Associations of Serum Concentrations of Persistent Organic Pollutants with the Prevalence of Periodontal Disease and Subpopulations of White Blood Cells

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BACKGROUND: Persistent organic pollutants (POPs), which are endocrine disruptors that accumulate in adipose tissue, can increase the risk of periodontal disease through the disturbance of the immune system.

OBJECTIVE: We examined associations of background exposure to POPs with periodontal disease in the general population.

DESIGN: Cross-sectional associations of concentrations of serum POPs with the prevalence of periodontal disease were investigated in 1,234 adults ≥ 20 years of age in the National Health and Nutrition Examination Survey 1999–2002.

RESULTS: Among several POPs, organochlorine (OC) pesticides were most strongly associated with periodontal disease. Adjusted odds ratios across quintiles of OC pesticides were 1.0, 1.3, 1.7, 2.4, and 2.7 (p for trend < 0.01) for the presence in any site of clinical attachment loss ≥ 4 mm and 1.0, 1.7, 2.6, 3.4, and 3.7 (p for trend < 0.01) for the presence of pocket depth ≥ 4 mm. Polychlorinated biphenyls and polychlorinated dibenzo-p-dioxins also showed significant positive associations with one or both definitions of periodontal disease. Results did not materially change when continuous variables of clinical attachment loss or pocket depth were used as outcomes. Although participants with periodontal disease had higher white blood cell and neutrophil counts, neutrophil counts were inversely related to OC pesticides (p for trend < 0.01). These inverse associations did not change after excluding subjects with C-reactive protein ≥ 3 mg/L.

CONCLUSION: POPs, especially OC pesticides, were positively associated with periodontal disease, possibly through immunomodulation due to OC pesticides.

KEY WORDS: immune system, neutrophil, organochlorine pesticides, periodontitis, persistent organic pollutants. Environ Health Perspect 116:1558–1562 (2008). doi:10.1289/ehp.11425 available via http://dx.doi.org/ [Online 3 July 2008]
The study protocol was reviewed and approved by the CDC institutional review board; additionally, informed written consent was obtained from all subjects before they took part in the study. Serum concentrations of various biologically important POPs or their metabolites were measured in subsamples of the NHANES 1999–2002 surveys (NCHS 2005).

The NHANES standardized home interview was followed by a detailed physical examination. Venous blood samples were collected and shipped weekly at −20°C. POPs were measured by high-resolution gas chromatography/high-resolution mass spectrometry using isotope dilution for quantification. All these analytes were measured in approximately 5 mL serum. The POPs were reported on a lipid-adjusted basis using concentrations of serum total cholesterol and triglycerides.

Detailed information about the oral health component protocol have been described elsewhere (NCHS 2001). Briefly, the periodontal examination was conducted at two sites, midbuccal and mesiobuccal, for each tooth, in two randomly chosen quadrants, one maxillary and one mandibular, on the assumption that conditions in these two quadrants would represent the mouth. Third molars were excluded, so a maximum of 14 teeth and 28 sites per individual were examined. We used various definitions of periodontitis to see if there were consistent patterns of associations regardless of definition. Clinical attachment loss (CAL), an indicator of active disease, was expressed in parallel. We repeated the same analyses for each of five categories of lipid-adjusted POPs (three PCDDs, three PCDFs, four dioxin-like PCBs, five non–dioxin-like PCBs, and four OC pesticides).

For each POP, subjects with serum concentrations < LOD were the reference group, and subjects with detectable values were categorized by cutoff points of 25th, 50th, and 75th percentile values. To yield a cumulative measure of three PCDDs, we summed the ranks of the three POPs that belong to the PCDDs. The summary values were categorized by cutoff points of 25th, 50th, and 75th percentile values. We assigned and cumulated POP subclasses similarly for the three PCDFs, the four dioxin-like PCBs, the five non–dioxin-like PCBs, and the four OC pesticides.

The cross-sectional associations of categories of POPs with periodontal disease were analyzed using linear regression with continuous CAL%4 or PD%4 and logistic regression with dichotomous anyCAL4 or anyPD4. Potential confounders were age, sex, race/ethnicity, poverty income ratio, body mass index (BMI), cotinine concentration (nanograms per milliliter), history of cigarette smoking, and history of diabetes. We substituted median values computed from nonmissing data for participants with missing poverty income ratio, BMI, or cotinine concentration in 134 subjects; exclusion of these individuals did not change any conclusions. We also examined associations between POPs and subpopulations of WBC, specifically neutrophils and lymphocytes. To limit the possibility that inflammatory reaction due to various subclinical and clinical diseases affects these associations, we repeated the same analyses among subjects with C-reactive protein (CRP) < 3 mg/L (n = 744).

All statistical analyses were performed with SAS 9.1 (SAS Institute Inc., Cary, NC, USA) and SUDAAN 9.0 (Research Triangle Institute, Research Triangle Park, NC, USA). Estimates of the main results were calculated assuming stratification and clustering (Korn and Graubard 1991), adjusting for age, race and ethnicity, and poverty income ratio instead of using sample weights. This adjustment has been regarded as a good compromise between efficiency and bias (Graubard and Korn 1999; Korn and Graubard 1991). Because results were very similar with SAS 9.1 and SUDAAN 9.0, we present the results based on SAS 9.1.

### Results

The sample of 1,243 participants included 45.5% men, 45.4% white, and 16.5% current smokers. Mean ± SD for age was 45.5 ± 17.6 years (range, 20–85). Table 1 summarizes the distribution of demographic or health behavior variables by the dichotomies anyCAL4 or anyPD4. Subjects with anyCAL4 tended to be older, male, smokers, and poor compared with those without anyCAL4. Subjects with anyPD4 showed a similar trend to that found with anyCAL4, except race; nonwhite race was common among subjects with anyPD4.

Table 2 shows the associations of five subclasses of POPs with demographic and health behavior factors. Age was the strongest correlate of serum concentrations of all five subclasses of POPs; correlation coefficients ranged among the five categories of lipid-adjusted POPs (three PCDDs, three PCDFs, four dioxin-like PCBs, five non–dioxin-like PCBs, and four OC pesticides) and demographic and health behavior factors.

### Table 2. Age-adjusted Spearman correlation coefficients between each of five categories of lipid-adjusted POPs (three PCDDs, three PCDFs, four dioxin-like PCBs, five non–dioxin-like PCBs, and four OC pesticides) and demographic and health behavior factors.

| Demographic/health factor | PCDDs | PCDFs | Dioxin-like PCBs | Non-dioxin-like PCBs | OC pesticides |
|---------------------------|-------|-------|------------------|----------------------|---------------|
| Age                       | 0.55 ** | 0.44 ** | 0.70 ** | 0.72 ** | 0.73 ** |
| Sex (male = 1; female = 0) | −0.16 ** | 0.01 | −0.10 | 0.08 ** | −0.07 ** |
| Race (white = 1; others = 0) | −0.04 | 0.06 ** | −0.09 ** | 0.11 ** | −0.32 ** |
| Poverty income ratio      | −0.01 | 0.06 ** | 0.12 ** | 0.16 ** | −0.17 ** |
| Serum cotinine level      | −0.13 ** | 0.02 | −0.05 | 0.13 ** | −0.02 |
| Cigarette smoking (current = 1; others = 0) | −0.14 ** | 0.01 | −0.05 | 0.10 ** | 0.02 |
| BMI                       | 0.13 ** | 0.03 | 0.03 | −0.13 ** | 0.03 |

*Before calculating correlations coefficients, detectable values of each POP were individually ranked, and the ranks were summed within subclass to arrive at the subclass value. All not detectable values were ranked as zero. *p < 0.05. **p < 0.01.

### Table 1. Comparison of demographic and health behavior factors between subjects with or without CAL ≥ 4 mm in any site and with or without PD ≥ 4 mm in any site.

| Demographic/health factor | CAL 4 mm | PD 4 mm | p-Value | CAL 4 mm | PD 4 mm | p-Value |
|---------------------------|----------|---------|---------|----------|---------|---------|
| No. of subjects           | 945      | 298     |         | 1,038    | 205     |         |
| Age (years)               | 41.6 ± 16.6 | 57.8 ± 14.9 | < 0.01 | 45.0 ± 17.8 | 47.9 ± 16.5 | 0.03 |
| Poverty income ratio      | 2.7 ± 1.6 | 2.3 ± 1.5 | < 0.01 | 2.7 ± 1.6 | 2.2 ± 1.4 | < 0.01 |
| BMI (kg/m²)               | 28.3 ± 6.2 | 28.1 ± 5.7 | 0.60 | 28.2 ± 6.1 | 28.4 ± 6.0 | 0.76 |
| Serum cotinine (ng/ml)    | 38.1 ± 94.7 | 61.0 ± 114.8 | < 0.01 | 39.6 ± 93.8 | 64.1 ± 126.5 | < 0.01 |
| Proportion (%)            | Male     | 40.7    | 60.4    | < 0.01 | 42.0    | 58.1    | < 0.01 |
|                          | White    | 45.2    | 46.0    | 0.81 | 49.1    | 26.3    | < 0.01 |
|                          | Smoker   | 14.5    | 22.8    | < 0.01 | 15.3    | 22.4    | 0.01 |

Values are mean ± SD except where indicated.
from 0.45 to 0.88. Men tended to have lower concentrations of most POPs, except non–dioxin-like PCBs. White subjects had lower concentrations of OC pesticides but higher concentrations of PCBs and PCDFs. Mexican Americans had the highest serum concentrations of OC pesticides. Those with lower incomes had higher concentrations of OC pesticides but lower PCBs and PCDFs. Serum cotinine levels and current status of smoking were inversely associated with PCDDs while positively associated with non–dioxin-like PCBs. PCDDs were positively associated with BMI, whereas non–dioxin-like PCBs showed an inverse association with BMI.

Mean number ± SD of missing teeth was 4.4 ± 6.2, and 81.4% of study subjects had > 75% of teeth. The number of missing teeth was strongly associated with CAL; the correlation coefficient with CAL4% was 0.45, whereas that with PD4% was only 0.14. There were 298 prevalent cases of anyCAL4 (24.0%) and 205 prevalent cases of anyPD4 (16.5%). OC pesticides showed the strongest associations with anyCAL4 or anyPD4 (Table 4). PCDDs and non–dioxin-like PCBs were significantly associated, but the relationships reached significance only with PD4%. Detailed associations of the four individual POPs belonging to OC pesticides with anyCAL4 or anyPD4 were presented in Table 5. Most specific POPs belonging to OC pesticides consistently showed associations with anyCAL4 or anyPD4.

We examined the association between OC pesticides and subtypes of differential WBC counts (Figure 1). Even though WBC and neutrophil counts were slightly higher among subjects with current periodontal disease, these counts generally had an inverse association with OC pesticides (p for trend < 0.01). This inverse association did not change after excluding subjects with CRP ≥ 3 mg/L and was even clearer after this exclusion in the last quintile of OC pesticides. Further adjustment for periodontal disease status did not change results (data not shown). On the other hand, there was a weak but not statistically significant positive trend of OC pesticides with lymphocyte counts. However, lymphocyte percentage of total white cells was significantly and positively associated with OC pesticides (data not shown).

### Discussion

In the present study we found that background exposure to POPs was positively associated with the prevalence of periodontal disease. This association was similarly observed using several definitions of periodontal disease, which could reflect various aspects of periodontal disease. Among five subclasses of POPs, OC pesticides were most strongly associated with periodontal disease. In fact, OC pesticides were the subgroup of POPs most strongly associated with type 2 diabetes, insulin resistance, and metabolic syndrome in our previous studies (Lee et al. 2006, 2007a, 2007b).

Because this is a cross-sectional study, temporality of events in any causal pathway that might link POPs exposure and periodontal disease cannot be established. However, it may be unlikely that periodontal disease increases

### Table 3. Adjusted ORs (95% confidence intervals (CIs)) of prevalence of CAL or PD by quintiles of PCDDs, PCDFs, dioxin-like PCBs, non–dioxin-like PCBs, and OC pesticides.

| Indicator/compound | Quintiles of POPs | < 20th | 20th to < 40th | 40th to < 60th | 60th to < 80th | ≥ 80th | p-Trend |
|--------------------|------------------|-------|--------------|--------------|--------------|-------|--------|
| CAL ≥ 4 mm (presence vs. absence in any site) | PCDDs | Cases/no. | 35/248 | 42/250 | 52/248 | 69/249 | 100/248 |
| | | Adjusted OR (95% CI) | Referent | 1.0 (0.6–1.8) | 1.1 (0.7–1.9) | 1.3 (0.8–2.3) | 1.7 (0.9–3.0) | 0.04 |
| | PCDFs | Cases/no. | 36/248 | 45/249 | 50/249 | 75/249 | 92/248 |
| | | Adjusted OR (95% CI) | Referent | 1.1 (0.6–1.8) | 1.0 (0.6–1.7) | 1.3 (0.8–2.2) | 1.3 (0.8–2.2) | 0.18 |
| | Dioxin-like PCBs | Cases/no. | 16/248 | 46/250 | 54/248 | 80/249 | 102/248 |
| | | Adjusted OR (95% CI) | Referent | 1.9 (1.0–3.6) | 2.0 (1.0–3.8) | 2.3 (1.2–4.4) | 2.3 (1.1–4.6) | 0.06 |
| | Non–dioxin-like PCBs | Cases/no. | 25/248 | 25/249 | 50/249 | 86/249 | 112/248 |
| | | Adjusted OR (95% CI) | Referent | 0.9 (0.5–1.8) | 1.3 (0.7–2.2) | 1.7 (0.9–3.1) | 1.8 (0.9–3.3) | 0.03 |
| | OC pesticides | Cases/no. | 17/248 | 30/250 | 53/248 | 86/249 | 112/248 |
| | | Adjusted OR (95% CI) | Referent | 1.3 (0.7–2.4) | 1.7 (0.9–3.2) | 2.4 (1.2–4.6) | 2.7 (1.3–5.5) | < 0.01 |
| PD ≥ 4 mm (presence vs. absence in any site) | PCDDs | Cases/no. | 35/248 | 40/250 | 39/248 | 43/249 | 48/248 |
| | | Adjusted OR (95% CI) | Referent | 1.3 (0.8–2.2) | 1.3 (0.8–2.2) | 1.4 (0.8–2.5) | 1.7 (1.0–3.1) | 0.10 |
| | PCDFs | Cases/no. | 31/248 | 43/249 | 41/249 | 51/249 | 39/248 |
| | | Adjusted OR (95% CI) | Referent | 1.4 (0.9–2.4) | 1.3 (0.8–2.2) | 1.6 (1.0–2.7) | 1.1 (0.6–2.0) | 0.49 |
| | Dioxin-like PCBs | Cases/no. | 27/248 | 44/250 | 44/248 | 40/249 | 50/248 |
| | | Adjusted OR (95% CI) | Referent | 1.5 (0.9–2.6) | 1.9 (1.1–3.3) | 1.6 (0.9–3.1) | 2.4 (1.2–4.7) | 0.03 |
| | Non–dioxin-like PCBs | Cases/no. | 31/248 | 42/249 | 32/249 | 47/249 | 53/248 |
| | | Adjusted OR (95% CI) | Referent | 1.4 (0.9–2.4) | 1.0 (0.6–1.8) | 1.6 (0.9–2.9) | 1.8 (1.0–3.5) | 0.08 |
| | OC pesticides | Cases/no. | 21/248 | 33/250 | 46/248 | 53/249 | 52/248 |
| | | Adjusted OR (95% CI) | Referent | 1.7 (0.9–3.0) | 2.6 (1.4–4.6) | 3.4 (1.8–6.5) | 3.7 (1.8–7.6) | < 0.01 |

*Adjusted for age, sex, race, poverty income ratio, serum cotinine levels, cigarette smoking, and diabetes. Detectable values of each POP were individually ranked, and the ranks were summed within subclass to arrive at the subclass value. All not detectable values were ranked as zero. The summary values were categorized by quintiles of the sum of ranks.
Infectious and inflammatory factors modulate changes in blood counts, the findings for POPs suggest that the basic hematopoietic process in bone marrow may be affected by POPs. There is a constant flow of neutrophils through the periodontal pocket, and they play a major role in the host response against invading periodontopathic microorganisms. As it is clear that deficiencies of the production rate or function of neutrophilic polymorphonuclear leukocytes can predispose to recurrent infections (Bogomolski-Yahalom and Matzner 1995), the subclinical decrease of neutrophils related to POPs’ exposure may predispose to bacterial infection in periodontal disease.

In the later years, it has become apparent that the pathogenesis of periodontal disease is more complex than the simple presence of virulent microorganisms (Van Dyke and Serhan 2003). An individual’s susceptibility to periodontal breakdown depends on a number of identified and unidentified characteristics of the host, including the nonspecific and specific immune systems (Pattini et al. 2000). Immunodeficiency was suspected in patients exhibiting periodontal inflammation or destruction that appears disproportionate to the degree of local irritants (American Academy of Periodontology 2000). It is well known that patients who have innate impaired immune responses or who are taking immune suppressive medications are at a higher risk for periodontal disease (American Academy of Periodontology 2000).

Several lines of experimental and epidemiologic evidence have shown that chemicals such as POPs markedly influence the function of many of the cellular, subcellular, or molecular components of the immune system (Baccarelli et al. 2002; Banerjee 1999). An alteration of the normal immune function may have two types of consequences. The first is a reduction of immune activity, which can evolve into an immune deficit and increased susceptibility to infectious diseases and neoplasms. The second is an enhancement of the normal immune response, which can evolve into allergy and autoimmunity. In relation to autoimmunity, we reported positive associations between serum concentrations of some POPs, especially PCBs, and rheumatoid arthritis, an autoimmune disease (Lee et al. 2007c). The current study also suggests that exposure to background levels of POPs, especially OC pesticides, may increase susceptibility to bacterial infection.

In addition to periodontal disease and rheumatoid arthritis, background exposure to POPs was strongly and positively associated with many inflammatory chronic diseases such as type 2 diabetes, metabolic syndrome, and cardiovascular disease (Ha et al. 2007; Lee et al. 2006, 2007a, 2007b), and persons with these proinflammatory conditions generally have higher levels of WBC counts. However, the current study found that POPs, especially OC pesticides, were inversely associated with WBC counts, particularly neutrophil counts. This association was similarly observed among participants with CRP < 3 mg/L as well as among all participants. Although many

Table 4. Adjusted* means (SEs) of CAL percentage of sites ≥ 4 mm or PD percentage of sites ≥ 4 mm by quintiles of PCDDs, PCDFs, dioxin-like PCBs, non-dioxin-like PCBs, and OC pesticides.

| Quintiles of POPs | 20th | 20th to < 40th | 40th to < 60th | 60th to < 80th | ≥ 80th | p-Trend |
|------------------|------|---------------|---------------|---------------|-------|--------|
| PCDDs            | 7.0 (1.1) | 5.9 (1.1) | 7.4 (1.1) | 7.1 (1.1) | 8.5 (1.2) | 0.30   |
| PCDFs            | 6.8 (1.1) | 6.7 (1.1) | 5.1 (1.1) | 8.8 (1.1) | 7.8 (1.1) | 0.27   |
| Dioxin-like PCBs | 6.0 (1.2) | 6.5 (1.1) | 6.5 (1.1) | 8.6 (1.1) | 8.4 (1.3) | 0.16   |
| Non-dioxin-like PCBs | 6.4 (1.2) | 5.3 (1.2) | 6.0 (1.1) | 8.3 (1.1) | 10.0 (1.3) | 0.06   |
| OC pesticides   | 6.0 (1.3) | 4.7 (1.1) | 5.1 (1.1) | 9.0 (1.1) | 11.1 (1.3) | < 0.01  |

*Adjusted for age, sex, race, poverty income ratio, serum cotinine levels, cigarette smoking, and diabetes.

Table 5. Adjusted* ORs (95% CIs) of prevalence of any CAL ≥ 4 mm or PD ≥ 4 mm by quintiles (Q) of specific POPs belonging to OC pesticides.

Abbreviations: p,p'-DDE, p,p'-dichlorodiphenyldichloroethane; β-HCH, beta-hexachlorocyclohexane.

*Adjusted for age, sex, race, poverty income ratio, cigarette smoking, serum cotinine, and diabetes. *(p,βp'-DDE were detected in all subjects.

Figure 1. Neutrophil and lymphocyte counts by quintiles of OC pesticides adjusted for age, sex, race, poverty income ratio, cigarette smoking, serum cotinine concentration, and diabetes. p-Values for trend for neutrophils were < 0.01 both in all participants and in those with CRP < 3 mg/L.
ple volume was unrelated to periodontal classification would be nondifferential if sample volume was higher. However, such misclassification bias is possible for subjects whose POPs would have been detectable with high sample volume. The biological plausibility of our findings. Next, associations between POPs and periodontal disease, despite long-term persistence of these features may lead to increased susceptibility to infection and autoimmune diseases among subjects with high exposure to OC pesticides.

Even though many epidemiologic studies have firmly established the association between periodontal disease and various systemic diseases (Demmer and Desvarieux 2006; Lee 1994), the nature and relevance of this association is still questionable (Paquette 2002). Specifically, it is an issue whether the infectious and inflammatory periodontal disease process contributes causally to various systemic diseases or these conditions are coincidentally associated with periodontal disease (Paquette 2002). Although inflammatory reactions in the periodontal region have been associated with the risk of various systemic diseases, our studies on POPs also suggest that the simultaneous exposure to environmental xenobiotics such as POPs, which consist of several hundred chemicals with various harmful effects, may contribute to the pathogenesis of these clinical outcomes, leading to the epidemiologic associations between periodontal disease and various systemic diseases.

This study has several limitations. First, the cross-sectional study design in NHANES does not allow inferences regarding the causality between POPs and periodontal disease, despite biological plausibility of our findings. Next, misclassification bias is possible for subjects whose POPs would have been detectable with a higher sample volume. However, such misclassification would be nondifferential if sample volume was unrelated to periodontal disease. Finally, there can be residual confounding due to unknown lifestyle factors, which can affect both body burden of POPs and periodontal disease. However, the findings presented do adjust for several lifestyle factors.

Taken together, serum concentrations of POPs, especially OC pesticides, were positively associated with periodontal disease. Immunomodulation due to exposure to OC pesticides may be a contributory mechanism.

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