and HDL in US adolescents, the inverse relationship was observed in Taiwanese adolescents (Lin et al., 2011). In addition, attention to the potential effects of exposure to other PFASs (such as PFHxS or PFNA) should not be neglected given that these have been used as alternatives to PFOS in industrial applications following the phase-out of PFOS in 2000–2002 (Beesoon et al., 2012). The renal elimination rate of various PFASs may be different, depending upon the chain length of the organic anion transport proteins involved in renal reabsorption (Han et al., 2011). Thus, the PFASs with longer carbon chain (such as PFOA) are considered to be more likely to bioaccumulate in mammals than their shorter-chained analogs (Haug et al., 2009).

Previous studies in Taiwan have shown that the serum PFOS concentration in children residing in the Taipei area increased three-fold between the time periods of 2006–2008 (Lin et al., 2011) to 2009–2010 (Bao et al., 2014), despite declining serum PFAS concentration occurred globally (Fitz-Simon et al., 2013; Kato et al., 2011; Toms et al., 2014). Contrary to the concentration of PFOS in serum, PFOA concentration is much lower in Taiwanese children compared to other countries or areas (Bao et al., 2014). It is also generally accepted that individuals are more sensitive to the effects of xenobiotic exposure during periods of development, such as childhood. Furthermore, studying the potential health consequences of an environmental exposure on children rather than adults might provide unique insights because the number of underlying factors confounding the associations is likely to be smaller (Lin et al., 2011). Given that studies focusing on the association between serum PFASs and lipids in children are limited, understanding their relationship in different exposure conditions could provide further insight. Accordingly, the objective of this study was to evaluate the cross-sectional association between measures of PFAS exposure and total cholesterol, HDL, LDL, and triglycerides in Taiwanese children. The present study sample was obtained as part of a community-based child population survey in Taiwan (Tsai et al., 2010).

2. Material and methods

2.1. Study participants

The study subjects were from the control group of the Genetic and Biomarkers study for Childhood Asthma (GBCA) in Taiwan. The control cohort was selected from seven public schools in the Taipei area from 2009 to 2010 (Tsai et al., 2010). These schools had diverse geographical and socioeconomic characteristics, being located in city, rural, and high-altitude communities. In each targeted school, children of the same age range and without a personal or family history of asthma were invited to participate. A total of 225 healthy children were enrolled, including 102 boys and 124 girls aged from 12 to 15 years (the response rate was 72% among those contacted by phone). A survey was used to acquire information regarding demographic variables and environmental exposure. Information was collected about the current and past smoking status of each participant's adult household members and regular household visitors. All children and their parents provided written informed consent. The study protocol was approved by the Institutional Review Board (National Taiwan University Hospital Research Ethics Committee).

2.2. Serum lipid determination

The main outcome of interest was serum lipid levels. Serum was separated from red blood cells, placed in transport tubes, and refrigerated before being shipped to the analytical laboratory. Four lipid levels were measured enzymatically: total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG), and units were recorded in mg/dl. LDL was calculated using the Friedewald formula for participants when TGs were lower than