Review

Circulating levels of persistent organic pollutants are related to retrospective assessment of life-time weight change

P.M. Lind,⇑ Duk-Hee Lee, David R. Jacobs, Samira Salihovic, Bert van Bavel, Mary S. Wolff, Lars Lind

Occupational and Environmental Medicine, Uppsala University, Uppsala, Sweden
Department of Preventative Medicine, School of Medicine, Kyungpook National University, Daegu, South Korea
Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA
Department of Nutrition, School of Medicine, University of Oslo, Oslo, Norway, USA
MTM Research Center, School of Science and Technology, Örebro University, Örebro, Sweden
Department of Preventive Medicine, Mount Sinai School of Medicine, New York, NY, USA
Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Highlights

► We examined associations between POP levels in human plasma and body weight.
► Body weight at age 70 was measured and participants reported their estimated weight at age 20.
► OC pesticides and less-chlorinated PCBs were associated with an increased estimated weight change over 50 years.
► The opposite was seen for highly-chlorinated PCBs.
► The results implicate a complex role of POPs in obesity.

Abstract

Background: Persistent organic pollutants (POPs) have been suggested to be linked to obesity. We have previously shown that less-chlorinated PCBs were positively related to fat mass, while highly-chlorinated PCBs were inversely related to obesity.

Objective: The aim of the present evaluation is to investigate the relationship between retrospective assessed life-time change in body weight (20–70 years) with circulating POP levels measured at age 70 years.

Methods: 1016 subjects aged 70 years were investigated in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUSs) study. 16 PCBs and 3 OC pesticides were analyzed using HRGC/HRMS. Current body weight was measured and participants self-reported their weight at age 20.

Results: The average estimated weight change over 50 years was 14.4 kg. Both the sum of OC pesticide concentrations (4.3 kg more weight gain in quintile 5 vs. quintile 1, p < 0.0001) and the sum of the less-chlorinated PCBs were positively related to the estimated weight change (3.7 kg more weight gain in quintile 2 vs. quintile 1, non-linear relationship p = 0.0015). In contrast, the sum of concentrations of highly-chlorinated PCBs were inversely related to estimated weight change (8.4 kg less weight gain in quintile 5 vs. quintile 1, p < 0.0001).

Conclusion: High levels of OC pesticides and the less-chlorinated PCBs at age 70 were associated with a pronounced estimated weight change over the previous 50 years. However, the opposite was seen for highly-chlorinated PCBs. Differences in mode of action, toxicokinetics, non-linear relationships and reverse causation might explain these discrepancies.

© 2012 Published by Elsevier Ltd.

Keywords: Obesity Persistent organic pollutants Fat mass Elderly Life time weight change

ARTICLE INFO

Article history:
Received 2 March 2012
Received in revised form 18 July 2012
Accepted 23 July 2012
Available online xxxx

Keywords:
Obesity Persistent organic pollutants Fat mass Elderly Life time weight change

ABBREVIATIONS:
BDE, brominated diphenyl ether; BMI, body mass index; DDE, dichlorodiphenyl dichloroethylene; DXA, dual-energy X-ray absorptiometry; HCB, hexachlorobenzene; HRGC/HRMS, high resolution chromatography coupled with high resolution mass spectrometry; OC, organochlorine; OCDD, octachlorodibenzo-p-dioxin; PIVUS, prospective Investigation of the Vasculature in Uppsala Seniors; PCBs, polychlorinated biphenyls; POPs, persistent organic pollutants; TNC, transnonachlordane.

⇑ Corresponding author. Address: Occupational and Environmental Medicine, Department of Medical Sciences, Uppsala University, 751 85 Uppsala, Sweden. Tel.: +46 18 6119745; fax: +46 18 519978.
E-mail address: monica.lind@medsci.uu.se (P.M. Lind).

0045-6535/$ - see front matter © 2012 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.chemosphere.2012.07.051

Please cite this article in press as: Lind, P.M., et al. Circulating levels of persistent organic pollutants are related to retrospective assessment of life-time weight change. Chemosphere (2012), http://dx.doi.org/10.1016/j.chemosphere.2012.07.051
1. Introduction

The prevalence of obesity (BMI $\geq 30$ kg m$^{-2}$) has risen dramatically in the Western world over the past two decades. In 2007–2008, 32% of adult men and 35.5% of adult women in the US were obese (Flegal et al., 2010). Obesity causes adverse effects on quality of life while also predisposing individuals to a number of diseases including type 2 diabetes and cardiovascular disease. It has recently been shown that the risk of diabetes over a 20-year period was 15-fold increased in obese vs. lean middle-aged subjects (Arnlöv et al., 2011). In addition it has also shown that obesity increased the risk of cardiovascular disease even in the absence of diabetes and other metabolic derangements (Arnlöv et al., 2011).

Obesity is caused by complex interactions among genetic, behavioral and environmental factors. Many researchers see obesity mainly as an unfavorable balance between a high energy intake and reduced energy expenditure due to inadequate exercise. However, recent research has suggested that environmental contaminants could play an important role in modulating the balance between energy intake and expenditure (Janesick and Blumberg, 2011). It was shown in animal studies that mice exposed prenatally to tributyltin (TBT) showed increased body-weight later in life; therefore, the term “obesogens” was coined (Grundy and Blumberg, 2006). This observation supports the emerging hypothesis of fetal programming as a source of certain disorders, such as obesity and diabetes, later in life (Barker et al., 2002). In addition to fetal programming, exposure to certain chemicals in adulthood may also be important. Adult rats given salmon oil contaminated with highly-chlorinated PCBs (congeners $\geq 156$) were inversely related to obesity when evaluated in a cross-sectional fashion (Rönn et al., 2011). Furthermore, the same pattern was found in the same cohort evaluated regarding the predictive power of POPs in relation to the development of abdominal obesity over a 5-year period in the same cohort (Lee et al., 2012). We have speculated that diverging effects of different PCBs could be either due to unique actions of different PCBs, or that the storage of PCBs in fat might differ amongst the PCBs. To investigate this further, the aim of the present evaluation is to investigate the relationship between retrospective assessments in life-time change in body weight (20–70 years) with circulating POP levels measured at age 70 years.

2. Materials and methods

2.1. Subjects

Eligible subjects were all aged 70 who lived in the community of Uppsala, Sweden. The subjects were randomly chosen from the community register. A total of 1016 subjects participated (investigated in between 2001 and 2004), giving a participation rate of 50.1%. The study was approved by the Ethics Committee of the University of Uppsala.

All subjects were investigated in the morning after an overnight fast. No medication or smoking was allowed after midnight. The participants were asked to answer a questionnaire about their medical history, smoking habits and regular medication. Furthermore, they were asked to report their body weight and height at age 20 years. The participants received the questionnaire in advance of the actual investigation, so they had time to go back to prior documents if they wanted.

Lipids were measured by standard laboratory techniques. Body weight was measured by a weight scale.

Basic characteristics are given in Table 1.

Approximately 10% of the cohort reported a history of coronary heart disease, 4% reported stroke, and 9% reported diabetes mellitus. Almost half the cohort reported some sort of cardiovascular medication (45%), with antihypertensive medication being the most prevalent (32%). Fifteen percent reported use of statins, while insulin and oral antiglycemic drugs were reported in 2% and 6%, respectively – see reference (Lind et al., 2005) for details.
2.2. POPs analyses

POPs 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 gas chromatography coupled to high resolution mass spectrometry (HRGC/HRMS) – based on the method by Sandau and co-workers (Sandau et al., 2003) with some modifications. All details on POPs analyses were presented elsewhere (Rönn et al., 2011). A total of 23 POPs were measured: 16 polychlorinated biphenyls (PCBs) congeners, five organochlorine (OC) pesticides, one octachlorodibenzo-p-dioxin (OCDD), and one brominated diphenyl ether (BDE) congener. Since the statistical analysis is seriously hampered by a large number of cases with undetectable levels, only those POPs found in the vast majority (>90%) of subjects were analyzed in detail. Among 23 POPs measured, two OC pesticides (trans-chlordane and cis-chlordane) with detection rate <10% were not included in the final analyses. Median values, 25th and 75th percentile for the POPs are given in Table 2.

A summary measure of the less-chlorinated PCBs (with ≤5 chlorine atoms) was calculated based on our previous experience (Rönn et al., 2011; Lee et al., 2012), as well as a summary measure of the highly chlorinated PCBs (>5 atoms) and a sum of three OC pesticides (2,2-bis (4-chlorophenyl)-1,1-dichloroethene (p,p’-DDE), trans-nonachlor (TNC) and Hexachlorobenzene (HCB)).

2.3. Statistical analysis

All variables were evaluated for non-normality and variables with a skewed distribution were ln-transformed, including all POPs. The POPs were also divided into quintiles to evaluate potential non-linear relationships.

Linear regression was used to evaluate the relationship between the change in body weight and POP levels. In the first set of models (Model A) adjustment was performed for gender, BMI, serum tri- and tetra chlorinated and cholesterol. According to the discussion by (Gaskins and Schisterman, 2009), we adjusted for serum lipids in the statistical analysis rather than normalizing the POP levels for lipids. In the next set of models (Model B) we further adjusted for education (three levels), exercise habits (four levels) and smoking habits (current smoking). In order to investigate any non-linear relationship, we modeled the POP levels as quintiles and performed trend test for both the linear term and also when adding the quadratic term. In all of the quintile analyses the adjustments were as in Model B. The POPs were investigated one by one in the linear regression models as well as in the quintile analysis. The software used was STATA 11 (College Station, TX, USA).

3. Results

3.1. Change in body weight

The mean measured body weight at age 70 years was 77.3 kg (SD 14.4 kg). The mean reported body weight at age 20 was 63.0 kg (SD 9.7 kg). The mean estimated change in body weight during these 50 years was 14.4 kg (SD 11.6 kg), and the frequency distribution was normally distributed.

No difference in estimated weight change was seen between men and women (p = 0.92). No significant difference between the three education levels were seen regarding the estimated weight change (p = 0.13).

3.2. POP levels at age 70 years vs. change in body weight

When analyzed as continuous variables, PCB105, PCB118, HCB and p,p’-DDE were related to the estimated change in body weight in a positive linear fashion, adjusting for gender, BMI, lipids, exercise habits, education and smoking. In contrast, PCB 126, PCB153, PCB156, PCB157, PCB169, PCB170, PCB180, PCB189, PCB194, PCB197, PCB209 were not related to the estimated change in body weight.

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD or N (%)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>169 ± 9.1 (169)</td>
<td>(151–190)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 ± 14 (76)</td>
<td>(49–116)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>91 ± 12 (90)</td>
<td>(67–123)</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>27.0 ± 4.3 (26.6)</td>
<td>(19.1–39)</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.90 ± 0.075 (0.90)</td>
<td>(0.73–1.08)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>150 ± 23 (148)</td>
<td>(105–210)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>79 ± 10 (78)</td>
<td>(56–105)</td>
</tr>
<tr>
<td>Serum cholesterol (mmol L⁻¹)</td>
<td>5.4 ± 1.0 (5.4)</td>
<td>(3.2–7.8)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol L⁻¹)</td>
<td>3.3 ± 0.88 (3.3)</td>
<td>(1.4–5.6)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol L⁻¹)</td>
<td>1.5 ± 0.60 (1.4)</td>
<td>(0.8–2.9)</td>
</tr>
<tr>
<td>Serum triglycerides (mmol L⁻¹)</td>
<td>1.3 ± 0.60 (1.15)</td>
<td>(0.46–3.6)</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol L⁻¹)</td>
<td>5.3 ± 1.6 (5)</td>
<td>(3.8–13.5)</td>
</tr>
</tbody>
</table>

BMI = body mass index.

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (25% and 75%)</th>
<th>Median (25th and 75th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCB74</td>
<td>937</td>
<td>90.6 (63.8, 127.8)</td>
</tr>
<tr>
<td>PCB99</td>
<td>937</td>
<td>91 (62.2, 132.6)</td>
</tr>
<tr>
<td>PCB105</td>
<td>937</td>
<td>31.8 (21.4, 46.8)</td>
</tr>
<tr>
<td>PCB118</td>
<td>936</td>
<td>200.4 (135.6, 280.2)</td>
</tr>
<tr>
<td>PCB126</td>
<td>931</td>
<td>40.6 (21.4, 71.6)</td>
</tr>
<tr>
<td>PCB138</td>
<td>937</td>
<td>816.3 (619.4, 1114.8)</td>
</tr>
<tr>
<td>PCB153</td>
<td>937</td>
<td>1426.2 (1115.6, 1844.8)</td>
</tr>
<tr>
<td>PCB156</td>
<td>937</td>
<td>153.8 (119.4, 196.8)</td>
</tr>
<tr>
<td>PCB157</td>
<td>937</td>
<td>27.8 (21.4, 36.6)</td>
</tr>
<tr>
<td>PCB169</td>
<td>931</td>
<td>171.8 (130.8, 219.2)</td>
</tr>
<tr>
<td>PCB170</td>
<td>937</td>
<td>496.4 (387.4, 629.4)</td>
</tr>
<tr>
<td>PCB180</td>
<td>937</td>
<td>1165.2 (921.8, 1481.8)</td>
</tr>
<tr>
<td>PCB189</td>
<td>937</td>
<td>19.2 (146, 25.6)</td>
</tr>
<tr>
<td>PCB194</td>
<td>937</td>
<td>119.2 (87.6, 158.2)</td>
</tr>
<tr>
<td>PCB206</td>
<td>937</td>
<td>26.6 (20.8, 35)</td>
</tr>
<tr>
<td>PCB209</td>
<td>937</td>
<td>26 (19.6, 34.2)</td>
</tr>
<tr>
<td>OCDD</td>
<td>932</td>
<td>2.6 (1.4, 4)</td>
</tr>
<tr>
<td>HCB</td>
<td>937</td>
<td>253 (188.4, 336.4)</td>
</tr>
<tr>
<td>TNC</td>
<td>937</td>
<td>139.2 (90.8, 211.6)</td>
</tr>
<tr>
<td>p,p’-DDE</td>
<td>937</td>
<td>1832 (1024, 3423.8)</td>
</tr>
<tr>
<td>BDE47</td>
<td>937</td>
<td>12.6 (9, 19.6)</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.

POPs. The POPs were also divided into quintiles to evaluate potential non-linear relationships.

Linear regression was used to evaluate the relationship between the change in body weight and POP levels. In the first set of models (Model A) adjustment was performed for gender, BMI, serum tri- and tetra chlorinated and cholesterol. According to the discussion by (Gaskins and Schisterman, 2009), we adjusted for serum lipids in the statistical analysis rather than normalizing the POP levels for lipids. In the next set of models (Model B) we further adjusted for education (three levels), exercise habits (four levels) and smoking habits (current smoking). In order to investigate any non-linear relationship, we modeled the POP levels as quintiles and performed trend test for both the linear term and also when adding the quadratic term. In all of the quintile analyses the adjustments were as in Model B. The POPs were investigated one by one in the linear regression models as well as in the quintile analysis. The software used was STATA 11 (College Station, TX, USA).

3. Results

3.1. Change in body weight

The mean measured body weight at age 70 years was 77.3 kg (SD 14.4 kg). The mean reported body weight at age 20 was 63.0 kg (SD 9.7 kg). The mean estimated change in body weight during these 50 years was 14.4 kg (SD 11.6 kg), and the frequency distribution was normally distributed.

No difference in estimated weight change was seen between men and women (p = 0.92). No significant difference between the three education levels were seen regarding the estimated weight change (p = 0.13).

3.2. POP levels at age 70 years vs. change in body weight

When analyzed as continuous variables, PCB105, PCB118, HCB and p,p’-DDE were related to the estimated change in body weight in a positive linear fashion, adjusting for gender, BMI, lipids, exercise habits, education and smoking. In contrast, PCB 126, PCB153, PCB156, PCB157, PCB169, PCB170, PCB180, PCB189, PCB194, PCB197, PCB209 were not related to the estimated change in body weight.
If the regression models described above were stratified in two way fashion (\(p = 0.97\), Fig. 1). Non-linear and the quadratic term trend, we found that, PCB74 was positively related to the estimated change in body weight in a non-linear fashion with the full effect achieved by quintile 2 (compared to quintile 1, \(p = 0.0015\), Fig. 1). In contrast, the inverse relationship described above for the highly chlorinated PCBs vs. the estimated change in body weight was fairly linear (\(p\)-value for quadratic term \(p = 0.97\), Fig. 1). Non-linearity was also seen for the relationship between the sum of OC pesticides and the estimated change in body weight (\(p = 0.029\) Fig. 1).

No major interactions between POPs and gender regarding the associations vs. the estimated change in body weight were found. Further adjustment for total energy intake, percentage fat intake and alcohol intake (based on 7 d dietary records collected in 90% of the sample at age 70) augmenting Model B did not change the results in any major way (data for Model B not shown).

Fig. 2 shows an overview of the differences between quintile 5 and 1 in estimated change in body weight for the different POPs.

### 4. Discussion

Similar to what we have reported in cross-sectional (Rönn et al., 2011) and prospective evaluations (Lee et al., 2012) for the relationships between circulating POP levels and measurements of obesity in the PIVUS cohort, the present study investigating the relationships between POP levels and estimated life-time change in body weight showed that high levels of OC pesticides and the less-chlorinated PCBs at age 70 were associated with a pronounced estimated increase in weight over the previous 50 years, but the opposite was seen for highly-chlorinated PCBs.

### 4.1. Comparison with the literature

During recent years analyses of evaluations of NHANES data have shown that a number of POPs are related to either BMI or waist circumference (Lee et al., 2007; Elobeid et al., 2010). However, none of these studies showed different directions for relationships with different PCBs. In a case-control study of obese and lean subjects (Dirinck et al., 2011), a similar inverse relationship between highly-chlorinated PCBs and obesity was found in this report, as in past investigations of the PIVUS study (Rönn et al., 2011; Lee et al., 2012). In the case-control study by Dirinck et al.
unfortunately no measurement of less-chlorinated PCBs was performed. In a recent prospective nested case-control study in young subjects, pesticide and PCB levels predicted future BMI (Lee et al., 2011) in complex U-shaped relationships.

### 4.2. Possible mechanisms

There are three major possible mechanisms behind the rather unexpected findings in the PIVUS study that different PCBs are related to estimated life-time gain in body weight in opposite directions. First, less-chlorinated and highly-chlorinated PCBs might have different actions regarding fat accumulation. There are however few mechanistic insights in the toxicokinetic properties of PCBs to support such a view. PCB126, a PCB with five chlorine atoms and a high dioxin-like activity did in fact induce impaired weight gain by age when given to rats (Lind et al., 2004).

The second alternative is that the pharmacokinematic properties of the PCBs and other similar POPs explain the observed relationships. PCBs are stored in lipid reservoirs, and their concentrations change predictably with changes in adipose tissue volume. Levels in blood are proportional to blood lipid content and weight gain increases the PCB and POP half-life. This has been amply documented (Thomas et al. and Salvan, 1998). Most recently, weight gain over 10 years resulted in lower levels of PCBs compared with weight-stable or weight-loss conditions (Lim et al., 2011). However, the pharmacokinetics are complex, and relationships between PCBs and BMI or weight change in direction over time. Therefore, the inter-relationships among these factors in a population where exposure and body size differ widely are not straightforward, especially as only a single POP measurement was made in our study. Temporal changes depend on the magnitude and timing of exposure, the time since exposure, ongoing exposure, body fat mass and changes in fat mass during the time between exposure and the time of blood sampling. In this cohort of Swedes born in the early 1930s, exposure probably was at maximum during the 1960s and 1970s when the PCB and pesticide contamination were highest in Sweden (Bignert et al., 1998).
women occurred during the period of maximal POP exposure. According to the models for TCDD (Thomaseth and Salvan, 1998) weight gain in lean subjects would lower their POP levels faster than if they were weight-stable; as a result the point of changing sign of the relationship between POPs and BMI/body weight would appear earlier. Thus, the observed stronger positive relationship between the less chlorinated PCBs in persons who were lean at age 20 and the stronger inverse relationship between the highly chlorinated PCBs in those with BMI above median might be explained by the difference in life time weight-gain between the two strata.

The present study use a cross-sectional design and might therefore be subject to reverse causation, in this case the estimated weight change would influence the POP levels. A greater fat accumulation would also lead to a greater accumulation of POPs in the adipose tissue. This will in turn lead to a longer time to metabolize especially highly chlorinated PCB with a long half-life and therefore an inverse relationship between the estimated weight gain and the levels of highly chlorinated PCBs would be found.

4.3. Non-linear effects

Low-dose effects, or even inverted U-shaped relationships, have previously been found for POPs regarding obesity and related traits such as insulin resistance or diabetes. (Lee et al., 2010, 2011). Also, when adipocytes were incubated with different doses of POPs, impaired insulin action was observed with very low dose of POPs without linear decreasing of insulin action with increasing dose of POPs (Ruzzin et al., 2010). As obesogens have been proposed to induce weight gain through endocrine disrupting properties of chemicals, low dose of chemicals would be sufficient to induce weight gain. In contrast, a high dose of any chemical may cause weight loss, due to cellular toxicity. In the present study, a substantial estimated weight gain was seen for the less-chlorinated PCBs even in the second quintile (compared to the first), and no further major effect was seen in the higher quintiles. Thus, non-linear relationships might provide a third factor that could explain the described discrepancies regarding the PCBs.

4.4. Multiple testing

In the present study, multiple tests were performed since 21 POPs were analyzed. Applying a strict Bonferroni correction would result in a critical p-value of 0.00238 (0.05/21). The associations between some of the main PCBs and DDE, as well as the sums of highly chlorinated PCBs, OC pesticides and less chlorinated PCBs (quadratic term) all show p-values below this critical threshold.

4.5. Brominated flame retardants

No significant relationship between BDE47 levels and estimated change in body weight was found. This might be explained by the fact that brominated flame retardants were introduced in large scale use much later than the other POPs investigated in the present sample at a stage when the major weight gain already had taken place in the present sample.
4.6. OC pesticides

A positive relationship between the sum of the OC pesticides and the estimated weight change was found. This relationship was mainly driven by the relationship between levels of \( p,p'-\text{DDE} \) and the estimated weight change. This finding is also in agreement with our previous findings in this cohort using a prospective design (Lee et al., 2012). Furthermore, in mother–child cohorts maternal levels of \( p,p'-\text{DDE} \) were related to an increased weight and body mass index in adult female offspring (Karmaus et al., 2009). \( p,p'-\text{DDE} \) is known to bind to the androgen receptor and might thereby be involved in the regulation of adipose tissue.

4.7. Limitations

First, this study was conducted in an elderly Caucasian sample and the findings might not be generalizable to younger subjects and other ethnic groups. Second, body weight and height at age 20 was self-reported and might therefore be subject to misclassification. However, if so, that would most likely lead only to false negative findings and not to the highly significant findings seen in the present study.

Another limitation is that we have no assessment of dietary intake throughout life, since especially fat intake could have impact on both POP levels and weight gain.

In conclusion, high levels of OC pesticides and the less-chlorinated PCBs at age 70 were associated with a pronounced estimated weight change over the previous 50 years. However, the opposite was seen for highly-chlorinated PCBs. Differences in mode of action, toxicokinetic, non-linear relationships and reverse causation might explain these discrepancies.

Disclosures

None.

Acknowledgements

This study was supported by the Swedish Research Council (VR) and the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (FORMAS).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chemosphere.2012.07.051.

References