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Influence of persistent organic pollutants on oxidative stress in population-based samples

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HIGHLIGHTS

- Environmental POPs, such as PCBs, are associated with markers of increased oxidative stress in the general population.
- A number of PCBs show strong positive associations with oxidized-LDL.
- LDL-activated endogenous antioxidant machinery forms an adaptive response to reduce damage by oxidative stress.

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ABSTRACT

Persistent organic pollutants (POPs) are a large group of chemicals widely used and produced in various industrial applications. Many cell culture/animal studies have shown that POPs can induce oxidative stress. Since such data is lacking in humans, we conducted a large population-based study to analyze associations between POPs and oxidative stress markers. We measured following POPs; 16 polychlorinated biphenyls (PCBs), 5 organochlorine (OC) pesticides, octachlorinated dibenzo-*p*-dioxin, and polybrominated diphenyl ether 47, and oxidative stress markers; homocysteine, reduced [GSH] and oxidized glutathione [GSSG], glutathione ratio [GSSG/GSH], total glutathione, oxidized low-density lipoprotein [ox-LDL], ox-LDL antibodies, conjugated dienes, baseline conjugated dienes of LDL, and total anti-oxidative capacity in plasma samples collected from 992 70-year old individuals (50% women) from the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohort. Linear regression analyses were performed to study the associations between oxidative stress markers and summary measures of POPs including the total toxic equivalence (TEQ), sums of PCBs and OC pesticides (main exposures) while adjusting for potential confounders. In multivariable-adjusted analyses, sum of PCBs showed strong associations with ox-LDL ($\beta = 0.94$; $P = 2.9 * 10^{-6}$). Further, sum of PCBs showed association with glutathione-related markers (GSSG: $\beta = -0.01$; $P = 6.0 * 10^{-7}$; GSSG/GSH: $\beta = -0.002$; $P = 9.7 * 10^{-10}$), although in reverse direction. Other summary measures did not show any significant association with these markers. In our study of elderly individuals from the general population, we show that plasma levels of POPs are associated with markers of increased oxidative stress thereby suggesting that even low dose background exposure to POPs may be involved in oxidative stress.

Abbreviations: POPs, persistent organic pollutants; PCBs, polychlorinated biphenyls; OC, organochlorine; OCDD, octachlorinated dibenzo-p-dioxin; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; TEQ, total toxic equivalency; TEF, toxic equivalency factors; ROS, reactive oxygen species; QA/QC, quality assurance/quality control; BDE, brominated diphenyl ether congener; LOD, limit of detection; CV, coefficient of variation; GSH, reduced glutathione; GSSG, oxidized glutathione; GSSG/GSH, glutathione ratio; TGSH, total glutathione; CD, conjugated dienes; LDL, low-density lipoprotein; BCD-LDL, baseline conjugated dienes of LDL; Ox-LDL, oxidized LDL; TAOC, total antioxidant capacity; HCB, hexachlorobenzene; p,p′-DDE, 2,2-bis (4-chlorophenyl)-1,1-dichloroethene; TNC, trans-nonachlordane; BMI, body mass index.

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1. Introduction

Persistent organic pollutants (POPs) are organic compounds generated either directly or as byproducts from different industrial processes. POPs are extremely persistent and can be detected in all compartments in our surrounding environment. A large group of compounds like polychlorinated biphenyls (PCBs), organochlorine (OC) pesticides, polychlorinated dibenzo-*p*-dioxins (dioxins), and polybrominated diphenyl ethers fall into this category. POPs tend to bioaccumulate in adipose tissues where they then may reach high concentrations and due to their toxic potential cause detrimental effects in animals and humans long after the initial exposure. In the general populations, consumption of POP contaminated food (including fish, meat or dairy products) have been shown to be the main sources of exposure to POPs (Letcher et al., 2010). A number of POPs have been detected in human adipose tissue, blood, and breast milk worldwide (Matuo et al., 1992; Ataniyazova et al., 2001; Salihovic et al., 2012a). PCBs are among the most studied group of contaminants, while the other POPs are less studied to date.

The combined effect of POPs is both dose- and concentration-dependent and studies suggest that they pose risk in an additive fashion (Lee et al., 2006). A total toxic equivalency (TEQ) value is generally utilized to measure the overall toxicological effect and risk of various POPs in different organisms (Van den Berg et al., 1998). TEQ value can be measured by utilizing toxic equivalency factors (TEF) that points toward the toxicity of POPs in relation to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TEF = 1), the most toxic congener among the dioxins (Van den Berg et al., 1998, 2006).

Elevated levels of POPs have been shown to be associated with a number of diseases like stroke, atherosclerosis, heart failure and cancers (Hardell et al., 2006; Ha et al., 2007; Lee et al., 2012; Lind and Lind, 2012; Lind et al., 2012). There are several mechanisms including oxidative stress, lipid changes in plasma, and immunomodulation that have been suggested to underlie the pathology of these conditions. Oxidative stress is one of the critical events in causing these diseases and can be defined as an imbalance between production of reactive oxygen species (ROS) and antioxidant compounds. ROS are among the unstable and very reactive compounds and their modest and controlled production is needed for numerous vital signaling pathways. In case of oxidative stress, there is pathological increase in the generation of ROS that overcomes the antioxidant capability and causes damage to various biomolecules. A number of mechanisms involving protein damage, lipid peroxidation, oxidation of important enzymes are responsible for damage caused by oxidative stress (Chapple, 1997).

To date, only a few studies, mainly in cell cultures or animals have shown that different POPs can induce production of ROS or superoxide (Mariussen et al., 2002; Song and Freedman, 2005; Mariussen and Fonnum, 2006; Schlezinger et al., 2006; Lim et al., 2007). Several experimental studies have reported that oxidative stress plays an important role in the toxicity caused by exposure to different POPs (Hassoun et al., 2000, 2002; Howard et al., 2003; Ramadass et al., 2003). To the best of our knowledge, no prior study has analyzed the impact of a large number of POPs on a variety of oxidative stress markers in a large population-based study of humans. Therefore, we investigated associations between different POPs and oxidative stress markers in 992 70-year old individuals (50% women) from the community-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohort. The primary aim of this study was to investigate associations of summary measures like TEQ values, sum of PCBs and sum of OC pesticides concentrations with a variety of oxidative stress markers reflecting their different aspects. The secondary aim was to address the associations of individual POPs with these oxidative stress markers.

2. Materials and methods

2.1. Study participants

Individuals who were 70 years old and living in the community of Uppsala, Sweden were randomly chosen from the population register of Sweden and invited to participate in the study. Of 2025 invited, 1016 individuals agreed to participate in the study and provided their written informed consent. The study was approved by Ethics Committee from Uppsala University, Uppsala and performed according to the principles of Helsinki declaration. The study participants observed overnight fast and refrained from using any medication or smoking before being evaluated next morning. Information regarding their smoking, medications and medical history was filled up in a detailed questionnaire. Fasting glucose and a number of lipid variables were measured utilizing the standard laboratory procedures. More details about study sample are available at http://www.medsci.uu.se/PIVUS and in previous publications (Lind et al., 2005). After exclusion of 24 individuals due to lack of measurements of POPs, 992 individuals were eligible for the present study. Out of the 992 individuals, a healthier sub-sample of individuals who were non-smokers, non-diabetic, and had no previous cardiovascular disease diagnosis ($N = 687$) was also selected from this cohort and studied for the association of summary measures of POPs with oxidative stress markers.

2.2. Measurement of POPs

A slightly modified method described by Sandau et al. was utilized to measure different POPs from serum samples (Sandau et al., 2003). A detailed description of the method can be found elsewhere (Salihovic et al., 2012b). Briefly, samples were prepared based on sample phase extraction using a custom made polystyrene–divinylbenzene sorbent for the extraction. The levels of POPs were determined using high resolution gas chromatography coupled to high resolution mass spectrometry. To ensure the quality, quality control plasma samples and procedural blank samples were incorporated in each batch of 10 samples. The blank samples incorporated were free of any target compounds at levels >5% of the levels in the samples except for *cis*- and *trans*-chlordane. Both of the chlordanes were present below the detection limit in 95% of the samples analyzed. The recoveries of the internal standards were found to be satisfactory and ranging from 60% to 110%. The relative standard deviation of the 100 quality assurance/quality control (QA/QC) samples was <25% for all compounds measured except for those present at low levels and just above the limit of detection in the QA/QC sample (Salihovic et al., 2012b). The levels of POPs were normalized for the lipid content in each plasma sample (Rylander et al., 2006). We were able to score a total of 21 POPs involving 16 PCB congeners, 3 OC pesticides, 1 brominated diphenyl ether congener (BDE) and 1 octachlorodibenzo-*p*-dioxin (OCDD) in >70% of the individuals that were taken up further for the analysis (Table 2). Two of the OC pesticides (*cis*-chlordane and *trans*-chlordane) could not be detected in >90% participants and hence were not studied further. Samples where POPs could not be detected (levels < LOD) were imputed with the values $LOD/2^{-0.5}$.

2.3. Summary measures of POPs

The TEQ value was calculated according to the method described by Van den Berg et al., where the concentration of seven PCBs (PCB-126, 169, 105, 118, 156, 157, 189) and OCDD were