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Longitudinal changes in persistent organic pollutants (POPs) from 2001 to 2009 in a sample of elderly Swedish men and women

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ABSTRACT

Background: Prospective cohort studies evaluating the temporal trends of background-level persistent organic pollutants (POPs) and their potential negative health effects in humans are needed.
Objective: The objectives of this study are to examine the five year longitudinal trend in chlorinated and brominated (Cl/Br) POP concentrations in a sample of elderly individuals and to investigate the relationship between gender, changes in body weight, plasma lipid levels and POP concentrations.
Methods: In the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, plasma samples were collected from the same individuals over a 5 year period. Originally 992 subjects (all aged 70) were sampled between 2001 and 2004 and 814 returning subjects (all aged 75) were sampled again from 2006 to 2009. Plasma concentrations of 16 polychlorinated biphenyls (PCBs), 5 organochlorine pesticides (OCPs), octachlorinated dibenzo-*p*-dioxin (OCDD), and one polybrominated diphenylether (BDE 47) were determined using high-throughput 96-well plate solid phase extraction and gas chromatography-high resolution mass spectrometry (GC-HRMS).
Results: During the 5-year follow-up, plasma concentrations of all POPs significantly decreased ($p < 0.00001$). Median reductions ranged from 4% (PCB105) to 45% (PCB 99), with most reductions being in the 30–40% range. For most POPs, a larger decline was seen in men than in women. The relationship between the weight change and change in POP concentrations was generally negative, but a positive relationship between lipid levels and POP concentrations when expressed as wet-weight was observed. In general, similar changes in POP concentrations and their relationships to body weight were observed regardless of using either wet-weight (pg/mL) or lipid-normalized (ng/g lipid) concentrations.
Conclusion: In this longitudinal cohort study, gender and minor, but varying changes in body weight and lipid levels greatly influenced the individual-based changes in POP concentrations. In general, our findings suggest that men and women with larger decreases in body weight and greater increases in lipid levels have the slowest decline in body burden of POPs. Based on the results from this study, either wet-weight or lipid normalized concentrations can be used to determine the percent change in POP concentrations and their relationships to physiological changes and differences.

1. Introduction

Chlorinated and brominated (Cl/Br) persistent organic pollutants (POPs) are still universally detected in humans at background levels due to their environmental persistence and long half-lives (Bu et al., 2015; Donaldson et al., 2010; Lee et al., 2014; Sjödin et al., 2014; Whitehead et al., 2015). Epidemiological studies have reported associations between specific POPs and negative health effects such as risk factors for heart failure, type 2 diabetes and breast cancer (Arrebola et al., 2016; Cohn et al., 2015; He et al., 2017; Lee et al., 2011; Lind et al., 2013b). Research has focused on monitoring human exposure in order to gain a better understanding of how background levels of POPs can effect health, and if regulations have a desired effect on decreasing human levels. A number of biomonitoring studies continue to evaluate the trend in four historically major groups of Cl/Br POPs that are listed on the Stockholm Convention (UNEP, 2010), including polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), and polychlorinated dibenzo-*p*-dioxins and

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furans (PCDD/Fs). Overall, the levels of most chlorinated POPs have decreased world-wide (Croes et al., 2014; Hardell et al., 2010; Nøst et al., 2013; Zietz et al., 2008) as a result of restricted pesticide and PCB production by the U.S. and other Western countries between the early 1970s and early 1990s (Breivik et al., 2004). The temporal trend in human PBDE levels is more conflicting with studies showing either stagnant or increasing concentrations (Hurley et al., 2017; Sjödin et al., 2014; Turyk et al., 2010) while other studies show decreasing (Guo et al., 2016; Ma et al., 2013) concentrations after the U.S. phased out penta and octa BDE formulation production in 2004 and deca BDE production in 2013 (Hurley et al., 2017; Lorber and Cleverly, 2010).

An important aspect of temporal trend evaluation of POPs is understanding how physiological factors like gender, weight change, and changes in lipids levels are associated with the changes in POP concentrations. Although many studies have reported higher concentrations of Cl/Br POPs in men (Agudo et al., 2009), women have been shown to have a greater increase in concentration than men with age (Pavuk et al., 2014). These observations are both dependent on the compound and when the sample was collected. Generally, studies have shown that weight loss is associated with increasing levels of POPs (Bräuner et al., 2011; Lignell et al., 2016; Lind et al., 2013a). Recent research from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study has shown that some POPs are related to the changes in lipids, particularly, LDL-cholesterol (Penell et al., 2014), but less is known about the relationship between longitudinal changes in lipid levels and changes in POP concentrations. Another important factor to consider when reporting changes in temporal trends of POP concentrations in humans is whether or not to use a lipid normalized (ng/g lipid) or wet-weight (pg/mL) value. There have been conflicting views on which representation is more accurate, as some studies claim that lipid normalized values provide a more accurate representation of the overall body burden of POPs (Rylander et al., 2006), while others have said wet-weight values are more appropriate because POPs can alter lipid metabolism (Lind et al., 2004; Penell et al., 2014). Furthermore, if the results differ depending on the use of lipid normalized or wet-weight POP concentrations, it is important to also consider if the changes in POP levels and their relationships with physiological changes, such as body weight will also be affected.

To minimize the influence of inter-individual variation, a cohort longitudinal design, where the same people are repeatedly sampled over time, should ideally be used to study trends. However, few biomonitoring studies have used a longitudinal cohort design, to investigate the temporal trend of Cl/Br POP concentrations in humans (Nøst et al., 2013; Turyk et al., 2010). Likewise, studies evaluating the relationship between gender, changes in body weight, changes in lipid levels and the change in POP concentrations using a longitudinal cohort sampling design are also limited. Usually, biomonitoring studies use repeated cross-sectional sampling, where different participants are sampled each time (CDC, 2015; Glynn et al., 2007; Hardell et al., 2010; Zietz et al., 2008). Therefore, the results obtained from cross-sectional studies include an unwanted error due to between-person variability.

To avoid the problems inherent in repeated cross-sectional sampling, the primary aim of this study was to evaluate the 5-year longitudinal change in plasma concentrations of Cl/Br POPs in men and women at ages 70 and 75 participating in the PIVUS study (Lind et al., 2006). Since gender, body weight, and plasma/serum lipids all affect the concentrations of the POPs, we also investigated the impact of those factors on the changes in POP levels in this prospective study.

2. Materials and methods

2.1. Sample collection

Plasma samples from 992 70 year-old participants (50.2% women) from Uppsala, Sweden were collected between April 2001 and June 2004 for an epidemiological study known as The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS), where three non-invasive techniques were simultaneously evaluated for arterial compliance (Lind et al., 2006). The same remaining participants were resampled when they turned 75 years old (n = 814; sampled from 2006 to 2009). During each sample collection, the participants underwent a medical assessment where over 20 health parameters, including body weight (at a standard scale) and plasma lipids were measured. Overall, 788 samples were present in both investigations. All blood samples were collected in the morning (8–10 a.m.) after an overnight fast. The same blood collection procedure was used at both sampling occasions. After plasma was separated from the blood, the plasma samples were stored at − 70 °C until analysis. The study was approved by the Ethics Committee of the University of Uppsala and the participants gave a written informed consent.

2.2. Sample preparation and analysis

The sample preparation method used for the extraction of POPs in plasma from the first investigation (n = 992) was previously described in detail (Salihovic et al., 2012b). For the follow-up (n = 814), a modified method was used (Stubleski et al., 2018). Briefly, plasma samples were diluted with protein precipitating solutions and applied to a 96-well plate Oasis HLB (Waters Corporation, Milford, MA, USA). The plate was rinsed with 40% methanol in water and dried prior to eluting the POPs using a 1:1 dichloromethane: hexane solution. Lipid degradation and water removal from the sample extracts was carried out using sulfuric acid modified silica and sodium sulfate. Sample extracts were transferred to GC vials and evaporated to 20 μL tetradecane. Two microliters were injected onto a DB-5MS capillary column (Agilent Technologies, Santa Clara, California, USA) using splitless injection and analyzed using a gas chromatograph (Agilent Technologies) coupled to a high resolution magnetic sector mass spectrometer (GC-HRMS) (Micromass Autospec Ultima, Waters Corporation, Milford, MA, USA) operating at ≥ 10,000 resolving power. POP concentrations were quantified using isotope dilution. Quality control (QC) samples including method blanks, in-house reference plasma, the National Institute for Standards and Technology (NIST) Standard Reference Material (SRM) 1957, instrument blanks and quantification standards were routinely analyzed to assess the method and instrument performance. To ensure that the observed temporal trends were not an artifact of using a modified extraction procedure, the same QC reference plasma was used throughout the analysis of the 70 and 75 year old samples to check for drift of the method over time and to test the reproducibility between methods. The mean value for differences over time for the analytes was − 2.4%, which we regard as being acceptable and therefore no correction was performed.

2.3. Lipid-adjustment

In the present study, we report POP concentrations both as wet-weight (pg/mL) and lipid-normalized (ng/g lipid) to see if changes in POP concentrations (pg/mL versus ng/g lipid) and their relationship to changes in body weight were similar. For the lipid normalization, plasma cholesterol and triglycerides were determined by standard enzymatic methods and an established formula was used to calculate the total amount of plasma lipids (Rylander, 2006).

2.4. Statistical analysis

Levels below the limit of detection (LOD) were replaced by LOD/$2^{0.5}$ for samples from both surveys. Changes over time were evaluated as the percentage change using the formula: (75-year value minus 70-year value)/ 70-year value. POPs detected in the majority (at least 70%) of the PIVUS cohort were included in the longitudinal assessment, with exception of BDE 47 which was detected in 34% (224 PIVUS men and women) of the follow-up samples. BDE 47 was still included in the