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# PCBs and Dioxins Either Cause or Make Worse Both Osteo and Rheumatoid Arthritis

**Azad Mohammad, DrPH[1]; David O. Carpenter, MD*[1]**

[1] Institute for Health and the Environment, University at Albany, Rensselaer, NY 121144

* dcarpenter@albany.edu

ABSTRACT

Rheumatoid arthritis is an autoimmune disease, while osteoarthritis is presumed to be a disease due to wear and tear causing damage to joints. Some environmental exposures, such as smoking, air pollution and possibly persistent organic pollutants, are known to increase the risk of both. We have utilized the National Health and Nutrition Examination Survey (NHANES) data to determine associations between self-reported prevalence of any form of arthritis, rheumatoid and osteoarthritis and various polychlorinated biphenyl (PCB) congeners, several chlorinated pesticides and 2.3,7,8-tetrachloro-dibenzo-dioxin (TCDD). We find that there is a statistically significant association between serum PCB levels of more highly chlorinated PCB congeners and both types of arthritis. The associations are stronger with rheumatoid arthritis than with osteoarthritis, and stronger in women than in men.

**Keywords:** Rheumatoid arthritis; Osteo-arthritis; NHANES; Persistent organic pollutants; Polychlorinated biphenyls; Chlorinated pesticides

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**Introduction:**

Arthritis is a chronic and disabling disease. The most common forms of arthritis are osteoarthritis (OA) which is caused by wear and tear of the lining of joints, and rheumatoid arthritis (RA), which is an autoimmune disease. The global prevalence of years lived with disability for OA was 12.8 million in 2013, up by 75% from the prevalence in 1990.[1] Osteoarthritis affects primarily large joints, and the global prevalence of knee OA was about 3.8%.[2] Rheumatoid arthritis global prevalence affects some 4.7 million people worldwide [3], and results in progressive disability, premature death and socioeconomic burden.[4] Rheumatoid arthritis affects primarily the small joints of the hands and feet, and incidence has been associated with elevated proinflammatory adipokines.[5] Both common forms of arthritis are increased with obesity [6] [7] [8], and proinflammatory adipokines have been implicated in both RA and OA.[9]

A number of environmental exposures have been documented to be risk factors for development of arthritis. Smoking increases the prevalence, incidence and progression of OA[10] and RA [11]. Air pollution has been considered to increase risk of autoimmune diseases in general, including RA [12]. Hart et al. found an elevated risk of RA among women living within 50 m of a major roadway as compared to those living 200 m or further away, and suggested that air pollution was a risk factor for RA.[13] However subsequent studies have not found associations with levels of particulate matter [14] but have suggested that ozone [15] or the gaseous pollutants, SO2 and NO2, were responsible for the elevated risk.[16]

In 1979 there was a mass poisoning event in Taiwan in which polychlorinated biphenyls (PCBs) accidentally contaminated cooking oil. PCBs have a number of biological effects, including on the immune system [17], and when heated can also generate the more toxic dibenzofurans. The contaminated cooking oil was consumed for about eight months, and individuals were estimated to have consumed up to one gram of PCBs and 3.8 mg of dibenzofurans.[18] In a 14-year follow-up of 795 exposed persons and 693 controls, Guo et al., reported that the risk of arthritis in men was 4.1 times higher than in the controls. Most cases appeared to be OA, not RA. There were also elevations in broken teeth and abnormal nails.[19]

PCBs are a mixture of a possible 209 different "congeners", depending upon how many chlorines are on the biphenyl rings and where they are located. A few of the PCB congeners and the dibenzofurans bind to and activate the aryl hydrocarbon receptor (AhR), often known as the dioxin receptor. Activation of this receptor results in gene induction and elevation in a variety of disease, including cancer.[17] However the non-dioxin-like PCBs also have a variety of adverse effects, and therefore there remains the question of whether the elevation in rates of arthritis are due to the dioxin-like activity or rather to the non-dioxin-like PCBs. There is some evidence supporting the view that both are important. Abella et al. have reported that non-dioxin-like PCBs induce chondrocyte cell death by altering the regulatory mechanism of apoptosis, necrosis and oxidative stress[20]. However, Lee and Yang (2012) reported that PCB 126, a dioxin-like congener, induces apoptosis of chondrocytes via oxidative stress, which they relate to OA[21]. Kobayashi et al investigated mRNA and protein levels in synovial tissue from RA and OA patients[22]. They found higher levels of AhR expression in RA than in OA synovial tissue, and suggested that this is the basis of the known increased risk of RA from smoking.

Lee et al. used NHANES data (1999-2002) to explore associations between persistent organic pollutants and both RA and OA[23]. They found

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associations between both dioxin-like and non-dioxin-like PCBs and RA in women, but no significant associations in men. There was also a weak but non-significant association with chlorinated pesticides.

The major goal of this study was to expand on the Lee et al. report by using additional years of NHANES data and to study in more detail the associations with individual PCB congeners with RA and OA in males and females.[23]

**Materials and Methods**

Three two-year cycles from 1999 to 2004 of the National Health and Nutrition Examination Survey (NHANES) were used in this study. NHANES data was designed to evaluate the health and nutritional status of adults and children in the United States and produce vital and health statistics for the nation. This cross-sectional survey utilizes interviews and physical examinations to estimate prevalence of health behaviors and diseases. Interview data focused on self-reported arthritis, smoking, and sociodemographic information; supplemented with physical measurements and laboratory tests. The physical examinations collect height and weight for determination of body mass index (BMI). In a previous study we have compared risk factors for osteo- and rheumatoid arthritis using NHANES data.[8] Exposure to environmental chemicals was measured in individual blood samples by the laboratory of the Centers for Disease Control and Prevention. We were unable to utilize the more recent NHANES data as only pooled blood samples were monitored in these years.

The total study sample included all NHANES participants above 20 years old with available medical examination and sufficient arthritis data, and who had their individual blood tested for PCBs, dioxin and chlorinated pesticides (Figure 1. Arthritis was measured with a definitive answer to the question "has a doctor or other health professional ever told you that you have arthritis?" Participants who answered "don't know" or refused to answer were excluded. For participants who reported arthritis, a subsequent question asked "Which type of arthritis was it?" The responses to this question were categorized as follows: RA, OA, psoriatic arthritis, other arthritis, don't know the type of arthritis and refused to answer the question.

Sociodemographic characteristics extracted from NHANES for analyses included age, sex, living in poverty, and race/ethnicity. All information was self-reported. Living in poverty is a variable calculated by NHANES based on household income and household occupants. Three categories of income were used: Below twice the official level of poverty, between twice and three-time the level of poverty and above three-time the level of poverty. Four race/ethnicity classes were identified as non-Hispanic white, non-Hispanic black, Hispanic and other. Smoking history was assessed by the answer to the question "Have you smoked at least 100 cigarettes in your entire life?"

**Collection and Analysis of Blood PCBs and Pesticides Data**

Blood samples were collected and shipped weekly at –20°C. High-resolution gas chromatography mass spectrometry was used to measure persistent organic pollutants using isotope dilution for quantification. Analyses were measured in approximately 5 mL serum using a modification of the method of Turner et al. (1997).[24] The sensitivity of the analysis methods was better in participants who provided a larger aliquot of blood and it was improved significantly in the 2003-2004 cycle.

We used NHANES data on seven persistent chlorinated pesticides, β hexachlorocyclohexane (β HCCH, but listed as BHC in NHANES), heptachlor epoxide (HPE), mirex (MIR), oxychlordane (OXY), 2,2-bis(4-chlorophenyl)-1,1-dichloroethene (DDE, the major metabolite of DDT, but listed as PDE in NHANES), 2,2-bis(4-chlorophenyl)-1,1-dichloroethan (DDT, but listed as PDT in NHANES) and trans-nonachlor (TNA). Individual pesticides and PCBs data were categorized into four categories: below the detection limit, less than the 25$^{th}$ percentile of all samples with detectible levels, 25$^{th}$ to 50$^{th}$ percentile and ≥50 percentile. Samples reported as "below detectable limit" and serum concentrations less than 25$^{th}$ percentile were combined and regarded as the reference group.

Because many of the PCB congeners were below the detection limit in a high number of samples, we limited our analysis to seven PCBs, seven chlorinated pesticides, and 2,3,7,8-tetrachlorodibenzodioxin (TCDD), the most potent of the dioxins in activation of the AhR. PCBs 52, 66 and 74 all have four chlorines, and are less persistent but more volatile than those congeners with more chlorines. Therefore inhalation is an important route of exposure to those PCBs. PCB 118 is a monoortho, five chlorine congener which has mixed activity. It is a relatively weak agonist

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of the AhR (toxic equivalent value of 0.00003 relative to TCDD) but also has additional action via other pathways. PCBs 153 and 180, with six and seven chlorines, respectively, have no agonist activity at the AhR but induce genes via other pathways. PCB 169 (listed as HXC in NHANES) is a co-planar congener PCB whose only known action is as an agonist of the AhR with a toxic equivalency of 0.03 relative to TCDD.

We used logistic regression models to calculate multivariate-adjusted odd ratios (ORs) and 95% confidence intervals (CIs). All analyses were performed separately in men and women. Adjusting variables were age (years), race/ethnicity, poverty income ratio, body mass index, and cigarette smoking. We performed all statistical analyses with SAS 9.1.

**Results**

Table 1 presents the information about the population within NHANES for which we have complete information about self-reported arthritis as well as serum measurement of selected PCB congeners, pesticides and TCDD. As we have previously reported[8], females (8.52%) were more likely to have rheumatoid arthritis compared to males (5.51%). Similarly, a higher proportion of women (12.1%) had osteoarthritis compared to men (6.94%). The table show that rheumatoid arthritis and osteoarthritis were more prevalent amongst older adults aged 70 years and above. The likelihood of having any arthritis, RA or OA, increased with age. A higher proportion of non-Hispanic blacks (10.77%) had RA compared to other racial groups while non-Hispanic whites had the higher proportion of OA (14.21%). Current smokers were more likely to have any arthritis, RA or OA compared to non-smokers. Being overweight or obese was associated with an increased risk of RA or OA.

Table 1. Characteristics of the Study Sample:

| Characteristics | No Arthritis | | Any Arthritis | | Rheumatoid Arthritis (RA) | | Osteoarthritis (OS) | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| **Gender** | | | | | | | | |
| Male | 1731 | 78.4 | 477 | 21.6 | 101 | 5.51 | 129 | 6.94 |
| Female | 1772 | 70.94 | 726 | 29.06 | 165 | 8.52 | 244 | 12.1 |
| **Age** | | | | | | | | |
| 20-49 | 2221 | 90.14 | 243 | 9.86 | 56 | 2.46 | 58 | 2.54 |
| 50-59 | 416 | 68.76 | 189 | 31.24 | 45 | 9.76 | 50 | 10.73 |
| 70+ | 866 | 52.9 | 771 | 47.1 | 165 | 16 | 265 | 23.43 |
| **Race** | | | | | | | | |
| Mexican American | 1018 | 80.79 | 242 | 19.21 | 67 | 6.18 | 51 | 4.77 |
| Non-H-White | 1673 | 70.44 | 702 | 29.56 | 107 | 6.01 | 277 | 14.21 |
| Non-H-Black | 663 | 75 | 221 | 25 | 80 | 10.77 | 36 | 5.15 |
| Others-Multi Racial | 149 | 79.68 | 38 | 20.32 | 12 | 7.45 | 9 | 5.7 |
| **Smoking status** | | | | | | | | |
| Current-smoker | 1625 | 70.22 | 689 | 29.78 | 167 | 9.32 | 197 | 10.81 |
| Non-smoker | 1874 | 78.48 | 514 | 21.52 | 99 | 5.02 | 176 | 8.59 |
| **Poverty income** | | | | | | | | |
| 1 to 2x poverty | 1415 | 72.68 | 532 | 27.32 | 145 | 9.29 | 143 | 9.18 |
| 2 to 3x poverty | 512 | 74.85 | 172 | 25.15 | 39 | 7.08 | 47 | 8.41 |
| 3+ poverty | 1253 | 76.22 | 391 | 23.78 | 64 | 4.86 | 160 | 11.32 |
| **BMI** | | | | | | | | |
| Normal (18.5-24.9) | 1224 | 81.27 | 282 | 18.73 | 54 | 4.23 | 97 | 7.34 |
| Overweight (25-29.9) | 1178 | 73.95 | 415 | 26.05 | 87 | 6.88 | 132 | 10.08 |
| Obese (≥30) | 979 | 68.56 | 449 | 31.44 | 109 | 10.02 | 129 | 11.64 |

Table 2 presents adjusted odds ratios for selected PCB congeners (those for which most samples had concentrations above the detection limit) and all forms of arthritis. For males there were no significant associations between arthritis and the lower chlorinated congeners, PCBs 52, 66, and 74 nor the dioxin-like congener, PCB 118. However there were significant associations for the more highly chlorinated PCBs 153 and 180. For females all of the congeners showed some statistically significant associations, although the ORs for the more highly chlorinated congeners were not higher than those seen in males.

Table 2: Relationships between reporting have any arthritis and selected PCB congeners

| **Analyte** | **Non-detectable < 25th %*** Cases/participants (no.) Adjusted OR (95% CI) | **25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) |
|---|---|---|---|
| **Males** | | | |
| PCB 52 | 259/1223 | 40/151 | 95/407 |
| | Referent | 1.18 (0.76-1.84) | 0.97 (0.71-1.32) |
| PCB 66 | 275/1372 | 28/163 | 113/387 |
| | Referent | 0.82 (0.51-1.32) | 1.22 (0.91 -1.64) |
| PCB 74 | 74/710 | 35/199 | 309/1021 |
| | Referent | 1.4 (0.86-2.25) | 1.34 (0.93-1.93) |
| PCB 118 | 74/646 | 45/253 | 296/1030 |
| | Referent | 1.4 (0.89-2.2) | 1.25 (0.88-1.8) |
| PCB 153 | 36/464 | 54/353 | 328/1117 |
| | Referent | 2.1 (1.26-3.45) | 1.94 (1.22-3.1) |
| PCB 180 | 17/434 | 53/379 | 349/1123 |
| | Referent | 4.01 (2.18-7.4) | 4.53 (2.5-8.21) |
| **Females** | | | |
| PCB 52 | 411/1438 | 56/173 | 153/396 |
| | Referent | 1.55 (1.03-2.33) | 1.71 (1.32-2.23) |
| PCB 66 | 396/1516 | 35/154 | 226/488 |
| | Referent | 1.13 (0.72-1.8) | 1.72 (1.32-2.23) |
| PCB 74 | 45/643 | 29/194 | 555/1329 |
| | Referent | 2.41 (1.40-4.14) | 3.44 (2.33-5.2) |
| PCB 118 | 54/593 | 41/263 | 535/1308 |
| | Referent | 1.77 (1.09-2.86) | 2.31 (1.58-3.39) |
| PCB 153 | 48/629 | 81/395 | 503/1143 |
| | Referent | 2.75 (1.8-4.21) | 2.93 (1.96-4.4) |
| PCB 180 | 42/671 | 108/472 | 478/1017 |
| | Referent | 3.24 (2.12-4.94) | 4.2 (2.7-6.5) |

Table 3 shows similar results but only for those individuals who report having rheumatoid arthritis. There was no significant association with any congener in males, but some very elevated and significant associations in females. Both PCBs 74 and 118 showed significant associations when comparing the reference group (undetectable and < than the 25h percentile) to those > than the 50$^{th}$ percentile. A dose-dependent increase in ORs is seen for PCBs 153 and 180 in females.

Table 3: Self-reported rheumatoid arthritis in relation to concentrations of selected PCB congeners:

| **Analyte** | **Non-detectable < 25th %*** Cases/participants (no.) Adjusted OR (95% CI) | **25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) |
|---|---|---|---|
| **Males** | | | |
| PCB 52 | 58/1022 | 8/119 | 19/331 |

| | | | |
|---|---|---|---|
| | Referent | 1.21 (0.54-2.70) | 0.798 (0.44 -1.44) |
| PCB 66 | 61/1158 | 7/142 | 19/293 |
| | Referent | 0.931 (0.40-2.15) | 0.80 (0.44-1.47) |
| PCB 74 | 18/654 | 8/172 | 61/773 |
| | Referent | 0.99 (0.4-2.47) | 0.82 (0.42-1.60) |
| PCB 118 | 17/589 | 12/220 | 57/791 |
| | Referent | 1.37 (0.62-3.03) | 0.75 (0.39-1.43) |
| PCB 153 | 7/435 | 9/308 | 71/860 |
| | Referent | 1.33 (0.50-3.72) | 1.53 (0.61-3.84) |
| PCB 180 | 5/422 | 7/333 | 75/849 |
| | Referent | 1.60 (0.50-5.17) | 2.63 (0.91-7.62) |
| **Female** | | | |
| PCB 52 | 97/1124 | 12/129 | 26/287 |
| | Referent | 1.23 (0.60-2.54) | 1.05 (0.62-1.80) |
| PCB 66 | 94/1241 | 4/123 | 44/306 |
| | Referent | 0.5 (0.17-1.46) | 1.50 (0.95-2.34) |
| PCB 74 | 12/610 | 6/171 | 125/899 |
| | Referent | 2.24 (0.73-6.90) | 5.80 (2.35-10.95) |
| PCB 118 | 17/556 | 6/228 | 119/892 |
| | Referent | 1.08 (0.34-2.95) | 2.55 (1.30-5.03) |
| PCB 153 | 12/593 | 20/334 | 111/751 |
| | Referent | 3.40 (1.50-7.81) | 4.23 (1.90-9.40) |
| PCB 180 | 10/639 | 23/387 | 108/647 |
| | Referent | 4.04 (1.73-9.42) | 7.06 (3.00-16.60) |

Table 4 shows similar results for osteoarthritis. Among males only PCB 180 showed dose-dependent, statistically significant ORs. For females there were significant ORs in the highest exposure category for PCBs 66 and 74, and dose-dependent significant association for PCB 180.

Table 4: Self-reported osteoarthritis in relation to concentrations of selected PCB congeners

| **Analyte** | **Non-detectable < 25th %*** Cases/participants (no.) Adjusted OR (95% CI) | **25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) |
|---|---|---|---|
| **Males** | | | |
| PCB 52 | 67/1031 | 14/125 | 26/338 |
| | Referent | 1.39 (0.69-2.77) | 0.98 (0.59-1.64) |
| PCB 66 | 71/1168 | 7/142 | 35/309 |
| | Referent | 0.77 (0.33-1.81) | 1.41 (0.87-2.28) |
| PCB 74 | 13/649 | 8/172 | 92/804 |
| | Referent | 2.10 (0.76-5.76) | 2.20 (0.98-4.86) |
| PCB 118 | 13/585 | 12/220 | 87/821 |
| | Referent | 2.34 (0.93-5.91) | 2.06 (0.95-4.46) |
| PCB 153 | 7/435 | 13/312 | 93/882 |
| | Referent | 2.57 (0.87-7.58) | 2.22 (0.81-6.11) |
| PCB 180 | 4/421 | 10/336 | 99/873 |
| | Referent | 3.60 (0.96-13.50) | 3.79 (1.05-13.63) |
| **Female** | | | |
| PCB 52 | 136/1163 | 19/136 | 52/313 |
| | Referent | 1.58 (0.87-2.86) | 1.28 (0.85-1.94) |
| PCB 66 | 110/1257 | 10/129 | 91/353 |
| | Referent | 1.10 (0.52-2.25) | 2.02 (1.40-2.91) |
| PCB 74 | 14/612 | 9/174 | 187/961 |

| | | | |
|---|---|---|---|
| | Referent | 1.87 (0.76-4.57) | 2.07 (1.04-4.11) |
| PCB 118 | 15/554 | 14/236 | 182/955 |
| | Referent | 1.67 (0.75-3.71) | 1.75 (0.91-3.39) |
| PCB 153 | 14/595 | 24/338 | 173/813 |
| | Referent | 1.88 (0.92-3.84) | 1.93 (0.97-3.87) |
| PCB 180 | 12/641 | 31/395 | 168/707 |
| | Referent | 2.30 (1.11-4.75) | 2.96 (1.40-6.26) |

Table 5 shows results for pesticides and any arthritis, osteoarthritis and rheumatoid arthritis in males. Exposure to MIR (≥50 percentile), OXY, and TNA in males was associated with an increased risk of any kind of arthritis, but there were no significant associations for either osteo- or rheumatoid arthritis.

Table 5: Relationships between concentrations of selected pesticides and arthritis in males

| **Male Analyte** | ANY ARTHRITIS | | OA | | RA | |
|---|---|---|---|---|---|---|
| | **Non-detectable < 25th % Vs. 25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable < 25th % Vs. ≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable < 25th % Vs. 25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable < 25th % Vs. ≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable < 25th % Vs. 25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable < 25th % Vs. ≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) |
| **BHC** | 42/161 | 57/211 | 13/132 | 21/175 | 3/122 | 7/161 |
| | 1.392 (0.762-2.546) | 1.377 (0.74-2.563) | 2.006 (0.637-6.318) | 2.579 (0.811-8.201) | 0.158 (0.027-0.927) | 0.201 (0.041-0.97) |
| **HPE** | 41/194 | 103/309 | 11/164 | 24/230 | 5/158 | 23/229 |
| | 1.063 (0.662 -1.705) | 1.441 (0.956-2.174) | 0.856 (0.352-2.086) | 1.113 (0.526-2.351) | 0.488 (0.171-1.39) | 1.007 (0.475-2.135) |
| **HXC** | 78/344 | 249/779 | 21/287 | 70/600 | 11/277 | 58/588 |
| | 1.528 (0.864-2.678) | 1.397 (0.923-2.114) | 1.95 (0.803-4.737) | 1.646 (0.699-3.875) | 0.984 (0.386-2.508) | 1.471 (0.644-3.357) |
| **MIR** | 26/95 | 60/191 | 7/76 | 14/145 | 8/77 | 18/149 |
| | 1.521 (0.864-2.678) | 1.656 (1.069-2.566) | 1.96 (0.782-4.911) | 1.172 (0.542-2.535) | 2.32 (0.918-5.86) | 1.862 (0.847-4.095) |
| **OXY** | 52/249 | 152/466 | 15/212 | 39/353 | 11/208 | 32/346 |
| | 1.752 (1.035-2.964) | 1.874 (1.115-3.149) | 1.771 (0.596-5.263) | 1.53 (0.527-4.414) | 1.594 (0.571-4.447) | 1.308 (0.467-3.663) |
| **PDE** | 79/376 | 465/617 | 23/320 | 40/505 | 19/316 | 33/498 |
| | 1.551 (0.94-2.56) | 1.124 (0.667-1.893) | 1.413 (0.561-3.561) | 0.866 (0.34-2.206) | 1.467 (0.568-3.79) | 0.699 (0.256-1.912) |
| **PDT** | 37/121 | 38/177 | 9/93 | 7/146 | 11/95 | 9/148 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 0.994 (0.413-2.393) | 0.824 (0.326-2.082) | 1.082 (0.645-1.816) | 0.842 (0.509-1.395) | 1.082 (0.437-2.683) | 0.812 (0.331-1.991) |
| **TNA** | 51/278 | 184/611 | 16/243 | 49/476 | 11/238 | 39/466 |
| | 1.89 (1.066-3.353) | 2.173 (1.239-3.81) | 2.037 (0.591-7.019) | 1.867 (0.553-6.299) | 1.351 (0.466-3.911) | 1.018 (0.347-2.989) |

Table 6 shows results for pesticides in females. There were statistically-significant associations among women reporting that they had any form of arthritis and BHC, HPE, HXE, OXY and TNA.

Only exposure to OXY (≥50 percentile) was significantly associated with an increased risk of rheumatoid arthritis. The risk of osteoarthritis was significantly higher in women in relation to concentrations of BHC, HPE (≥50 percentile), OXY and TNA.

Table 6: Pesticides concentrations in women and self-reported prevalence of arthritis:

| **Female Analyte** | ANY ARTHRITIS | | OA | | RA | |
|---|---|---|---|---|---|---|
| | **Non-detectable < 25th % Vs. 25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable < 25th % Vs. ≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable < 25th % Vs. 25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable < 25th % Vs. ≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable < 25th % Vs. 25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable < 25th % Vs. ≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) |
| **BHC** | 33/121 | 138/348 | 12/100 | 46/256 | 5/93 | 29/239 |
| | 2.538 (1.352-4.763) | 1.935 (1.042-3.593) | 3.41 (1.282-9.069) | 3.046 (1.146-8.098) | 2.117 (0.616-7.273) | 1.819 (0.564-5.838) |
| **HPE** | 50/167 | 180/400 | 11/128 | 57/277 | 13/130 | 45/265 |
| | 1.528 (0.964-2.422) | 1.752 (1.208-2.54) | 1.15 (0.53-2.489) | 1.754 (1.001-3.072) | 1.256 (0.566-2.784) | 1.599 (0.848-3.015) |
| **HXC** | 129/376 | 330/665 | 38/285 | 123/458 | 32/279 | 66/401 |
| | 1.847 (1.308-2.609) | 1.727 (1.213-2.458) | 1.567 (0.887-2.768) | 1.457 (0.825-2.574) | 1.751 (0.969-3.162) | 1.505 (0.807-2.807) |
| **MIR** | 27/83 | 60/147 | 9/65 | 18/105 | 7/63 | 16/103 |
| | 0.786 (0.426-1.451) | 1.263 (0.798-2) | 0.947 (0.385-2.329) | 1.25 (0.639-2.443) | 0568 (0.196-1.645) | 1.006 (0.472-2.145) |
| **OXY** | 64/258 | 253/566 | 21/215 | 79/392 | 14/208 | 65/378 |
| | 2.793 (1.692-4.611) | 3.737 (2.27-6.151) | 4.567 (1.82-11.458) | 5.667 (2.245-14.302) | 1.986 (0.794-4.958) | 3.96 (1.632-9.302) |
| **PDE** | 66/328 | 290/789 | 25/287 | 88/587 | 17/279 | 71/570 |
| | 1.193 (0.746-1.191) | 1.464 (0.925-2.317) | 1.451 (0.658-3.201) | 1.871 (0.843-4.154) | 0.86 (0.371-1.998) | 0.733 (0.317-1.692) |
| **PDT** | 41/147 | 132/337 | 17/123 | 35/240 | 8/114 | 39/244 |
| | 0.74 (0.458-1.195) | 1.51 (0.771-1.719) | 1.157 (0.585-2.287) | 1.669 (0.891-3.124) | 0.472 (0.193-1.157) | 1.202 (0.626-2.31) |
| **TNA** | 87/352 | 277/651 | 29/294 | 86/460 | 18/283 | 75/449 |
| | 1.929 (1.211-3.07) | 2.454 (1.53-3.992) | 2.311 (1.039-5.1139) | 2.933 (1.307-6.584) | 1.362 (0.581-3.195) | 2.035 (0.887-4.67) |

Table 7 shows results for TCDD and PCB 169, a dioxin-like PCB, in males and females. In the highest exposed category there are significant associations for both males and females for TCDD. For PCB 169 there were no significant associations

in males, but there were in females but only for any arthritis, not either OA or RA.

Table 7: Associations between self-reported prevalence of any kind of arthritis, osteoarthritis and rheumatoid arthritis in relation to serum concentration of TCDD and PCB 169 in males and females.

| | **ANY ARTHRITIS** | | **OA** | | **RA** | |
|---|---|---|---|---|---|---|
| **Analyte** | **Non-detectable >25th % Vs. 25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable >25th % Vs. ≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable >25th % Vs. 25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable >25th % Vs. ≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable >25th % Vs. 25th% to 50th%** Cases/participants (no.) Adjusted OR (95% CI) | **Non-detectable >25th % Vs. ≥ 50th%** Cases/participants (no.) Adjusted OR (95% CI) |
| Males TCDD | 25/81<br>1.219 (0.712-2.086) | 68/162<br>1.631 (1.095-2.428) | 9/65<br>1.502 (0.674-3.352) | 22/116<br>1.982 (1.082-3.631) | 3/59<br>0.682 (0.2 -2.313) | 9/103<br>0.933 (0.429-2.029) |
| Females TCDD | 36/83<br>1.968 (1.173-3.3) | 176/311<br>1.626 (1.188-2.227) | 9/56<br>1.415 (0.619-3.234) | 71/206<br>1.997 (1.307-3.051) | 12/59<br>2.405 (1.137-5.085) | 30/165<br>1.262 (0.735-2.166) |

**Discussion**

These results add to the body of evidence that implicates exposure to persistent organic pollutants (POPs) as being risk factor for the development of arthritis. Of the non-coplanar PCBs studied, the more highly chlorinated congeners showed stronger associations than those with fewer chlorines, and associations were stronger in females than males and generally for RA than for OA. But there were some significant associations for OA in males. For example, PCB 180, a very highly chlorinated congener, showed an OR=3.79 in males but the OR was 2.96 in females.

There are three analytes with dioxin-like activity. The most potent is TCDD, which showed significant associations of about equal magnitude in both males and females for OA (with ORs less than 2.0) and in females for RA for one level of measurement. PCB 169 is a coplanar PCB with no known mechanism of action other than binding to and activating the Ah receptor. PCB 169 showed no significant results in males, and was significant in females only for all arthritis, not either OA or RA. PCB 118 is a mixed congener, having some activity at the AhR but also having other types of activity. There were significant ORs for PCB 118 for any arthritis and for RA in females but not in males.

The results with the pesticides are of interest for both hose compounds that were possibility associated with arthritis and especially for those that were not. There was no association with DDE or DDT, in spite of the fact that these chemicals are present in most people at much higher concentrations than any other pesticide and total PCB concentrations.[25] βHCCH, HPE, OXY and TNA all showed some positive associations, and these were stronger in females and males. The strongest and most consistent associations were for OXY and TNA, with some ORs above 5.0.

Our results are in general agreement with those of Lee et al. (2007) who reported on associations between PCBs and chlorinated pesticides with RA and OA using the 1999-2002 NHANES data. They reported significant associations, stronger for RA than for OA, for both dioxin-like and non-dioxin-like PCBs with weak associations with pesticides. They also found associations to be stronger in women than men. Our results are similar but not identical, as expected since we now have additional data from the 2004

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NHANES and have used similar but slightly different ways of dealing with the exposure variables.

We report a clear association between RA and more highly chlorinated PCB congeners in females but only non-significant associations in males. There was little indication of an association between levels of lower chlorinated congeners (PCBs 52 and 66), which are more volatile and water soluble than those with more chorines. Their presence is often taken to reflect inhalation as the route of exposure.[26] However, PCB 74, with four chlorines, did show a significant OR of 5.80 in the highest exposure category. The other three congeners, PCBs 118, 163 and 189, all showed significant associations and they increased with level of chlorination. The more highly chlorinated congeners are more persistent and their presence usually reflects ingestion as the primary route of exposure. [27] [17] The differences between males and females were less remarkable for OA as compared to RA. The associations were significant only for PCB 180 in both males and females. But the OR in males in the highest exposure category was even higher than that in females.

The patterns seen for all arthritis are very similar to those for OA and RA. This category includes all NHANES individuals who had arthritis but did not identify which kind, as well as the relatively few who reported psoriatic and injury-induced arthritis. While we assume that that majority of those with an unknown type of arthritis have OA we have no additional information.

As reported by Lee et al, the associations between both RA and OA with chlorinated pesticides are much weaker, especially for RA. However, all but two of the pesticides showed significant associations with the "all arthritis" category and four showed associations with OA but only one with RA. This result is consistent with our expectation that the majority of those with arthritis but who are uncertain of which kind actually have OA.

There were two accidental episodes of contamination of cooking oil with PCBs that had been heated, resulting in the additional formation of dibenzofurans. In survivors of these exposures, arthritis was found to be more frequent in exposed persons than controls in both the 1968 Yusho episode in Japan [28] and the 1979 Yu-Cheng episode in Taiwan.[29] These reports do not identify which type of arthritis. Li et al. (2013) have reported on all causes of mortality in the YuCheng cohort, and found an SMR = 6.4 (95% CI = 2.8=12.7). [30]

Given the very different etiologies of RA and OA, it is at first glance surprising that both forms of arthritis are vulnerable to exposure to POPs. While the patterns of associations are not identical they are similar. There is a major role of inflammation that is central to both forms of arthritis. Azamar-Llamas et al have noted that OA can also be detected in no-weight-bearing joints, and attribute this to effects of adipokines on cartilage homeostasis[31]. Proinflammatory adipokines are well-known to be components of autoimmune rheumatic disease.[5] There is evidence that C-reactive protein levels are higher in women than in men [32] and in blacks than in whites.[33] Furthermore, adiposity is independently associated with elevated levels of C reactive protein.[34] These patterns of inflammation may well be the basis of the sex, racial and BMI differences seen in both forms of arthritis.

The mechanisms whereby POPs influence the prevalence of OA and RA are uncertain, but there are a number of clues. Most POPs bind to and activate several different kinds of nuclear receptors.[35] [36] [37] [38] The best studied is the aryl hydrocarbon receptor (AhR), which is activated by TCDD and coplanar and some mono-ortho PCBs, such as PCB 118. [39] [40] Activation of these nuclear receptors induce many different genes controlling a great variety of physiological functions. Kobayashi et al. have identified the AhR in human synovial tissue from RA and OA patients, and found expression to be greater in rheumatoid tissue. [21]

The dioxin-like PCB 126 has been reported to induce apoptosis of chrondrocytes via generation of reactive oxygen species [21]. Abella et al. have

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found that non-dioxin-like PCBs also can induce chondrocyte cell death through oxidative stress. [20]

Our study has several strengths and several notable weaknesses. The NHANES is a random samples of the US population with some oversampling of specific groups, and the chemical analysis of POPs is a major strength, given the expense and difficulty of obtaining such information in a smaller study. Unfortunately, the more recent NHANES data presents only POPs analysis of pooled serum samples, and so these results are limited to the NHANES data from 2004 and earlier. There are also limitations within these data. Many individual chemicals were present in concentrations below the detection limits. Furthermore, the detection limit was often influenced by the quantity of serum available for analysis. This results in the fact that having a result of below the detection limit may mean either that the concentration of the chemical was low, or that the volume of serum available for analysis was too little. Thus, some samples reported as being below the detection limit may actually have contained high concentrations but they were not detected only because of the size of the serum sample. However, in spite of these limitations, positive findings are unlikely to be artifactual. Indeed, it is likely that positive findings are an underestimation of the true associations because of these limitations.

These results add to the body of knowledge showing that exposure to the various POPs has impact on a great variety of human diseases.

**Conflict of Interest**

The authors report no conflicts of interest. The project was supported by internal funds of the Institute for Health and the Environment, University at Albany. We are grateful for helpful discussions and advice from Profs. Louise-Anne McNutt and Victoria Lazariu. We also thank Dr. Duk-Hee Lee for sharing her SAS code with us in order to compare our results with hers.

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**References**


1. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017 [published correction appears in Lancet. 2019 Jun 22;393(10190):e44]. Lancet. 2018;392(10159):1859-1922. doi:10.1016/S0140-6736(18)32335-3
2. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1323-1330. doi:10.1136/annrheumdis-2013-204763
3. GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet. 2015;386(10009):2145-2191. doi:10.1016/S0140-6736(15)61340-X
4. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res. 2018;6:15. Published 2018 Apr 27. doi:10.1038/s41413-018-0016-9
5. Medina G, Vera-Lastra O, Peralta-Amaro AL, et al. Metabolic syndrome, autoimmunity and rheumatic diseases. Pharmacol Res. 2018;133:277-288. doi:10.1016/j.phrs.2018.01.009
6. Hartz AJ, Fischer ME, Bril G, et al. The association of obesity with joint pain and osteoarthritis in the NHANES data. J Chronic Dis. 1986;39(4):311-319. doi:10.1016/0021-9681(86)90053-6
7. Gremese E, Tolusso B, Gigante MR, Ferraccioli G. Obesity as a risk and severity factor in rheumatic diseases (autoimmune chronic inflammatory diseases). Front Immunol. 2014;5:576. Published 2014 Nov 11. doi:10.3389/fimmu.2014.00576
8. Mohammed A, Alshamarri T, Adeyeye T, Lazariu V, McNutt LA, Carpenter DO. A comparison of risk factors for osteo- and rheumatoid arthritis using NHANES data. Prev Med Rep. 2020;20:101242. Published 2020 Nov 5. doi:10.1016/j.pmedr.2020.101242.
9. MacDonald IJ, Liu SC, Huang CC, Kuo SJ, Tsai CH, Tang CH. Associations between adipokines in arthritic disease and implications for obesity. Int J Mol Sci. 2019;20(6):1505. Published 2019 Mar 26. doi:10.3390/ijms20061505
10. Haugen IK, Magnusson K, Turkiewicz A, Englund M. The prevalence, incidence, and progression of hand osteoarthritis in relation to body mass index, smoking, and alcohol consumption. J Rheumatol. 2017;44(9):1402-1409. doi:10.3899/jrheum.170026
11. Stolt P, Bengtsson C, Nordmark B, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. Ann Rheum Dis. 2003;62(9):835-841. doi:10.1136/ard.62.9.835
12. Farhat SC, Silva CA, Orione MA, Campos LM, Sallum AM, Braga AL. Air pollution in autoimmune rheumatic diseases: a review. Autoimmun Rev. 2011;11(1):14-21. doi:10.1016/j.autrev.2011.06.008
13. Hart JE, Laden F, Puett RC, Costenbader KH, Karlson EW. Exposure to traffic pollution and increased risk of rheumatoid arthritis. Environ Health Perspect. 2009;117(7):1065-1069. doi:10.1289/ehp.0800503
14. Gan RW, Deane KD, Zerbe GO, et al. Relationship between air pollution and positivity of RA-related autoantibodies in individuals without established RA: a report on SERA. Ann Rheum Dis. 2013;72(12):2002-2005. doi:10.1136/annrheumdis-2012-202949
15. De Roos AJ, Koehoorn M, Tamburic L, Davies HW, Brauer M. Proximity to traffic, ambient air pollution, and community noise in relation to incident rheumatoid arthritis. Environ Health Perspect. 2014;122(10):1075-1080. doi:10.1289/ehp.1307413

16. Hart JE, Källberg H, Laden F, et al. Ambient air pollution exposures and risk of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013;65(7):1190-1196. doi:10.1002/acr.21975
17. Carpenter DO. Polychlorinated biphenyls (PCBs): routes of exposure and effects on human health. Rev Environ Health. 2006;21(1):1-23. doi:10.1515/reveh.2006.21.1.1
18. Lan SJ, Yen YY, Lan JL, Chen ER, Ko YC. Immunity of PCB transplacental Yu-Cheng children in Taiwan. Bull Environ Contam Toxicol. 1990;44(2):224-229. doi:10.1007/BF01700140
19. Guo, Y. L. L., Yu, M. L., Hsu, C. C., & Rogan, W. J. (1999). Chloracne, goiter, arthritis, and anemia after polychlorinated biphenyl poisoning: 14-year follow-up of the Taiwan Yucheng cohort. Environmental Health Perspectives, 107(9), 715-719. doi:Doi 10.2307/3434656
20. Abella V, Santoro A, Scotece M, et al. Non-dioxin-like polychlorinated biphenyls (PCB 101, PCB 153 and PCB 180) induce chondrocyte cell death through multiple pathways. Toxicol Lett. 2015;234(1):13-19. doi:10.1016/j.toxlet.2015.02.001
21. Lee HG, Yang JH. PCB126 induces apoptosis of chondrocytes via ROS-dependent pathways. Osteoarthritis Cartilage. 2012;20(10):1179-1185. doi:10.1016/j.joca.2012.06.004
22. Kobayashi S, Okamoto H, Iwamoto T, et al. A role for the aryl hydrocarbon receptor and the dioxin TCDD in rheumatoid arthritis. Rheumatology (Oxford). 2008;47(9):1317-1322. doi:10.1093/rheumatology/ken259
23. Lee DH, Steffes M, Jacobs DR. Positive associations of serum concentration of polychlorinated biphenyls or organochlorine pesticides with self-reported arthritis, especially rheumatoid type, in women. Environ Health Perspect. 2007;115(6):883-888. doi:10.1289/ehp.9887
24. Turner W., DiPietro E., Lapeza C., Green V., Gill J., Patterson, D.G. , Jr. A fast universal automated cleanup system for the isotope-dilution highresolution mass spectrometric analysis of pcdds, pcdfs, coplanar pcbs, pcb congeners, and persistent pesticides from the same serum sample. Organohalogen compounds 31: 26-31 (1997).
25. Patterson DG Jr, Wong LY, Turner WE, et al. Levels in the U.S. population of those persistent organic pollutants (2003-2004) included in the Stockholm Convention or in other long range transboundary air pollution agreements. Environ Sci Technol. 2009;43(4):1211-1218. doi:10.1021/es801966w
26. Carpenter DO. Exposure to and health effects of volatile PCBs. Rev Environ Health. 2015;30(2):81-92. doi:10.1515/reveh-2014-0074
27. ATSDR, Thallium. "ATSDR (Agency for toxic substances and disease registry)." Prepared by clement international corp., under contract 205 (2000): 88-0608.
28. Kanagawa Y, Matsumoto S, Koike S, et al. Association of clinical findings in Yusho patients with serum concentrations of polychlorinated biphenyls, polychlorinated quarterphenyls and 2,3,4,7,8-pentachlorodibenzofuran more than 30 years after the poisoning event. Environ Health. 2008;7:47. Published 2008 Oct 2. doi:10.1186/1476-069X-7-47
29. Guo YL, Yu ML, Hsu CC, Rogan WJ. Chloracne, goiter, arthritis, and anemia after polychlorinated biphenyl poisoning: 14-year follow-Up of the Taiwan Yucheng cohort. Environ Health Perspect. 1999;107(9):715-719. doi:10.1289/ehp.99107715
30. Li MC, Tsai PC, Chen PC, Hsieh CJ, Leon Guo YL, Rogan WJ. Mortality after exposure to polychlorinated biphenyls and dibenzofurans: 30 years after the "Yucheng accident". Environ Res. 2013;120:71-75. doi:10.1016/j.envres.2012.09.003
31. Azamar-Llamas D, Hernández-Molina G, Ramos-Ávalos B, Furuzawa-Carballeda J. Adipokine contribution to the pathogenesis of osteoarthritis. Mediators Inflamm. 2017;2017:5468023. doi:10.1155/2017/5468023
32. Valentine, R. J., Vieira, V. J., Woods, J. A., & Evans, E. M. (2009). Stronger relationship between central adiposity and C-reactive protein in older women than men. *Menopause*, *16*(1), 84-89
33. Khera A, McGuire DK, Murphy SA, et al. Race and gender differences in C-reactive protein levels. J Am Coll Cardiol. 2005;46(3):464-469. doi:10.1016/j.jacc.2005.04.051
34. Giles JT, Bartlett SJ, Andersen R, Thompson R, Fontaine KR, Bathon JM. Association of body fat

with C-reactive protein in rheumatoid arthritis. Arthritis Rheum. 2008;58(9):2632-2641. doi:10.1002/art.23766.

35. Tabb MM, Kholodovych V, Grün F, Zhou C, Welsh WJ, Blumberg B. Highly chlorinated PCBs inhibit the human xenobiotic response mediated by the steroid and xenobiotic receptor (SXR). *Environ Health Perspect*. 2004;112(2):163-169. doi:10.1289/ehp.6560
36. Al-Salman F, Plant N. Non-coplanar polychlorinated biphenyls (PCBs) are direct agonists for the human pregnane-X receptor and constitutive androstane receptor, and activate target gene expression in a tissue-specific manner. Toxicol Appl Pharmacol. 2012;263(1):7-13. doi:10.1016/j.taap.2012.05.016
37. Kamata R, Shiraishi F, Kageyama S, Nakajima D. Detection and measurement of the agonistic activities of PCBs and mono-hydroxylated PCBs to the constitutive androstane receptor using a recombinant yeast assay. Toxicol In Vitro. 2015;29(7):1859-1867. doi:10.1016/j.tiv.2015.07.021
38. Kamata R, Nakajima D, Shiraishi F. Measurement of the agonistic activities of monohydroxylated polychlorinated biphenyls at the retinoid X and retinoic acid receptors using recombinant yeast cells. Toxicol In Vitro. 2019;57:9-17. doi:10.1016/j.tiv.2019.01.022
39. Johnson CD, Balagurunathan Y, Tadesse MG, et al. Unraveling gene-gene interactions regulated by ligands of the aryl hydrocarbon receptor. Environ Health Perspect. 2004;112(4):403-412. doi:10.1289/ehp.6758
40. Maier MS, Legare ME, Hanneman WH. The aryl hydrocarbon receptor agonist 3,3',4,4',5-pentachlorobiphenyl induces distinct patterns of gene expression between hepatoma and glioma cells: chromatin remodeling as a mechanism for selective effects. Neurotoxicology. 2007;28(3):594-612.