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Original Publication:

Ylva Sjöberg Lind, Monica P. Lind, Samira Salihovic, Bert van Bavel and Lars Lind, Circulating levels of persistent organic pollutants (POPs) are associated with left ventricular systolic and diastolic dysfunction in the elderly, 2013, Environmental Research, (123), , 39-45.

http://dx.doi.org/10.1016/j.envres.2013.02.007
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Postprint available at: Linköping University Electronic Press
http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-93966
Circulating levels of persistent organic pollutants (POPs) are associated with left ventricular systolic and diastolic dysfunction in the elderly

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ABSTRACT

Background and objective: Major risk factors for congestive heart failure (CHF) are myocardial infarction, hypertension, diabetes, atrial fibrillation, smoking, left ventricular hypertrophy (LVH) and obesity. However, since these risk factors only explain part of the risk of CHF, we investigated whether persistent organic pollutants (POPs) might also play a role.

Methods: In the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, left ventricular ejection fraction, (EF), E/A-ratio and isovolumic relaxation time (IVRT), were determined by echocardiography and serum samples of 21 POPs were analyzed in serum measured by high-resolution chromatography coupled to high-resolution mass spectrometry (HRGC/HRMS) in 998 subjects all aged 70 years.

Results: In this cross-sectional analysis, high levels of several of the polychlorinated biphenyls (PCB congeners 99, 118, 105, 138, 153, and 180) and octachlorodibenzo-p-dioxin (OCDD) were significantly related to a decreased EF. Some POPs were also related to a decreased E/A-ratio (PCBs 206 and 209). All the results were adjusted for gender, hypertension, diabetes, smoking, LVH and BMI, and subjects with myocardial infarction or atrial fibrillation were excluded from the analysis.

Conclusions: Circulating levels of POPs were related to impairments in both left ventricular systolic and diastolic function independently of major congestive heart failure risk factors, suggesting a possible role of POPs in heart failure.

1. Introduction

Congestive heart failure (CHF) is a major cardiovascular disease associated with poor long-term prognosis, decreased life quality and high risk of hospitalization. Hypertension and ischemic heart disease are the most powerful known risk factors for CHF in elderly patients (Levy et al., 1996). Atrial fibrillation is also an independent risk factor for congestive heart failure (Maisel and Stevenson, 2003), as well as diabetes, smoking, left ventricular hypertrophy (LVH) and obesity (Eriksson et al., 1989; Ho et al., 1993). However, as these established risk factors can only explain part of the risk of CHF, other factors might be of importance.

Measurable levels of persistent organic pollutants (POP) have been reported in humans for several decades. In recent years, data on associations between elevated circulating levels of POPs and a number of CHF risk factors, such as hypertension, obesity, and diabetes, as well as metabolic syndrome have been established (Everett et al., 2011; Lee et al., 2007, 2012, 2011; Ronn et al., 2011). Furthermore, prevalent myocardial infarction has also been found to associate with elevated levels of certain POPs including dioxins and PCBs (Dalton et al., 2001; Flesch-Janys et al., 1995; Ha et al., 2007; Sergeev and Carpenter, 2005).

Animal studies indicate that environmental pollutants, such as dioxins, hexachlorobenzene (HCB) and polychlorinated biphenyls (PCB 126) increase heart weight and induce hypertension (Arnold et al., 1986; Kopf et al., 2008; Lind et al., 2004). We hypothesize that certain POPs influence the left ventricular (LV) systolic and diastolic function. To test this hypothesis, we used the population-based prospective investigation of the vasculature in Uppsala Seniors (PIVUS) study (Lind et al., 2005), in which echocardiographic
data on LV systolic and diastolic function and circulating POP levels in almost 1,000 subjects have been measured.

2. Material and methods

2.1. Subjects

Eligible for the study were all subjects aged 70 living in the community of Uppsala, Sweden. The subjects were chosen from the register of community residents in a randomized order, and were invited in a randomized order April 2001 to June 2004 (Lind et al., 2005). The subjects received an invitation by letter within two months of their 70th birthday. The PIVUS study aimed to investigate an elderly population standardized to the age of 70, since age is such an important characteristic, especially in the elderly. Of the 2025 subjects invited, 1016 subjects participated, yielding a participation rate of 50.1%. The study was approved by the Ethics Committee of the Uppsala University, and the participants gave their informed consent.

Subjects with myocardial infarction that had been treated in hospital were excluded. So, too, were those with atrial fibrillation. Approximately 10% of the cohort reported a history of coronary heart disease; 4% reported stroke, 38% congestive heart failure, and 9% diabetes mellitus. Almost half the cohort reported any cardiovascular medication (45%), with antihypertensive medication being the most prevalent (32%). Fifteen percent reported use of statins, while insulin and oral antihyperglycemic drugs were reported in 2 and 6%, respectively. As the participation rate in this cohort was only 50%, we carried out an evaluation of cardiovascular disorders and medications in 100 consecutive nonparticipants. The prevalences of cardiovascular drug intake, history of myocardial infarction, coronary revascularization, antihypertensive medication, statin use and insulin treatment were similar to those in the investigated sample, while the prevalences of diabetes (17%), congestive heart failure (6.9%) and stroke (6.7%) tended to be higher among the non-participants.

2.2. Basic investigation

Before the examination the participants were asked to fill in a questionnaire about their medical history, smoking habits, and regular medication. All subjects were investigated in the morning after fasting since midnight, thus with a fasting period of at least eight hours. No medication or smoking was allowed after midnight. Blood pressure was measured by a calibrated mercury sphygmomanometer to nearest mm Hg after at least 30 min of rest, and the average of three recordings was used. Lipid variables and fasting blood glucose were measured by standard laboratory techniques. Diabetes was defined as fasting plasma glucose ≥7.0 mmol/l or antidiabetic treatment. Smoking was defined as current smoking; all basic characteristics are given in Table 1.

2.3. Echocardiography

A comprehensive two-dimensional and Doppler echocardiography was performed with an Acuson XP1244 cardiac ultrasound unit (Acuson, California, USA). A 2.5 MHz transducer was used for the majority of the examinations. Presence ofstenosis or regurgitations in the mitral and aortic valves was recorded by use of color and continuous Doppler. LV ejection fraction (EF) was visually assessed from examinations from the parasternal view using the Penn convention and was indexed to body surface area. LV mass was determined from M-mode recordings from the parasternal view using the Penn convention and was indexed to body surface area. LV ejection fraction (EF) was visually assessed from examinations from the parasternal view using the Penn convention and was indexed to body surface area. LV mass was determined from M-mode recordings from the parasternal view using the Penn convention and was indexed to body surface area.

2.4. POPs analyses

POP were measured in stored serum samples collected at baseline. Analyses of POPs were performed using a Micromass AutoSpec Ultima (Waters, Milford, MA, USA) high-resolution chromatography coupled to high-resolution mass spectrometry (HRGC/HRMS). All details on POP analyses have been reported elsewhere (Salihovic et al., 2012). A total of 23 POPs were measured, 16 polychlorinated biphenyls (PCBs), five organochlorine (OC) pesticides, one octachlorodibenzo-p-dioxin (OCDD), and one brominated biphenyl ether (BDE). Among the 23 POPs measured, two OC pesticides (trans-chlordane and cis-chlordane) with detection rates <10% were not included in the final results/statistical analyses. An established summation formula based on serum cholesterol and serum triglyceride concentrations was used to calculate the total amount of lipids in each plasma sample (Bylander et al., 2006). Thereafter the weight concentrations of the POPs were divided by this estimation of lipids to obtain lipid-normalized values. See Table 2 for details.

2.5. Statistics

All POPs levels and E/A ratios were log-transformed, to achieve normal distributions. Since POP levels tend to differ between men and women, the first set of linear regression models between LV variables and POPs were adjusted for gender only. Since no interactions between gender and POPs were found, no

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (25th and 75th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCB 74</td>
<td>13.9 (10; 18.8)</td>
</tr>
<tr>
<td>PCB 99</td>
<td>13.8 (9.5; 19.4)</td>
</tr>
<tr>
<td>PCB 105</td>
<td>4.9 (3.3; 7.0)</td>
</tr>
<tr>
<td>PCB 118</td>
<td>30.2 (21.6; 41.7)</td>
</tr>
<tr>
<td>PCB 126</td>
<td>6.2 (3.3; 10.8)</td>
</tr>
<tr>
<td>PCB 138</td>
<td>124.9 (95.3; 168.2)</td>
</tr>
<tr>
<td>PCB 153</td>
<td>217.2 (166.8; 279.8)</td>
</tr>
<tr>
<td>PCB 156</td>
<td>23.6 (18.2; 29.9)</td>
</tr>
<tr>
<td>PCB 157</td>
<td>4.3 (3.2; 5.5)</td>
</tr>
<tr>
<td>PCB 169</td>
<td>20 (20.1; 34.2)</td>
</tr>
<tr>
<td>PCB 170</td>
<td>74.8 (59.6; 96.3)</td>
</tr>
<tr>
<td>PCB 180</td>
<td>1763.3 (1393.3; 229)</td>
</tr>
<tr>
<td>PCB 189</td>
<td>2.9 (2.2; 3.9)</td>
</tr>
<tr>
<td>PCB 194</td>
<td>18.4 (13.6; 24.3)</td>
</tr>
<tr>
<td>PCB 206</td>
<td>4.2 (3.1; 5.4)</td>
</tr>
<tr>
<td>PCB 209</td>
<td>4.1 (3; 5.3)</td>
</tr>
<tr>
<td>OCDD</td>
<td>0.4 (0.2; 0.6)</td>
</tr>
<tr>
<td>HCB</td>
<td>38 (29; 50.2)</td>
</tr>
<tr>
<td>TN</td>
<td>20.8 (14.1; 31.6)</td>
</tr>
<tr>
<td>p,p’–DDE</td>
<td>290.6 (158.1; 538.4)</td>
</tr>
<tr>
<td>BDE 47</td>
<td>1.9 (1.5; 2.9)</td>
</tr>
</tbody>
</table>

Table 2

Distribution of serum concentrations (ng/g lipid) by median and 25th and 75th percentile of individual persistent organic pollutants. (n=988).
gender-specific analysis was performed. Interaction between the different POPs and gender was evaluated by including an interaction term (POP × gender) in the statistical analysis (data not shown).

As a second step to deal with confounding, adjustments were also performed for the classical risk factors for CHF, gender, blood pressure, antihypertensive treatment, diabetes, smoking, LVH, and BMI. The occurrence of potential non-linear relationships was evaluated by multiple fractional polynomial regression analysis. The statistical program package STATA 11 (College Station, TX, USA) was used.

3. Results

3.1. POPs vs. LV systolic function

When relating the POP levels to LV EF, seven out of the PCBs (congeners 74, 99, 105, 118, 138, 153, 180), four of the pesticides (HCB, TNC, and p,p′-DDE), and OCDD were significantly associated with a decreased ejection fraction after adjustment for gender only ($p < 0.05–0.001$, see Table 3 for details). Six of the PCBs (congeners 99, 105, 118, 138, 153, 180) and OCDD were still significantly correlated after adjustment for multiple established risk factors (gender, hypertension, diabetes, smoking, LVH and obesity) ($p < 0.05–0.001$, see Table 3 for details).

A very similar picture emerges when the POP levels in those with a reduced LV EF (< 50%, 15.2% of the population) were compared to those with a normal LV EF. Following adjustment for the multiple risk factors, the levels of PCB74 ($p = 0.01$), PCB105 ($p = 0.005$), PCB118 ($p = 0.0001$), PCB126 ($p = 0.01$), PCB138 ($p = 0.01$), PCB153 ($p = 0.01$), PCB180 ($p = 0.01$), and OCDD ($p = 0.005$) were all higher in those with a reduced LV EF.

3.2. POPs vs. LV diastolic function

None of the POPs was significantly related to the E/A ratio when adjusted for gender only, but two of the higher chlorinated PCBs (congeners 206 and 209) showed associations following the multiple adjustment ($p < 0.01$, see Table 4 for details).

A very similar picture emerges when we divide the sample according to whether the E/A-ratio is above or below 1.0, as a sign of LV diastolic dysfunction. High levels of PCB congeners 206 and 209 were then related to LV diastolic dysfunction (OR 1.52 using ln-transformed values for the PCBs, 95%CI 1.09–2.13, $p$-value 0.012 for PCB206, and OR 1.42, 95%CI 1.06–1.93, $p$-value 0.021 for PCB209) following the multiple adjustment.

Only borderline significant associations were found between the POPs and IVRT (Table 5).

No significant interactions were seen between POP levels and gender regarding the relationships described above. Therefore, gender was treated as a confounder, and the analysis was not stratified according to gender. Using multiple fractional polynomial regression analysis to screen for possible non-linear relationships, only the relationship between PCB105 and the E/A-ratio was non-linear with a significant squared term ($p = 0.004$) giving a U-shaped form of the relationship. However, this relationship was not significant following adjustment for multiple risk factors.

4. Discussion

Several of the POPs were related significantly to a decreased LV EF even following adjustment for established risk factors for CHF following exclusion of subjects with myocardial infarction, valvular disease or atrial fibrillation, suggesting that POPs might play a role in LV systolic dysfunction that is not mediated by the traditional risk factors. Some of the POPs were also related to LV diastolic function.

To the best of our knowledge, no other study has investigated whether POPs are related to LV function or to clinically manifest CHF. Several studies have reported associations between POP levels and risk factors for CHF, such as hypertension, diabetes and obesity (Everett et al., 2011; Lee et al., 2007, 2012, 2011; Ronn et al., 2011), but all of these factors were adjusted for in the analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCB 74</td>
<td>$-1.216$ (−2.198; −0.235)</td>
<td>0.0154</td>
</tr>
<tr>
<td>PCB 99</td>
<td>$-1.497$ (−2.343; −0.651)</td>
<td>0.0005</td>
</tr>
<tr>
<td>PCB 105</td>
<td>$-1.465$ (−2.303; −0.627)</td>
<td>0.0006</td>
</tr>
<tr>
<td>PCB 118</td>
<td>$-1.888$ (−2.813; −0.962)</td>
<td>0.0001</td>
</tr>
<tr>
<td>PCB 126</td>
<td>$-0.157$ (−0.727; 0.413)</td>
<td>0.5894</td>
</tr>
<tr>
<td>PCB 138</td>
<td>$-1.784$ (−2.862; −0.705)</td>
<td>0.0012</td>
</tr>
<tr>
<td>PCB 153</td>
<td>$-1.905$ (−3.079; −0.732)</td>
<td>0.0015</td>
</tr>
<tr>
<td>PCB 169</td>
<td>$-0.805$ (−1.909; 0.3)</td>
<td>0.1539</td>
</tr>
<tr>
<td>PCB 156</td>
<td>$-0.968$ (−2.195; 0.258)</td>
<td>0.1220</td>
</tr>
<tr>
<td>PCB 157</td>
<td>$-0.631$ (−1.755; 0.495)</td>
<td>0.2725</td>
</tr>
<tr>
<td>PCB 170</td>
<td>$-1.173$ (−2.493; 0.148)</td>
<td>0.0821</td>
</tr>
<tr>
<td>PCB 180</td>
<td>$-1.376$ (−2.678; −0.073)</td>
<td>0.0387</td>
</tr>
<tr>
<td>PCB 189</td>
<td>$-0.591$ (−1.397; 0.216)</td>
<td>0.1513</td>
</tr>
<tr>
<td>PCB 194</td>
<td>$-0.343$ (−1.007; 0.322)</td>
<td>0.3124</td>
</tr>
<tr>
<td>PCB 206</td>
<td>$-0.637$ (−1.766; 0.493)</td>
<td>0.2695</td>
</tr>
<tr>
<td>PCB 209</td>
<td>$-0.13$ (−0.882; 1.142)</td>
<td>0.8014</td>
</tr>
<tr>
<td>OCDD</td>
<td>$-1.155$ (−1.99; −0.319)</td>
<td>0.0069</td>
</tr>
<tr>
<td>HCB</td>
<td>$-1.207$ (−2.393; −0.02)</td>
<td>0.0466</td>
</tr>
<tr>
<td>TNC</td>
<td>$-1.032$ (−1.999; −0.154)</td>
<td>0.0214</td>
</tr>
<tr>
<td>p,p′-DDE</td>
<td>$-0.577$ (−1.11; −0.042)</td>
<td>0.0347</td>
</tr>
<tr>
<td>BDE 47</td>
<td>$-0.112$ (−0.872; 0.648)</td>
<td>0.7727</td>
</tr>
</tbody>
</table>

PCB = polychlorinated biphenyls, OCDD = octachlorodibenzo-p-dioxin, HCB = hexachlorobenzene, TNC = trans-nonachlor, p,p′-DDE = 2,2-bis(4-chlorophenyl)-1,1-dichloroethene, BDE = bromodiphenyl ether.
Subjects with myocardial infarction or atrial fibrillation were excluded from the analysis.

PCBs and OCDD showed different PCBs might have different effects on the heart.

In the present study it was mainly the PCBs with a low degree of chlorination (PCB105 and PCB118) that together with OCDD showed the closest relationships vs. a low EF. On the other hand, it was the PCBs with the highest degree of chlorination that were related to a poor E/A-ratio. Thus, from this perspective it could be suspected that different PCBs might have different effects on the heart.

PCBs are usually classified in dioxin-like and non-dioxin-like in terms of their mode of action. However, the PCBs with the highest affinity to the acyl hydrocarbon receptor (AhR) measured in the present study (PCB126 and PCB169) did not relate strongly to either the EF or the E/A-ratio. PCB105 and PCB118 are dioxin-like, but their effects on the AhR are weak (TEQ 0.001). PCB206 and 209 are not dioxin-like, so in this case other mechanisms of action must be involved both in their association to LV diastolic function.

4.1. Possible pathophysiological mechanisms
function. There are some data supporting that also non-dioxin-like PCBs could induce estrogen receptor responses by binding to the estrogen receptor alpha (Li et al., 2012). It has also been suggested that non-dioxin-like PCBs would influence dopamine receptors (Lesmana et al., 2012), as well as influence the action of glutathione S-transferases (GSTs) being responsible for detoxification by catalyzing the conjugation reaction of glutathione (GSH) to xenobiotics (Tian et al., 2012).

Furthermore, non-dioxin-like PCBs enhance the activity of ryanodine receptor (RyR) calcium ion (Ca(2+)) channels, which play a central role in regulating the dynamics of intracellular Ca(2+) signaling (Wayman et al., 2012). Thus, several mechanisms have been described whereby non-dioxin-like PCBs could affect different organs, such as the myocardium. How this relates to LV diastolic dysfunction is not well understood, however. A main driver of LV diastolic dysfunction is increased wall thickness mainly due to increased fibrosis.

Most experimental studies on mechanisms for how POPs affect different organ systems have focused on dioxin activity using the potent dioxin TCDD as a model compound for dioxins. Persistent cardiac effects of dioxins have been noted in many species, such as zebra fishes, mice, and chicken (Puga, 2011). For example, developmental exposure to TCDD resulted in dose-dependent increase in pericardial effusion and circulatory failure in small aquarium fish (Dong et al., 2010). Exposing adult, as well as fetal, mice to TCDD led to cardiac hypertrophy and increased blood pressure (Aragon et al., 2008; Kopf et al., 2008). Studies have also shown that TCDD affects cardiac gene expression during development in the murine heart in a manner that may increase the susceptibility to cardiovascular dysfunction (Aragon et al., 2008; Thackaberry et al., 2005).

The heart muscle is a highly oxidative tissue that produces >90% of its energy from mitochondrial respiration (Neubauer, 2007). One recent experimental study performed in cardiomyocytes derived from embryonic mice stem cells showed that TCDD down-regulated genes, several of which were involved in the oxidative phosphorylation pathway. Furthermore, the arrangement of mitochondria was altered, and ATP production was reduced (Neri et al., 2011). Another experimental study (Ruzzin et al., 2010) observed alterations in mitochondrial function and oxidative capacity in the liver of rats exposed to a mixture of POPs including dioxins and PCBs.

It has also been shown experimentally that POP exposure induces oxidative stress (Kopf et al., 2008; Park et al., 1996; Shertzer et al., 1998) and inflammation (Majkova et al., 2009; Vogel et al., 2007), two putative players in the development of myocyte dysfunction. This could also be a link between POP exposure and LV dysfunction, since ROS and proinflammatory cytokines could affect myocardial function (Suggilam et al., 2007; Mellin et al., 2005) and have been found to be elevated in heart failure patients or to predict future heart failure (Barac et al., 2012; Ingelsson et al., 2005). Some of these potential pathophysiological mechanisms are summarized in Fig. 1.

However, when toxic equivalents (TEQ) were calculated in the present sample as a marker of activation of the AHR due to the POP exposure (Van den Berg et al., 1998; Van den Berg et al., 2006) using PCB 105, 118, 126, 156, 157, 169, 189 and OCDD, no associations with EF, E/A-ratio and IVRT were found (data not shown).

4.2. POP levels

The median concentrations and the pattern of PCBs detected in the current study are comparable to those observed in previous studies from Sweden and Europe (Covaci et al., 2002; Koppen et al., 2002; Weiss et al., 2006). When we extracted data from 1128 participants aged 70 years and older from the fourth report of the United States National Health and Nutrition Exposure Survey (NHANES 2003-2004) (http://www.cdc.gov/nchs/nhanes.htm), we found PCB levels to be higher in the PIVUS sample, but the organochlorine pesticide levels (HCB, TNC and DDE) to be lower compared to the US sample. Thus, regional differences in exposures to POPs do exist (Lampa et al., 2012).

4.3. Clinical implications

The present study suggests an association between POP exposure and LV function in a population with a low prevalence of overt heart failure. The clinical implication of this study is yet unknown. The first step forward to resolve this matter would be to study POP levels in heart failure in case-control and prospective studies. The prevalence of overt heart failure in the present study is unfortunately too low for a meaningful evaluation.

4.4. Multiple comparisons

Correction for multiple comparisons was not performed for several reasons. First, this is an exploratory study. It is the first study of its kind about circulating levels of persistent organic pollutants versus LV systolic and diastolic dysfunction in a large population. Secondly, we have recently published a cluster analysis in combination with a principal component analysis of the PCBs (and also other environmental contaminants) (Lampa et al., 2012). One of the major findings was that less chlorinated PCBs are closely related, while a separate cluster was seen for the highly chlorinated PCBs. Thus, based on these findings a strict Bonferroni adjustment would not be appropriate. Schematically it appears that the highly chlorinated PCBs (206 and 209) were related to the LV diastolic function, while several of the lower chlorinated PCBs were associated with LV systolic function. In such a case, calculation of the sum of PCBs is not an informative way forward.

4.5. Limitations

As the present sample was limited to Caucasians aged 70, caution should be observed in drawing conclusions regarding other ethnic and age groups. Furthermore, the present study had a moderate participation rate. In the present study outmoded ultrasonographic equipment was used that did not allow for modern measurements of LV EF. Therefore, rather than using the Teichholz formula for LV EF determinations, which we have found inaccurate in the elderly that have very divergent shapes of the LV (Andren et al., 1998; Ingelsson et al., 1998) or the more modern biplanar or 3D techniques, we estimated LV EF by visual inspection. This was performed by the same observer throughout the study to whom no other clinical or biochemical data was disclosed. Since visual

![Fig. 1. Potential mechanisms whereby persistent organic pollutants might affect left ventricular function.](image-url)
determinations of LV EF are inferior to modern ways to measure LV EF, false negative results might be presented. However, it is very unlikely that observed relationships between some of the PCBs and LV EF (p < 0.001 for PCB118) are due to the fact that a less modern way to determine LV EF was used. In fact, if superior techniques had been used, it is likely that the observed relationships would have been even stronger.

Using more modern techniques, such as tissue Doppler, it is possible to categorize subjects into those with diastolic dysfunction or not (Wu et al., 2012). Since we did not have such measurements, we treated the E/A-ratio as a continuous variable in the primary analysis following exclusion of subjects with a presumed restrictive transmural filling pattern. However, we cannot be sure that some subjects with pseudo-normalization of the E/A-ratio might not have been misclassified this way, although the numbers of such individuals are likely to be low in this cohort when subjects with myocardial infarction have been removed. If misclassification has occurred, this will only tend to lead to false negative findings and not induce the relationships between the highly chlorinated PCBs and the E/A-ratio found in the present sample.

In conclusion, circulating levels of POPs were related to impairments in both systolic and diastolic function independently of major congestive heart failure risk factors, suggesting that it is worthwhile to investigate the role of POPs in heart failure.

Ethics

The study was approved by the Ethics Committee of the Uppsala University, and the participants gave their informed consent.

Acknowledgments

The work was supported by funds from the Swedish Council for the Environment, Agricultural Sciences, and Spatial Planning (FORMAS) and the Swedish Research Council (VR).

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