| Number of New Cases and Deaths Per 100,000 People (All Races, Females), Age-Adjusted |
| --- |
| **Year** | **New Cases - SEER 9**  | **New Cases - SEER 13** | **Deaths - US** |
| 1975 | 105.1 | - | 31.4 |
| 1976 | 101.9 | - | 31.8 |
| 1977 | 100.8 | - | 32.5 |
| 1978 | 100.6 | - | 31.7 |
| 1979 | 102.1 | - | 31.2 |
| 1980 | 102.3 | - | 31.7 |
| 1981 | 106.4 | - | 31.9 |
| 1982 | 106.5 | - | 32.2 |
| 1983 | 111.1 | - | 32.1 |
| 1984 | 116.0 | - | 32.9 |
| 1985 | 124.3 | - | 33.0 |
| 1986 | 126.9 | - | 32.9 |
| 1987 | 134.5 | - | 32.7 |
| 1988 | 131.3 | - | 33.2 |
| 1989 | 127.2 | - | 33.2 |
| 1990 | 131.9 | - | 33.1 |
| 1991 | 133.8 | - | 32.7 |
| 1992 | 132.1 | 130.0 | 31.6 |
| 1993 | 129.2 | 127.2 | 31.4 |
| 1994 | 131.0 | 128.8 | 30.9 |
| 1995 | 132.6 | 130.9 | 30.6 |
| 1996 | 133.7 | 132.1 | 29.5 |
| 1997 | 138.0 | 136.0 | 28.2 |
| 1998 | 141.4 | 139.0 | 27.5 |
| 1999 | 141.5 | 138.5 | 26.6 |
| 2000 | 136.5 | 134.2 | 26.6 |
| 2001 | 138.8 | 135.8 | 26.0 |
| 2002 | 135.7 | 132.7 | 25.6 |
| 2003 | 126.9 | 124.0 | 25.3 |
| 2004 | 128.0 | 124.8 | 24.5 |
| 2005 | 126.5 | 124.3 | 24.1 |
| 2006 | 126.1 | 122.7 | 23.6 |
| 2007 | 128.1 | 125.9 | 23.0 |
| 2008 | 128.1 | 126.0 | 22.6 |
| 2009 | 130.5 | 127.4 | 22.2 |
| 2010 | 126.5 | 122.9 | 21.9 |
| 2011 | 129.6 | 126.2 | - |

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| **Figure 1.5: Estimated Breast Cancer Incidence (New Cases) Rates among Women by State, 2006-2010**  |
| **State**  | **Rate of Invasive Breast Cancer (per 100,000 women)**  | **State**  | **Rate of Invasive Breast Cancer (per 100,000 women)**  |
| United States | 122 | Missouri | 122 |
| Alabama | 119 | Montana | 124 |
| Alaska | 128 | Nebraska | 122 |
| Arizona | 110 | Nevada | 113 |
| Arkansas | 110 | New Hampshire | 132 |
| California | 122 | New Jersey | 129 |
| Colorado | 125 | New Mexico | 109 |
| Connecticut | 136 | New York | 128 |
| Delaware | 127 | North Carolina | 125 |
| District of Columbia | 140 | North Dakota | 123 |
| Florida | 114 | Ohio | 121 |
| Georgia | 122 | Oklahoma | 122 |
| Hawaii | 123 | Oregon | 130 |
| Idaho | 120 | Pennsylvania | 126 |
| Illinois | 126 | Rhode Island | 131 |
| Indiana | 117 | South Carolina | 122 |
| Iowa | 123 | South Dakota | 118 |
| Kansas | 123 | Tennessee | 129 |
| Kentucky | 121 | Texas | 114 |
| Louisiana | 120 | Utah | 111 |
| Maine | 127 | Vermont | 131 |
| Maryland | 128 | Virginia | 125 |
| Massachusetts | 134 | Washington | 131 |
| Michigan | 120 | West Virginia | 110 |
| Minnesota | Not available | Wisconsin | 123 |
| Mississippi | 114 | Wyoming | 111 |
| Source: American Cancer Society, 2014 [[37](http://ww5.komen.org/BreastCancer/BreastFactsReferences.html)] |

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| http://ww5.komen.org/images/popup/spacer.gif | http://ww5.komen.org/images/popup/spacer.gif | http://ww5.komen.org/images/popup/spacer.gif |
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| EPIDEMIOLOGYExposure to polychlorinated biphenyl (PCB) congeners measured shortly after giving birth and subsequent risk of maternal breast cancer before age 50Barbara A. Cohn • Mary Beth Terry • Marj Plumb • Piera M. CirilloReceived: 24 July 2012/Accepted: 12 September 2012 The Author(s) 2012. This article is published with open access at Springerlink.comAbstract Discrete windows of susceptibility to toxicants have been identiﬁed for the breast, including in utero, puberty, pregnancy, and postpartum. We tested the hypothesis that polychlorinated biphenyls (PCBs) mea- sured during the early postpartum predict increased risk of maternal breast cancer diagnosed before age 50. We ana- lyzed archived early postpartum serum samples collected from 1959 to 1967, an average of 17 years before diagnosis (mean diagnosis age 43 years) for 16 PCB congeners in a nested case–control study in the Child Health and Devel- opment Studies cohort (N = 112 cases matched to controls on birth year). We used conditional logistic regression to adjust for lipids, race, year, lactation, and body mass. We observed strong breast cancer associations with three congeners. PCB 167 was associated with a lower risk (odds ratio (OR), 75th vs. 25th percentile = 0.2, 95 % conﬁ- dence interval (95 % CI) 0.1, 0.8) as was PCB 187 (OR, 75th vs. 25th percentile = 0.4, 95 % CI 0.1, 1.1). In con- trast, PCB 203 was associated with a sixfold increased risk (OR, 75th vs. 25th percentile = 6.3, 95 % CI 1.9, 21.7).The net association of PCB exposure, estimated by a post- hoc score, was nearly a threefold increase in risk (OR, 75th vs. 25th percentile = 2.8, 95 % CI 1.1, 7.1) among women with a higher proportion of PCB 203 in relation to the sum of PCBs 167 and 187. Postpartum PCB exposure likely also represents pregnancy exposure, and may predict increased risk for early breast cancer depending on the mixture that represents internal dose. It remains unclear whether individual differences in exposure, response to exposure, or both explain risk patterns observed.Keywords PCBs Polychlorinated biphenyls Breast cancer Pregnancy Postpartum Prospective HumanAbbreviations OR Odds ratio PCB(s) Polychlorinated biphenyl(s) 95 % CI 95 percent conﬁdence intervalIntroductionDiscrete windows of susceptibility to toxicants have been identiﬁed for the breast, including in utero, during puberty, and during pregnancy and postpartum [1–4]. Human studies of breast cancer have not been able to assess the effects of measured exposure to environmental chemicals during windows of susceptibility for the breast [2, 5]. The existing literature on polychlorinated biphenyls (PCBs) and breast cancer typically has focused primarily on postmen- opausal breast cancer [6–8]. In addition, exposure in prior studies was largely measured in middle age or at time of diagnosis, was variable on how PCBs were classiﬁed andB. A. Cohn (&) P. M. Cirillo Child Health and Development Studies, Public Health Institute, 1683 Shattuck Avenue, Ste. B, Berkeley, CA 94709, USA e-mail: bcohn@chdstudies.orgM. B. Terry Department of Epidemiology, Mailman School of Public Health of Columbia University, New York, NY, USAM. B. Terry Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY, USAM. Plumb Plumbline Coaching and Consulting, Inc., 2759 Park Street, Berkeley, CA 94702, USA123Breast Cancer Res Treat DOI 10.1007/s10549-012-2257-4whether individual congeners were considered, and was based on samples obtained after PCB use was regulated [6– 8].TheliteratureonthepesticideDDTandbreastcanceris subject to similar limitations [9]. Findings on the relation of PCBs measured in middle age to breast cancer are complex and have been reviewed previously in detail (see Table 3, pp. 2872–2876 in Brody et al. [8]). Brieﬂy, some studies reported positive associa- tions with individual congeners, others reported no asso- ciations for total PCBs or any individual congeners, and others reported negative associations with some tumor types. The most consistent, positive ﬁndings were reported where interaction between exposure and CYP1A1 gene polymorphisms could be considered. Three studies found higher PCB exposures with postmenopausal breast cancer in combination with the CYP1A1 polymorphism, M2 type [10–12]andanotherreportedthisassociationwithpre- menopausal breast cancer [13]. The present prospective study adds a unique perspective by testing the hypothesis that exposure to PCBs, measured during the early postpartum, is associated with increased risk of early breast cancer. Because of the long half-life of PCBs [14], early postpartum levels also reﬂect exposure during pregnancy [15] and possibly during childhood and adolescence. To our knowledge, this is the ﬁrst study to report on breast cancer associations in relation to measured PCBs levels during critical periods of vulnerability for the breast.Materials and methodsSubjectsSubjects were participants in the Child Health and Devel- opment Studies (CHDS), residents of the Oakland, Cali- fornia area and members of the Kaiser Permanente Health Plan who sought obstetric care between 1959 and 1967 [16].SubjectsvoluntarilyparticipatedintheCHDS,giving an oral informed consent for an in-person interview, col- lection of blood specimens at several points in pregnancy and the early postpartum, and permission for medical record access. This study was reviewed and approved by The Institutional Review Board of the Public Health Institute and we have complied with all federal guidelines governing use of human participants. Breast cancer cases were identiﬁed by linkage to the California Cancer Registry, and the California Vital Status Records [17]. All names for each CHDS subject are sub- mitted for cancer linkages using ﬁxed (i.e. birth date, sex, race, and name) and changeable (i.e. address and patient record number) identiﬁers. A rigorous protocol is used to verify cases, comparing ﬁxed versus changeable identiﬁersby manual review. The California Cancer Registry is reported to be [99 % complete after a lag time of about 2 years [18]. Cases were deﬁned as women with incident invasive or non-invasive breast cancer diagnosed before age 50, or deaths due to breast cancer before age 50, obtained from linkage conducted in early 1998. There were 133 cases who met study criteria. All members of the CHDS cohort are additionally linked to the California Department of Motor Vehicles (DMV) ﬁles on a regular basis to determine res- idence history allowing us to assess their control status and to update any name changes. All names registered with the DMV are used in establishing a match. Simultaneous linkage of multiple family members enhances matching. The regular DMV matching provides a history of location for each subject which is used to determine the population at risk for cancer, corresponding with geographic surveil- lance by California’s cancer registries. Subjects who can- not be located are considered lost to follow-up at the date of their last deﬁnitive classiﬁcation as a California resident. One control, matched exactly on birth year, was selected at random for each case from those who were under cancer surveillance and known to be free of breast cancer at the age of diagnosis for the matching case. The median time to diagnosis for cases was 17 years. The mean age at diag- nosis was 43 years.Serum assaysExposure to PCBs was measured by assays of serum samples drawn during the early postpartum period, within 1–3 days of delivery. Postpartum samples were used to conserve valuable archived serum samples drawn in each trimester for future studies where timed samples are essential. PCBs have a long half-life and prior work has established stability of organochlorine levels assayed across all trimesters of pregnancy and the early postpartum [15].Forthisreason,postpartumlevelsofPCBsmay accurately rank women on their pregnancy exposure, covering two potential vulnerable periods of susceptibility of the breast to toxicants. PCBs were assayed in the laboratory of Dr. Mary Wolff [19] using modiﬁcations of methods developed previously by Brock et al. [20]. Brieﬂy, a polar extraction of serum lipids is followed by a column chromatographic clean-up and enrichment step, with analysis by gas chromatography with electron capture detection. Limits of detection were approximately 0.07 ng/mL for individual compounds based on three times the standard deviation of the levels found in the lowest quality control plasma pool [21]. When the serum pool and blanks were considered together [22], the limit of detection was 0.01–0.1 ng/mL; the instru- mental limit of detection based on a peak-to-noise ratio ofBreast Cancer Res Treat1233 was 0.01–0.03 ng/mL for tetra- through hepta-chlorobi- phenyls, using 1–1.5 mL plasma. As described previously [23],weusedallobservedpositivevaluesofPCBsin analyses, even those reported to be below the limit of detection. We were able to assay archived serum samples for the PCB congeners which are shown in Table 1.Thesecong- eners include those most commonly reported in prior studies, comprised the congeners with highest concentra- tions, or grouped by potential biological activity as previ- ously recommended [24]. We randomly assigned the order of samples within and across batches and analyzed case– control pairs in the same batches to minimize differences due to laboratory drift. The laboratory was blind as to case or control status of the samples. Intra-batch coefﬁcients of variation ranged from 5 % for PCB 180 to 18 % for PCB 101. Total cholesterol and total triglycerides were mea- sured enzymatically on the Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN) in a lab certiﬁed by the Centers for Disease Control and Prevention and theNational Heart Lung and Blood Institute Lipid Standardi- zation Program.Statistical analysisThis report is based on 112 case–control pairs, matched on year of birth, after excluding 2 pairs with insufﬁcient serum for lipid assays, 2 pairs with missing data on body mass index, and 17 pairs where one or more member of the pair was missing information on PCB 167, which was not quantiﬁed in one of the assay batches. In a sensitivity analysis, we imputed missing PCB 167 by matching on case status and date of blood draw and assigning a PCB value for the missing individual based on a random pick of all matches. Results were similar (associations were of a similar magnitude with overlapping 95 % conﬁdence intervals and all associations remained statistically signif- icant, deﬁned as p\0.05) whether or not the individuals with imputed values were included. We present ﬁndings only for individuals with non-missing data on all studyTable 1 Distribution of PCBs in breast cancer controls and casesClassiﬁcation [24] PCB Controls (N = 117) Cases (N = 123) Difference within matched pairs (case–control, N = 112)Percent[LODPercentile (mmol/l) Percentile (mmol/l)25th 50th 75th 25th 50th 75th Mean (mmol/l) p valueEstrogenic 101 0.37 0.74 1.07 0.34 0.55 0.92 -0.06 0.19 89 187 0.38 0.48 0.66 0.38 0.48 0.63 -0.07 0.30 100 201 0.09 0.23 0.33 0.14 0.23 0.30 -0.01 0.71 71 Anti-estrogenic A. Non-ortho, mono-ortho, dioxin-like 66 0.89 1.34 1.78 0.96 1.47 1.95 0.10 0.17 99 74 0.62 0.89 1.23 0.62 0.86 1.27 0.01 0.54 95 105 0.25 0.40 0.64 0.25 0.43 0.61 -0.01 0.92 81 118 1.19 1.62 2.02 1.19 1.53 2.11 -0.03 0.94 100 156 0.11 0.28 0.42 0.11 0.28 0.39 -0.03 0.68 64 167 0.08 0.19 0.30 0.08 0.14 0.25 -0.03 0.12 49 B. Di-ortho, limited dioxin activity 138 1.58 2.05 2.55 1.50 2.02 2.77 -0.09 0.56 100 170 0.30 0.46 0.66 0.35 0.48 0.63 -0.01 0.74 97 Phenobarbital, CYP1A, and CYP2B inducers 99 0.28 0.58 0.80 0.25 0.52 0.86 -0.04 0.30 83 153 1.88 2.38 3.08 1.86 2.43 3.08 -0.08 0.40 100 180 0.89 1.21 1.54 0.94 1.21 1.57 0.01 0.63 100 183 0.13 0.23 0.35 0.10 0.23 0.33 -0.03 0.32 66 203 0.21 0.30 0.42 0.23 0.35 0.47 0.02 0.20 90 203/167 ? 187 0.34 0.43 0.52 0.38 0.50 0.63 0.09 NA NAVariable number of subjects in each group is due to missing data on one or more of the PCB congeners shown. The PCB score (PCB 203/(PCB 187 ? PCB 167)) was based on the best ﬁtting model as described in the text, and is provided to describe the distribution of the mixture of signiﬁcant PCB predictors. p values are not presented for the PCB score because the score was created after analysis, as described in text. p values shown are for Wilcoxon Signed Rank Test of differences (case–control) within age-matched case–control pairs LOD limit of detectionBreast Cancer Res Treat123variables, as this is a conservative choice based on observed values. We performed data analysis using age-matched condi- tional logistic regression as in our prior study of DDT and breast cancer in this same population [25]. We began with a full model, entering all PCBs classiﬁed by Wolff et al. [24]. as potentially relevant to human health: Group 1 consisted of congeners detected in the CHDS serum sam- ples that were considered to be potentially estrogenic and persistent (PCB 101,187, 201). Group 2 consisted of congeners detected in the CHDS serum samples that were considered to be potentially antiestrogenic, immunotoxic, dioxin-like: Group 2A which are non-ortho or mono-ortho in their structure (PCB 66, 74,105,118,156,167) and Group 2B which are di-ortho and have more limited dioxin-like activity (PCB 138 and 170). Group 3 consisted of pheno- barbital, CYP1A and CYP2B inducers (PCB 99, 153,180, 183, 203). Congeners that had individual p[0.20 were tested for removal as a group, based on a likelihood ratio test (p\0.15 as the criterion). At the next step, we used a more stringent criterion, eliminating remaining PCB terms with individual signiﬁcance probabilities [0.05. In addi- tion to using the likelihood ratio test to test the hypothesis that the coefﬁcients for these terms were each 0 using the criterion, p\0.15, we also examined the sign and size of coefﬁcients of remaining predictors before and after elim- ination to rule out major confounding by the eliminated predictors. Our goal was to identify the minimal number of PCBs that predicted risk. Once the best PCB model was identiﬁed, we examined whether further adjustment for blood lipids (total cholesterol, total triglycerides), parity, year of blood draw, body mass index (lower tertile, upper tertile vs. middle tertile as the reference category) and breast feeding following the current pregnancy altered PCB associations with breast cancer. To describe the net effect of PCB exposure on breast cancer, we constructed a post-hoc score that consisted of the ratio of the sum of PCB congener(s) associated with higher risk of breast cancer to the sum PCB congeners associated with lower risk as in a previous report on health effects of PCB exposure in this population [26]. We then examined the variation in the post-hoc score and described its association with breast cancer in this population.ResultsTable 1 shows the distribution of PCB congeners and a post-hoc PCB score based on the ﬁnal model shown in Table 2. In this study population, PCB congener concen- trations and the distribution of the PCB score were highly variable. The comparisons between cases and controls in Table 1 show no remarkable, statistically signiﬁcantassociations between single PCB congeners and breast cancer risk, in the absence of control for other congeners. This observation suggests that confounding would play a role in any associations observed in multivariate models. There were no associations between the sum of total PCBs or with PCB groups (groups shown in Table 1) and risk of breast cancer (data not shown). Table 2 shows results of multivariate conditional logistic regression models for individual PCB congeners. PCB 203 is the only congener with a consistent and statistically signiﬁcant positive coefﬁcient, indicating that it was associated with increased risk of breast cancer (Table 2, both models). In contrast, PCB 167 and PCB 187 were inversely associated with risk of breast cancer (Table 2, both models). To check for dose response, we also estimated associations for these PCBs by quartile shown in Table 3. Results were largely consistent with a monotonic trend for each congener.Table 2 Associations of individual PCB congeners with breast can- cer diagnosed before 50 years of ageClassiﬁcation [24]PCB Model with all PCBs Final modelCoefﬁcient p value Coefﬁcient p valueEstrogenic 101 0.39 0.41 187 -4.18 0.03 -2.07 0.02 201 -2.70 0.23 Anti-estrogenic A. Non- ortho, mono- ortho, dioxin- like 66 0.11 0.61 74 0.36 0.53 105 1.37 0.19 118 -0.82 0.07 156 -0.42 0.61 167 -2.50 0.17 -2.88 0.03 B. Di-ortho, limited dioxin activity 138 0.10 0.87 170 -1.45 0.34 Phenobarbital, CYP1A, and CYP2B inducers 99 -0.45 0.56 153 0.10 0.91 180 1.26 0.28 183 1.15 0.48 203 6.17 0.01 4.36 0.001In the column labeled, ‘‘Model with all PCBs’’, congeners were entered into a single model as the ﬁrst step in model selection. Congeners PCB 203, 187, 167 118, and 105 were initially retained based on the criterion of p\0.20. PCB 118 and 105 were then removed either one at a time or together. They were deleted from the ﬁnal model by applying the likelihood ratio test where v2 = 3.81, 2df, p = 0.15 for the test to retain both PCB 105 and PCB 118 in the model. Both were tested for removal simultaneously because deleting either PCB 118 or PCB 105 alone greatly affected the size of coef- ﬁcient for the other. There were N = 112 age-matched case–control pairs for all models shown and all models tested. Coefﬁcients are reported per 1 mmol/lBreast Cancer Res Treat123Based on the results in Tables 2 and 3, a PCB score was constructed as the ratio of PCB 203 (positively related to risk) to the sum of PCBs 167 and 187 (each negatively related to risk). The PCB score was highly variable in the cohort, ranging from 8 % PCB 203 (compared to the sum of PCBs 187 and 167) to 131 % PCB 203. Overall for cases and controls combined, the median of the 4th quartile (0.67) was 2.3 times higher than the median of the 1st quartile (0.30). Among controls, the median of the 4th quartile of the PCB score (0.61) was 2.5 times higher than the median of the 1st quartile of the PCB score (0.25). Among cases, the median of the 4th quartile of the PCB score (0.71) was 2.2 times higher than the median of the 1st quartile of the PCB score (0.32). Table 4 shows the net effect of exposure based on the proportion of PCB 203 compared to the sum of PCBs 167 and 187. Women in the top 25 % of the PCB score had nearly three times the risk of breast cancer as women in the bottom 25 % of the PCB score. Adjustment for lipids or other breast cancer risk factors had little effect on this result (Table 4), nor did adjustment for the denominator of the PCB score or adjustment for p,p0-DDT, o,p0-DDT, and p,p0-DDE (data not shown). Figure 1 shows the actual distribution of the within-pair differences for the PCB score for cases versus controls in this study sample. In the majority of case–control pairs (62 %), the PCB score was higher among the woman who subsequently developed breast cancer. Pairs where the case had a higher PCB score also showed greater differences on the PCB score than pairs where the control had a higher score (seen in Fig. 1; compare the right side of the Y-axis (center axis) which shows pairs where cases within the pair had a higher PCB score to the left side of the Y-axis which shows pairs where controls had a higher PCB score). Fig- ure 1 is consistent with the modeling results shown in Tables 2, 3 and 4.DiscussionThe net effect of PCB exposure in this study population was nearly a threefold increase in breast cancer risk among women who had a higher proportion of PCB 203 in relation to the sum of PCB 167 and PCB 187 (75th percentile vs. 25th percentile). These results are novel, but not incon- sistent with the prior literature on PCBs and breast cancer. Three comprehensive reviews concluded previously that human studies of PCBs and breast cancer, which measured exposure in midlife, had variable ﬁndings [6–8]. Most prior studies reported primarily on total PCBs, which are largely determined by the PCBs found in highest concentration in humans (PCB 153, PCB 138, PCB 118, and PCB 180). We too found no associations for total PCBs, highTable 3 Associations of PCB 167, 187, and 203 with breast cancer diagnosed before 50 years of agePCB Quartile Odds ratio (95 % CI) p value for linear trend167 Q1 1.00 \0.04 Q2 1.09 (0.48, 2.47) Q3 0.70 (0.27, 1.78) Q4 0.24\*\* (0.07, 0.79) 187 Q1 1.00 \0.02 Q2 0.94 (0.41, 2.17) Q3 0.92 (0.36, 2.38) Q4 0.35\* (0.11, 1.14) 203 Q1 1.00 \0.001 Q2 1.21 (0.46, 3.18) Q3 2.89\*\* (0.98, 8.55) Q4 6.34 (1.85, 21.73)Each of the three PCBs is coded as quartiles, based on the distribution in controls. Quartile 1 is the reference category and quartiles 2, 3, 4 are entered as dummy variables for each PCB shown. Associations shown are based on a single model where quartile terms for all PCBs are entered. P value for trend is estimated from a linear model where all three PCBs are entered as continuous variables. N = 112 case– control pairs CI conﬁdence interval, p signiﬁcance probability \* p B 0.10 \*\* p B 0.05 p B 0.01Table 4 Estimated net effects of PCB exposure on risk of breast cancer before 50 years of ageLevel of adjustment Quartile of PCB scoreaOdds ratio (95 % CI)Unadjusted Q1 1.00 Q2 1.26 (0.53, 3.00) Q3 1.52 (0.64, 3.62) Q4 3.01 (1.34, 6.78) Cholesterol and triglycerides Q1 1.00 Q2 1.23 (0.53, 3.07) Q3 1.53 (0.64, 3.68) Q4 3.09 (1.34, 7.16) Cholesterol, triglycerides, race, parity, lactation, body mass index, and year of blood sampling Q1 1.00 Q2 1.36 (0.53, 3.52) Q3 1.78 (0.70, 4.55) Q4 2.81 (1.11, 7.09)CI conﬁdence interval a A post-hoc PCB score was deﬁned to describe the net effect of PCB exposure in this study sample (described in text). PCB 203 was associated with increased risk, while PCBs 167 and 187 were asso- ciated with decreased risk (see ﬁnal model, Table 2). Therefore, the PCB score was deﬁned as the proportion of PCB 203 relative to the sum of PCBs 167 and 187: PCB 203/(PCB 167 ? PCB 187). N = 112 age-matched case–control pairs for all models shownBreast Cancer Res Treat123concentration PCBs or sums of PCBs in functional groupings previously proposed by Wolff et al. [24]. No prior studies reported on the independent contribution of the three lower concentration congeners that predicted breast cancer in this study. It is notable that prior studies did not measure exposure in young women, during windows of susceptibility during early life, when the breast might be more susceptible to endocrine disruption, including in utero, puberty, preg- nancy, or the postpartum [1–3]. Our ability to directly measure exposure during the early postpartum is a partic- ular strength of this study. A recent meta-analysis of pregnancy-associated breast cancer outcomes found that women diagnosed with breast cancer in pregnancy, and particularly women diagnosed postpartum, had poorer survival [4], providing further evidence supporting the hypothesis that pregnancy and the postpartum period are vulnerable periods for the breast. As PCBs are highly persistent, it is likely that post- partum levels also reﬂect pregnancy levels, as suggested by one longitudinal study that reported high correspondence between early postpartum levels and levels across all three trimesters of pregnancy [15]. As women were young at the time of blood collection, it is also possible that the early postpartum levels of PCBs reﬂect exposure even prior topregnancy, possibly during puberty, as well. This might explain the strength of the association observed for PCB 203, a higher chlorinated compound, as compounds with this structure tend to have longer half-lives [14]. Other strengths of this study include prospective assessment of exposure an average of 17 years before diagnosis, simultaneous consideration of individual PCB congener effects, and the opportunity to observe a popu- lation during active exposure because blood samples were obtained before PCBs were restricted. Our focus on breast cancer at a young age is an addi- tional strength. Molecular studies strongly suggest that pre- menopausal breast cancer may not share the same features or risk factors as breast cancer diagnosed in middle age and older [27, 28]. Our ﬁndings could lead to better under- standing about etiology, prevention, and treatment of early breast cancer, if the mechanisms for the associations we observed can be validated and investigated by experimental toxicology and molecular studies. Our choice to estimate the net effect of exposure to observed PCB mixtures found in our study participants is an additional strength. While our approach will likely be improved upon as the methods for analyzing mixed expo- sures advances; here, we applied an empirical approach to describe more than individual congener associations. It is of interest that the protective associations for PCBs 187 and 167 did not overcome the stronger, deleterious asso- ciation observed for PCB 203. There are several specula- tive explanations for this ﬁnding, the ﬁrst being that PCB 203 is a particularly strong risk factor, as evidenced by its point estimate. Alternatively, as the higher chlorinated PCBs are eliminated more slowly, it is possible that post- partum levels of PCB 203 more accurately reﬂect exposure even earlier in life, including accumulations in utero, childhood and during puberty, periods of susceptibility for the breast in addition to pregnancy and postpartum. Limitations of our study include the possibility of unmeasured confounding by other exposures. In particular, we were unable to measure dioxin exposure or activity, raising the possibility that this or other unmeasured con- founders could have masked or accounted for the associ- ations we report here. However, as we observed dose response, unmeasured confounding would have to follow the same pattern, making this alternative explanation of our ﬁndings less likely. It is also possible that host factors that inﬂuence the metabolism or selective excretion of various PCB congeners underlie the associations we observed. We used early postpartum samples to save valuable timed serum samples during pregnancy for other studies in the cohort. However, prior studies conducted in serum samples of the same age found good correspondence of these per- sistent organochlorines across all trimesters and the early postpartum [15], suggesting that postpartum PCB levels0102030405060708090100-1.05 -0.75 -0.45 -0.15 0.15 0.45 0.75 1.05Intra-pair difference for the PCB score (case-control)Cumulative PercentFig. 1 Cumulative distribution of case–control differences for the PCB score (N = 112 age-matched case control pairs). Each point represents one case–control pair. The points on the right side of the y- axis (center axis) are positive values that represent pairs where the woman who developed breast cancer had a higher PCB score postpartum than her matched control. In a majority of pairs (62 %), the woman who subsequently developed breast cancer had a higher PCB score. The differential for the PCB score was also greater for pairs where the case had a higher score than her matched control (compare points on the right of the y-axis to points on the left of the y- axis)Breast Cancer Res Treat123may also reﬂect pregnancy exposures. Still our study can- not establish the age or developmental period when PCB exposure was acquired, other than establishing that expo- sure preceded the mean age of blood collection (age 26 years). Storage of serum samples is unlikely to have biased study results, as all samples were similarly stored. Randomization of samples within and between batches and inclusion of controls and cases in the same batches mini- mized inter- and intra-batch laboratory error. Interpretation is limited by a lack of understanding about the potential mechanism for PCB associations observed. The direct association between PCB 203 and early breast cancer was sizable and signiﬁcant. However, the mode of action for PCB 203, classiﬁed as a phenobarbital (PB) inducer [24], is unknown. A PubMed search for ‘‘PCB 203’’ returned no citations, compared to 589 citations for ‘‘PCB 153,’’ for example. The Agency for Toxic Sub- stances and Disease Registry report on the toxic effects of PCBs makes no speciﬁc mention of PCB 203 effects [29]. PCB 187 has been classiﬁed as potentially estrogenic [24], but it is unclear how postpartum or pregnancy exposure might be associated with a lower risk of breast cancer. This study provides little information regarding the validity of the classiﬁcation of PCB 187 as estrogenic. In our previous report on the relation of prenatal PCB expo- sure to time to pregnancy in daughters in this same cohort [26], we found that a longer time to pregnancy in daughters was associated with prenatal exposure to PCB 187. The signiﬁcant associations observed for breast cancer in mothers and time to pregnancy in daughters following prenatal exposure to PCB 187 deserves additional study, perhaps in experimental models or in vitro systems. It could be of interest to characterize PCB 187 effects in the case of low versus high endogenous levels of estrogen and during pregnancy and postpartum in particular. We were unable to investigate gene/PCB interactions in this study. The absence of associations for some of the PCBs investigated might be explained by failure to identify susceptible sub-populations of women. Previously, asso- ciations were more consistently observed in sub-popula- tions characterized by variant alleles for enzymes that metabolize PCBs (Cytochrome P4501A1 variants) [10–13]. We were also unable to characterize the receptor status of the breast tumors in our study. We cannot account for lactation in subsequent pregnancies. However, breast feeding following the current pregnancy did not predict breast cancer in this sample and was not a confounder of PCB associations. There was no correlation between breast feeding following the observed pregnancy and PCB 203, 187, or 167. These ﬁndings may be explained by the low frequency of long-term breast feeding in our cohort. Rates of lactation in this sample were low (34 %) and among those who did breast feed, most (60 %) breast fed for\4 months [25]. We suggest that it is unlikely that lacta- tion in subsequent pregnancies explains our results, as lactation behavior is highly correlated among pregnancies [30], but this remains a possibility. The variable distribution of PCB congeners observed in study subjects is to be expected as the distribution of congeners depends on source of exposure which is inﬂu- enced by the chemical structure of each congener. Expo- sure also depends on the fate of the congener in the ecosystem which ultimately forms the source of human exposure and on the individual response to the exposure. All these factors contribute differently to the measured serum level [31]. In a previous report on in utero PCB exposure and daughter’s time to pregnancy, we also found considerable variability in the mixture of PCB congeners in CHDS mothers [26]. In the US, total PCB levels in adipose tissue declined steadily after 1972 when restrictions were implemented. A decline in PCBs was also observed in archived blood samples in Norway during the same period [32] and in human adipose tissue in the United States [33]. However, secular trends in the mix of congeners are unknown [33]. As the fate of individual congeners in the environment depends on their structure, environmental topography, and climate, and because individual charac- teristics may determine routes of exposure, and metabolic fate, it is unlikely that trends for individual congeners are the same over time, or within individuals, or across geo- graphic areas [14]. There is little human data on this topic, but results of repeated blood sampling in a Danish cohort provides limited support for the concept that congener proportions vary over time: over a 5-year period (1976–1978 vs. 1981–1983) median concentration of total PCBs declined 11 %, but median concentration of PCB 118 declined 34 %, PCB 180 declined 4 %, and PCB 153 declined 9 %.(adapted from Hoyer, et al., Table 1, p. 179) [34]. If congener mixture is the underlying risk factor, then we might expect different results for epidemiological studies, depending on place, time, age, and other individual characteristics that might alter external and internal dose to these compounds. Given the variability of congener mixtures observed in our cohort, we speculate that an underlying host factor related to metabolism of these compounds might contribute to the PCB associations with breast cancer that we have observed in this study. These data do not allow us to determine whether PCB exposure would be necessary to trigger an effect, or whether some host factor might be sufﬁcient to increase breast cancer risk. Our analysis does indicate that PCB associations observed in this study are independent of DDT associations previously observed in this cohort [25]. Mechanistic studies in experimental models, or in vitro are likely to be very important to explaining the associations we report here, and forBreast Cancer Res Treat123explaining the human breast cancer associations previously reported for CYP1A1 polymorphisms in relation to PCB exposure in middle-aged women [10–13]. In summary, in this study, the mixture of PCB congeners predicted the estimated effect of PCB exposure on risk of breast cancer. Overall, women in this study showeda variable distribution for the three PCB congeners that predicted breast cancer. Women with a high proportion of PCB 203 (top 25 % of the study population) relative to PCBs 167 and 187 had a nearly threefold increase in subsequent risk of breast cancer, compared to women with a lower proportion of PCB 203 (bottom 25 % of the study population). The relation of PCB exposure to breast cancer might be clariﬁed by additional laboratory, experimental and human population studies that account for timing of exposure in relation to windows of susceptibility for the breast and for concomitant host factors. It is likely to be particularly important to study congener mixtures and individual response to multiple exposures. It remains unclear whether individual differences in exposure, response to exposure, or both explain risk patterns observed.Acknowledgments This publication was made possible by the Breast Cancer and the Environment Research Program (BCERP) award number (U01 ES/CA 019471 to B.A.C. and M.B.T.), from the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute (NCI), NIH, DHHS; the National Cancer Institute award number (R01 CA72919 to B.A.C); and The National Institute of Child Health and Human Development award numbers (N01 HD 6 3258 and N01 HD 1 3334 to B.A.C.). 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The ideas and opinions expressed here in are those of the author(s) and endorsement by the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.Conﬂict of interest The authors declare that they have no conﬂict of interest.Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which per- mits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.References1. Fenton SE (2006) Endocrine-disrupting compounds and mam- mary gland development: early exposure and later life conse- quences. Endocrinology 147(6):s18–s24 2. 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| Number of New Cases and Deaths Per 100,000 People (All Races, Males and Females), Age-Adjusted |
| --- |
| **Year** | **New Cases - SEER 9**  | **New Cases - SEER 13** | **Deaths - US** |
| 1975 | 11.1 | - | 5.6 |
| 1976 | 11.2 | - | 5.7 |
| 1977 | 11.2 | - | 5.8 |
| 1978 | 11.9 | - | 5.9 |
| 1979 | 12.5 | - | 5.9 |
| 1980 | 12.6 | - | 6.2 |
| 1981 | 13.6 | - | 6.2 |
| 1982 | 13.4 | - | 6.6 |
| 1983 | 14.0 | - | 6.7 |
| 1984 | 15.2 | - | 6.8 |
| 1985 | 15.5 | - | 7.1 |
| 1986 | 15.9 | - | 7.3 |
| 1987 | 16.7 | - | 7.3 |
| 1988 | 17.2 | - | 7.5 |
| 1989 | 17.4 | - | 7.8 |
| 1990 | 18.5 | - | 7.9 |
| 1991 | 18.8 | - | 8.2 |
| 1992 | 18.6 | 18.5 | 8.2 |
| 1993 | 18.9 | 18.5 | 8.2 |
| 1994 | 20.0 | 19.6 | 8.6 |
| 1995 | 20.0 | 19.7 | 8.7 |
| 1996 | 19.4 | 19.4 | 8.8 |
| 1997 | 20.0 | 19.5 | 8.9 |
| 1998 | 19.6 | 19.3 | 8.7 |
| 1999 | 19.9 | 19.8 | 8.3 |
| 2000 | 19.7 | 19.4 | 8.2 |
| 2001 | 20.0 | 19.7 | 7.9 |
| 2002 | 20.2 | 19.7 | 7.7 |
| 2003 | 20.7 | 20.2 | 7.4 |
| 2004 | 21.4 | 20.8 | 7.1 |
| 2005 | 20.8 | 20.2 | 6.9 |
| 2006 | 20.4 | 20.0 | 6.7 |
| 2007 | 21.1 | 20.4 | 6.6 |
| 2008 | 20.7 | 20.2 | 6.4 |
| 2009 | 20.7 | 20.4 | 6.3 |
| 2010 | 21.1 | 20.6 | 6.1 |
| 2011 | 19.6 | 19.2 | - |

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Review Article

Plasma Levels of Polychlorinated Biphenyls, Non-Hodgkin Lymphoma, and Causation

[Michael D. Freeman](http://www.hindawi.com/10285352/)1 and [Sean S. Kohles](http://www.hindawi.com/18574897/)2

1Department of Public Health and Preventive Medicine, Oregon Health & Science University School of Medicine, 1234 SW 18th Avenue, Suite 102, Portland, OR 97205, USA
2Regenerative Bioengineering Laboratory, Department of Mechanical & Materials Engineering, Portland State University, 1930 SW 4th Avenue, Suite 400, Portland, OR 97201, USA

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Abstract

Polychlorinated biphenyls (PCBs) are synthetic chlorinated hydrocarbons that have extensively polluted the environment and bioaccumulated in the food chain. PCBs have been deemed to be probable carcinogens by the Environmental Protection Agency, and exposure to high levels of PCBs has been consistently linked to increased risk of non-Hodgkin lymphoma (NHL). In the present article we present a forensic epidemiologic evaluation of the causal relationship between NHL and elevated PCB levels via application of the Bradford-Hill criteria. Included in the evaluation is a meta-analysis of the results of previously published case-control studies in order to assess the strength of association between NHL and PCBs, resulting in an odds ratio in which the lowest percentile PCB concentration (quartile, quintile, or tertile) has been compared with the highest percentile concentration in the study groups. The weight-adjusted odds ratio for all PCB congeners was 1.43 with a 95% confidence interval of 1.31 to 1.55, indicating a statistically significant causal association with NHL. Because of the lack of an unexposed comparison group, a rationale for the use of a less than 2.0 relative risk causal contribution threshold is presented herein, including an ecologic analysis of NHL incidence and PCB accumulation (as measured by sales volume) over time. The overall results presented here indicate a strong general causal association between NHL and PCB exposure.

1. Introduction

Polychlorinated biphenyls (PCBs) are a class of commercially-produced organochlorines known as chlorinated hydrocarbons [[1](http://www.hindawi.com/journals/jeph/2012/258981/#B1)]. PCBs are nonflammable, chemically stable, have a high boiling point, and are nearly insoluble in water. In addition, they are resistant to the effects of oxidation, acids, bases, and other chemicals [[2](http://www.hindawi.com/journals/jeph/2012/258981/#B2), [3](http://www.hindawi.com/journals/jeph/2012/258981/#B3)]. A PCB molecule consists of a pair of joined 6-carbon rings, with chlorine(s) attached or “substituted” at any one of the free 10-carbon positions. There are 209 possible chlorine arrangements, which are called congeners. It is the number of the chlorines and where they are attached that determine the congener’s properties. A congener’s two-carbon rings can be twisted, relative to each other, or they can be aligned in the same plane (coplanar). Coplanar carbon ring alignment occurs when the chlorine(s) are attached to the carbons closest to the link between the two rings, called the ortho position. Coplanar congeners exhibit dioxin-like properties [[4](http://www.hindawi.com/journals/jeph/2012/258981/#B4), [5](http://www.hindawi.com/journals/jeph/2012/258981/#B5)].

For approximately 50 years (beginning in 1929), PCBs were manufactured in the United States (USA) and were used in numerous industrial and commercial applications in the form of mixtures called Aroclors [[6](http://www.hindawi.com/journals/jeph/2012/258981/#B6)]. One manufacturer (Monsanto Company) has produced ~99% of all the PCBs used in the USA [[2](http://www.hindawi.com/journals/jeph/2012/258981/#B2)]. Worldwide, Monsanto has produced between 39 and 48 percent of all PCBs. Widespread industrial use of PCBs, combined with improper disposal practices, has led to the introduction of PCBs into the environment, where these chemicals are found in all environmental media, including air, water, and soil. Based on mounting evidence that PCBs were accumulating and persisting in the environment and that this accumulation was causing adverse health effects in humans and animals, PCB production in the USA was halted in the late 1970s [[1](http://www.hindawi.com/journals/jeph/2012/258981/#B1)].

PCBs are highly soluble in lipids, and as such, are absorbed by fish and other animals, leading to considerable bioaccumulation in the food chain. PCBs are typically absorbed into the human body through ingestion, inhalation, and/or dermal exposure [[1](http://www.hindawi.com/journals/jeph/2012/258981/#B1), [7](http://www.hindawi.com/journals/jeph/2012/258981/#B7)–[9](http://www.hindawi.com/journals/jeph/2012/258981/#B9)]. Bioaccumulation in humans and animals occurs when PCBs are absorbed into the body at a rate greater than the rate at which they are metabolized and excreted from the body. Detectable levels of PCBs have been found in humans in adipose (fat) tissue, breast milk, hair, and serum lipids [[3](http://www.hindawi.com/journals/jeph/2012/258981/#B3), [10](http://www.hindawi.com/journals/jeph/2012/258981/#B10)]. Consumption of contaminated food is the major source of PCB exposure for the general United States population that is not occupationally exposed to PCBs [[1](http://www.hindawi.com/journals/jeph/2012/258981/#B1), [2](http://www.hindawi.com/journals/jeph/2012/258981/#B2), [8](http://www.hindawi.com/journals/jeph/2012/258981/#B8), [10](http://www.hindawi.com/journals/jeph/2012/258981/#B10), [11](http://www.hindawi.com/journals/jeph/2012/258981/#B11)]. Unsurprisingly, populations that are at particular risk to high exposure to PCBs include people who consume sport-caught fish and other contaminated foods, workers occupationally exposed to PCBs, individuals residing near hazardous waste sites containing PCBs, and nursing infants [[7](http://www.hindawi.com/journals/jeph/2012/258981/#B7), [8](http://www.hindawi.com/journals/jeph/2012/258981/#B8), [10](http://www.hindawi.com/journals/jeph/2012/258981/#B10), [12](http://www.hindawi.com/journals/jeph/2012/258981/#B12)].

PCBs are deemed to be probable carcinogens by the Environmental Protection Agency based on the results of both animal and human studies [[1](http://www.hindawi.com/journals/jeph/2012/258981/#B1)]. A number of animal studies have demonstrated a direct dose-response relationship between PCB levels and liver tumor occurrence [[13](http://www.hindawi.com/journals/jeph/2012/258981/#B13)–[16](http://www.hindawi.com/journals/jeph/2012/258981/#B16)]. In humans, there is also good evidence of an association between increased cancer rates and PCBs. A number of epidemiologic studies have indicated increased rates of liver and biliary cancer [[17](http://www.hindawi.com/journals/jeph/2012/258981/#B17)], breast cancer [[18](http://www.hindawi.com/journals/jeph/2012/258981/#B18)], skin cancer [[19](http://www.hindawi.com/journals/jeph/2012/258981/#B19)], and Non-Hodgkin Lymphoma (NHL), among other cancers [[20](http://www.hindawi.com/journals/jeph/2012/258981/#B20)].

PCBs appear to have a number of toxic qualities that potentially explain these observed associations, including dioxin-like characteristics of some congeners (118, 156, and 169) [[5](http://www.hindawi.com/journals/jeph/2012/258981/#B5)], the ability to mimic hormones for others [[11](http://www.hindawi.com/journals/jeph/2012/258981/#B11)], and neuro- and immunotoxicity as well [[21](http://www.hindawi.com/journals/jeph/2012/258981/#B21)–[23](http://www.hindawi.com/journals/jeph/2012/258981/#B23)]. This last quality (immunotoxicity) is helpful in explaining the observed association between elevation of certain congener titers (118, 138, 153, 170, and 180) and the increased incidence of NHL, as immune system depression is considered to be one of the strongest risk factors for NHL [[24](http://www.hindawi.com/journals/jeph/2012/258981/#B24), [25](http://www.hindawi.com/journals/jeph/2012/258981/#B25)]. Immunotoxicity is a characteristic shared by other organochlorines as well, including dioxins and chemicals found in pesticides and herbicides such as hexachlorobenzene, heptachlor, chlordane, and others [[26](http://www.hindawi.com/journals/jeph/2012/258981/#B26)], which have also been found to be associated with increased risk of NHL [[27](http://www.hindawi.com/journals/jeph/2012/258981/#B27)]. It is most likely the quality of immunotoxicity that links both PCBs and non-PCB organochlorines to increased incidence of NHL, and when both are present, each contribute to the risk of NHL independently [[26](http://www.hindawi.com/journals/jeph/2012/258981/#B26)].

NHL includes all cancers of lymphoid tissues except Hodgkin’s disease, a malignancy of the lymph nodes [[28](http://www.hindawi.com/journals/jeph/2012/258981/#B28)]. The incidence of NHL in many parts of the world is rising more rapidly than the incidence of virtually all other human cancers [[29](http://www.hindawi.com/journals/jeph/2012/258981/#B29), [30](http://www.hindawi.com/journals/jeph/2012/258981/#B30)]. In the US, the incidence of NHL increased at an average of 3.6% per year from 1975–1991 and continued to rise over the period 1991–2005, albeit at a slower rate (~0.5% annually) [[31](http://www.hindawi.com/journals/jeph/2012/258981/#B31), [32](http://www.hindawi.com/journals/jeph/2012/258981/#B32)]. It is widely accepted that changes in diagnostic practices and known risk factors such as age, autoimmune disease incidence, and prevalence of immune-suppressing infections are insufficient to explain the emerging “epidemic” of NHL observed in most of the world [[33](http://www.hindawi.com/journals/jeph/2012/258981/#B33), [34](http://www.hindawi.com/journals/jeph/2012/258981/#B34)]. Additionally, it is hypothesized that exposures shared by many populations worldwide are the most likely explanation for the steep increases in NHL incidence [[31](http://www.hindawi.com/journals/jeph/2012/258981/#B31), [33](http://www.hindawi.com/journals/jeph/2012/258981/#B33)–[35](http://www.hindawi.com/journals/jeph/2012/258981/#B35)], and that this exposure is likely immunotoxic or immunosuppressive [[36](http://www.hindawi.com/journals/jeph/2012/258981/#B36)]. Thus, exposure to PCBs and other persistent organic pollutants provides a reasonably plausible explanation, at least in part, for the rise in NHL incidence during the latter half of the 20th century.

The underlying physiologic mechanisms for the development of NHL secondary to PCB exposure are not fully known. It is well established that the dioxin-like congeners can bind to and activate the aryl hydrocarbon receptor (AhR), a normally inactive transcription factor [[37](http://www.hindawi.com/journals/jeph/2012/258981/#B37)]. The overactivation of the AhR can induce enzymes that produce cytotoxic metabolites or otherwise adversely affect cellular metabolism [[38](http://www.hindawi.com/journals/jeph/2012/258981/#B38)]. The degree to which a particular coplanar dioxin-like congener can act on the AhR is measured in Toxic Equivalents (TEQ), a comparison with a standard set to the highly toxic dioxin-like compound 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) [[39](http://www.hindawi.com/journals/jeph/2012/258981/#B39)]. Less is known about the noncoplanar nondioxin-like congeners, however, they appear to affect immune function by direct cellular effects, including inhibition of leukocytic phagocytosis, among other actions [[22](http://www.hindawi.com/journals/jeph/2012/258981/#B22)].

Although there are some differences in the specific congeners measured and variations in the PCB levels associated with increased risk of NHL, the literature generally supports, via both case-control and cohort studies, the concept that populations with higher levels of exposure to certain PCB congener and with higher body burdens of these same congeners are at increased risk for NHL. Multiple representative publications describe groups of previously identified cases of NHL from various registries and clinical investigations and compared them with age and gender-matched controls, resulting in quantitative descriptions of relative influence of percentile groupings of blood plasma PCB on NHL risk via conditional logistic regression (Table [1](http://www.hindawi.com/journals/jeph/2012/258981/tab1/)) [[26](http://www.hindawi.com/journals/jeph/2012/258981/#B26), [40](http://www.hindawi.com/journals/jeph/2012/258981/#B41)–[48](http://www.hindawi.com/journals/jeph/2012/258981/#B79)]. An additional study [[49](http://www.hindawi.com/journals/jeph/2012/258981/#B50)], analyzed adipose tissue in a postmortem assessment. Rothman et al. [[40](http://www.hindawi.com/journals/jeph/2012/258981/#B41)], Engel et al. [[41](http://www.hindawi.com/journals/jeph/2012/258981/#B42), [48](http://www.hindawi.com/journals/jeph/2012/258981/#B79)], all used prediagnosis blood samples (not subject to weight loss bias). Additionally, three landmark exposure studies investigated the association between environmental levels of various Aroclor products and mortality rates from NHL (Table [2](http://www.hindawi.com/journals/jeph/2012/258981/tab2/)) [[50](http://www.hindawi.com/journals/jeph/2012/258981/#B51)–[52](http://www.hindawi.com/journals/jeph/2012/258981/#B53)]. These studies collectively have provided a foundation for a reasonable conclusion that a causal relationship exists between high levels of PCBs, both in the environment and in the body and increased risk of NHL.



Table 1: Summary of published case-control study populations examining risk of NHL and PCB blood content including those meta-analyzed in the present study. Summed or total PCB metrics shown here.



Table 2: Summary of published cohort studies examining mortality from NHL as associated with PCB exposure. Note the cohort described in Prince et al., [[50](http://www.hindawi.com/journals/jeph/2012/258981/#B51)] were included in the Prince et al., [[51](http://www.hindawi.com/journals/jeph/2012/258981/#B52)] study. Here, the standardized mortality ratio (SMR) was calculated as an indirect adjustment method where the observed number of events (deaths) in each occupational cohort is compared with the number of expected events (based on a “standard” rate).

A few authors have reported subgroups of NHL that are linked to PCB exposure, including an association between diffuse large cell lymphoma and congener 118 and T-cell lymphoma and congener 180 [[42](http://www.hindawi.com/journals/jeph/2012/258981/#B43)]. Hardell reported the highest observed association in their cohort between elevated PCB burdens and low-grade B-cell lymphomas, the most prevalent category of NHL subtypes [[43](http://www.hindawi.com/journals/jeph/2012/258981/#B46)]. DeRoos found an association between congeners 180 and 187 and diffuse but not follicular NHL, whereas Morton reported an association between follicular NHL and congener 180, as well as marginal zone NHL subtype [[54](http://www.hindawi.com/journals/jeph/2012/258981/#B45)].

Given a reasonable basis for a conclusion of general (population-based) causation, the question arises of how to determine, in an individual case of NHL in which elevated blood and/or adipose levels of total or individual PCB congeners have been observed, if the relationship between the two is causal. Far more has been written in epidemiology about the evaluation of general (population) causation than specific (individual) causation. Epidemiologic methods are used for the investigation of specific causation in both short acting exposure/outcome situations (i.e., outbreak/injury investigation) and in settings in which disease onset is latent, sometimes for decades, following exposure, such as with exposure to environmental toxicological or radiological hazards. The discipline of forensic epidemiology is directed at addressing, often for presentation in legal settings, the specific causal correlation between a suspected hazard and a disease or injury outcome [[55](http://www.hindawi.com/journals/jeph/2012/258981/#B54)–[57](http://www.hindawi.com/journals/jeph/2012/258981/#B56)]. The ultimate goal of the investigation is to answer the “but-for” question, which is “but-for the exposure to the hazard, would the individual still have the disease or injury?” [[58](http://www.hindawi.com/journals/jeph/2012/258981/#B57)]. The forensic epidemiologic approach to answering this question is accomplished by first assessing the plausibility of a causal relationship via application of the Bradford-Hill criteria and then estimating the attributable risk percent or probability of causation (PC) that quantifies the probability that, but for the exposure, the disease or injury outcome would not have occurred [[59](http://www.hindawi.com/journals/jeph/2012/258981/#B58)]. Generally, if the PC exceeds 50% then the hazardous exposure is considered most probably causally related to the disease or injury outcome [[60](http://www.hindawi.com/journals/jeph/2012/258981/#B59)]. PC is derived from comparative epidemiologic data that adequately represent the relative risk (RR) of disease or injury between hazard-exposed populations most meaningfully similar to the individual versus nonhazard-exposed populations most meaningfully similar to the individual. A PC of >50% is the equivalent of an RR >2.0 and implies that the cause of disease or injury in an individual randomly selected from the exposed population is the hazard of interest more often than not. This approach is relatively straightforward for evaluating the causal relationship between, for example, cigarette smoking and pancreatic cancer, as there are clearly defined and easily identified exposed (smoking) and unexposed (nonsmoking, not exposed to second-hand smoke) populations.

For the evaluation of PCB exposure and NHL, the issue of causation is more complicated, as the ubiquitous nature of PCBs in the environment means that there are no truly unexposed populations. In combination with the likely multifactorial etiology of NHL (viral infections, immune system depression, autoimmune conditions, and genetic anomalies are all thought to play a role), it is much easier to conclude that the prominence of a single “suspect” hazard-like elevated serum levels of PCBs serves to contribute to the cause of an individual’s NHL such that the hypothetical complete subtraction of the hazard would likely result in the individual not developing the disease (the factor is necessary for the development of the condition). Conversely, the development of NHL most likely requires a number of components along with the suspect hazard, any number of which may also be necessary in order for the disease to manifest.

In the present endeavor, we propose a methodologic framework for the evaluation of specific causation of NHL associated with PCB exposure that takes into account the pervasive and persistent nature of PCBs in the environment and the difficulties with setting an absolute threshold for specific causation. To accomplish this task, we present a meta-analysis of the previously published case-control studies that have examined the risk of NHL relative to PCB titer by congener. Additionally, we discuss a rationale for the use of an adjusted relative risk or probability of causation threshold for concluding that a causally contributory relationship is more probably than not present in an individual with NHL and elevated PCB titers.

2. Methods

2.1. Application of Hill Criteria for Causal Assessment

For the purposes of the present study, a causal relationship is defined as when an exposure is found to have served as an antecedent event or condition that was necessary for the occurrence of a specific disease or injury at the moment that it occurred, given that other conditions are fixed [[61](http://www.hindawi.com/journals/jeph/2012/258981/#B60)]. That is to say, the cause of the disease or injury is an event or condition that preceded the disease or injury and without which the disease or injury would not have occurred. Forensic applications of epidemiology that address the evaluation of causation generally follow the criteria set forth by Sir Austin Bradford-Hill in 1965 [[55](http://www.hindawi.com/journals/jeph/2012/258981/#B54), [56](http://www.hindawi.com/journals/jeph/2012/258981/#B55), [62](http://www.hindawi.com/journals/jeph/2012/258981/#B61)–[66](http://www.hindawi.com/journals/jeph/2012/258981/#B65)]. Hill’s nine criteria, in the order in which they were given in the original publication, are briefly as follows.(1)Strength of association: strength of association is the most important determinant of both general and specific causation and quantified by RR, in that the larger the ratio between the incidence of the condition in the exposed group versuses the incidence in the unexposed group, the greater the probability that the relationship is causal. As described previously, an RR >2.0 is the equivalent of a PC >50%, meaning that it is more probable than not that the suspected causal relationship is true.(2)Consistency: the repetitive observation of a relationship in different circumstances strengthens the causal inference.(3)Specificity: the degree to which a suspected causal factor is associated with a particular outcome or population.(4)Temporality: the potential causal factor must precede the outcome it is assumed to affect, and the outcome cannot either occur before it is physiologically feasible or after too great of a latency period. Temporality is the one factor that must always be present in general and specific causation in order to conclude that a cause and effect relationship is present.(5)Biological gradient: the injury outcome increases proportionately with increasing dose of exposure (also known as dose-response).(6)Plausibility: the degree to which the observed association can be explained by known scientific principles.(7)Coherence: a causal conclusion should not fundamentally contradict present substantive knowledge; it should “make sense” given current knowledge.(8)Experiment: in some cases, there may be evidence from randomized experiments on animals or humans.(9)Analogy: an analogous exposure and outcome may be translatable to the circumstances of a previously unexplored causal investigation.

For application in a forensic setting, these criteria are sometimes modified to include cessation (of exposure) as a test-retest criteria and consideration of alternative explanations for the association (such as bias and confounding), in place of the less frequently useful experiment criterion [[60](http://www.hindawi.com/journals/jeph/2012/258981/#B59)]. The only criterion that is truly essential for a causal association is temporality, as the outcome must follow the exposure in time. In fact, none of the criteria (with the exception of temporality) are applicable in all circumstances [[67](http://www.hindawi.com/journals/jeph/2012/258981/#B66), [68](http://www.hindawi.com/journals/jeph/2012/258981/#B67)].

The causation criteria can be lumped into three main groups by their utility: (1) those used to evaluate whether there is a reasonably plausible relationship between outcome and exposure (consistency, specificity, biological gradient, plausibility, coherence, experiment, and analogy and cessation); (2) temporality; (3) strength of association (or probability of causation). An analysis involving the application of these criteria to the evaluation of the plausibility of a causal relationship between NHL and elevated PCB congener titers, as well as temporality, is presented in the results and discussion sections. The final criterion, strength of association, is discussed below.

2.2. Meta-Analysis of Individual Congeners as a Measure of Strength of Association (Causal Contribution)

In order to assess the utility of PCB congener level as an index of causal contribution, it was necessary to meta-analyze data from previously published case-control studies in which the risk of NHL was compared with serum levels of individual congeners through the application of conditional logistic regression. In order to be included in the meta-analysis, the studies needed to have the following characteristics in common: they examined individual PCB congeners identified in plasma samples acquired from cases of NHL (as opposed to groups of congeners), they included age and gender frequency-matched controls, they ranked their results by percentile of congener concentration (from lowest to highest tertile, quartile, or quintile), they quantified their results in terms of natural log odds ratios as a measure of NHL risk by comparing the minimum percentile with the maximum, and multiple strata were available for any included congener. For the meta-analysis, the fixed-effect Mantel-Haenszel (MH)-adjusted odds ratio (ORMH) was calculated as a weighted average (𝑤𝑖) of the natural log (ln) odds ratio (OR𝑖) for each study in which the minimum percentile was compared with the highest percentile concentration (Table [3](http://www.hindawi.com/journals/jeph/2012/258981/tab3/)). This minimum-maximum comparison was chosen for the meta-analysis in order to summarize the comparison of the extrema. The following calculation was used: ORMH=∑𝑘𝑖=1𝑏𝑖𝑐𝑖/𝑁𝑖×𝑎𝑖𝑑𝑖/𝑏𝑖𝑐𝑖∑𝑘𝑖=1𝑏𝑖𝑐𝑖/𝑁𝑖=∑𝑘𝑖=1𝑤𝑖OR𝑖∑𝑘𝑖=1𝑤𝑖.(1) This approach utilized the subpopulations within each study (𝑎𝑖, 𝑏𝑖, 𝑐𝑖, and 𝑑𝑖) as identified in the two-by-two contingency tables stratified by 𝑘 studies. The confidence interval for the ORMH was determined by first calculating the standard error (SE) of the OR estimate (OR𝑖) and given by the following equation [[69](http://www.hindawi.com/journals/jeph/2012/258981/#B68)]:SElnORMH=⎷∑𝑘𝑖=1𝑃𝑖𝑅𝑖2∑𝑘𝑖=1𝑅𝑖2+∑𝑘𝑖=1𝑃𝑖𝑤𝑖+𝑄𝑖𝑅𝑖2∑𝑘𝑖=1𝑅𝑖∑𝑘𝑖=1𝑤𝑖+∑𝑘𝑖=1𝑄𝑖𝑤𝑖2∑𝑘𝑖=1𝑤𝑖2,(2) where𝑃𝑖=𝑎𝑖+𝑑𝑖𝑁𝑖,𝑄𝑖=𝑏𝑖+𝑐𝑖𝑁𝑖,𝑅𝑖=𝑎𝑖×𝑑𝑖𝑁𝑖,𝑤𝑖=𝑏𝑖×𝑐𝑖𝑁𝑖.(3) The meta-analyzed 95% confidence level (CI) was then calculated in the natural logarithmic (ln) scale to match the scale of the OR:[].95%CI(lnOR)=lnOR±1.96×SE(lnOR)(4)



Table 3: Notation for the calculation of Mantel-Haenszel-adjusted odds ratios from the published case-control studies reporting association of NHL and PCB blood content for specific congeners. Here, “exposed” and “unexposed” populations noted in traditional meta-analyses were replaced with “upper” and “lower” acknowledging the upper and lower percentiles of exposure reported in the literature, respectively. The subscript “𝑖” indicates each stratum (published congener).

A test for homogeneity was also conducted to assess the application of the fixed-effect model applied here to the published ORs. This approach was applied to test whether the population ORs are in fact constant across the different strata [[70](http://www.hindawi.com/journals/jeph/2012/258981/#B70)]. If the test fails, the ORs can simply be reported as distinct values or be further meta-analyzed using a random-effects model [[27](http://www.hindawi.com/journals/jeph/2012/258981/#B27), [71](http://www.hindawi.com/journals/jeph/2012/258981/#B72)]. The test for homogeneity evaluates the null hypothesis (𝐻𝑜) where the population odds ratios for the 𝑔 tables are assumed statistically identical, or equivalently, 𝐻𝑜=OR1=OR2=⋯=OR𝑖=⋯=OR𝑔. To perform this test, we calculated the chi-square statistic (𝑄or𝜒2):𝑄=𝜒2=𝑔𝑖=1𝑤𝑖𝑦𝑖−𝑌2.(5) Here the natural logarithm of each estimated OR is determined:𝑦𝑖=lnOR𝑖(6) and used to produce a weighted average (𝑌) applying the weighting value described in ([1](http://www.hindawi.com/journals/jeph/2012/258981/#EEq1)), such that:∑𝑌=𝑔𝑖=1𝑤𝑖𝑦𝑖∑𝑔𝑖=1𝑤𝑖.(7) The resulting statistic from ([5](http://www.hindawi.com/journals/jeph/2012/258981/#EEq5)) has a distribution that is approximately chi-square with g-1 degrees of freedom. A chi-square distribution table was then consulted for each test, producing a 𝑃 value as an assessment of the null hypothesis, where 𝑃<0.05 was considered as a rejection of the null [[70](http://www.hindawi.com/journals/jeph/2012/258981/#B70)]. An alternative test statistic for assessing homogeneity is the likelihood ratio test, which is computationally more cumbersome than the 𝑄 statistic applied here [[72](http://www.hindawi.com/journals/jeph/2012/258981/#B73)].

2.3. Ecological Analysis

In order to explicate the correlation between changes in environmental levels of PCBs and changes in the incidence of NHL an ecologic effect analysis was performed. Data were acquired from the National Institute of Cancer [[32](http://www.hindawi.com/journals/jeph/2012/258981/#B32)] and compared to PCB production and sales levels [[6](http://www.hindawi.com/journals/jeph/2012/258981/#B6), [73](http://www.hindawi.com/journals/jeph/2012/258981/#B71)]. Time-dependent accumulation of PCBs was calculated from the annual sales data of the open source materials including heat transfer products, hydraulics/lubricants, miscellaneous industrial products, plasticizers, and petroleum additives. The environmental PCB accumulation data are presented in three forms: first, only the sales data are plotted over time; second, the sales data are extended in time, assuming a static level of accumulation where the maximum presence of PCB in the environment remains fixed and constant after production ceased; third, the sales data are used as a basis from which to assume a dynamic accumulation of PCB, where environmental levels increase as devices and materials break down, continuously releasing congeners into the environment. This last approach required forecasting the accumulation beyond the end of production following a similar initial growth curve into the future. A polynomial curvefit produced a strong phenomenological model representing the time-dependent accumulation in units of kilo-lbs (𝑅2=0.9772), with time measured in years:PCBAccumulation=16,488.2+1048.9(Time)2.(8) This model was then applied to years beyond the end of the sales period, extending the accumulation data into the future, matching the surveillance period for NHL incidence. Plotted comparisons were made over the actual dates (calendar years) as well as relative time from origination (both in sales and cancer incidence monitoring).

The environmental PCB accumulation model was juxtaposed with the incidence over time of a number of major cancer types. A correlation coefficient was calculated for each NHL and non-NHL association, where 𝑅2>0.80 was considered a strong statistical correlation.

3. Results

3.1. Assessment of the Hill Criteria for Causation

3.1.1. Plausibility

In the present context, plausibility does not refer to Hill’s narrow use of the term as one of the nine causal criteria, in which he referred to the specific biologic action by which an environmental factor caused a disease, but rather to the group of criteria (all but temporality and strength of association) that answer the question “can the exposure cause the outcome?” Interestingly, Hill did not consider the biological plausibility criterion to be particularly critical to a finding of cause and effect, stating that he was “convinced this is a feature that we cannot demand” [[62](http://www.hindawi.com/journals/jeph/2012/258981/#B61)]. This was because of the recognition that an environmental toxin may, in fact, cause a disease by a currently unexplicated mechanism that may be described in the future.

In examining the plausibility of a causal relationship between PCB exposure and NHL, there is a substantial amount of published information to rely upon that indicates that the relationship is indeed plausible. Analogy is strongly supported for PCB exposure as a cause of NHL, as they belong to the same chemical family of organochlorines as other chemicals that have been associated with NHL in prior epidemiologic studies [[27](http://www.hindawi.com/journals/jeph/2012/258981/#B27)]. From a biological plausibility perspective, NHL is a disease that has been repeatedly shown to be related to compromise of the body’s immune response [[24](http://www.hindawi.com/journals/jeph/2012/258981/#B24), [25](http://www.hindawi.com/journals/jeph/2012/258981/#B25)], and there are a number of PCB congeners that have been deemed immunotoxic [[74](http://www.hindawi.com/journals/jeph/2012/258981/#B74)]. Additionally, the dioxin-like PCB congeners have the ability to bind to the aryl hydrocarbon receptor, a normally inactive transcription factor that when bound can alter genetic transcription.

Consistency of the relationship is seen with the number of published epidemiologic studies, both case-control and cohort design, of various populations in various settings in which an association between PCB congener titer levels has been linked to NHL risk (Tables [1](http://www.hindawi.com/journals/jeph/2012/258981/tab1/) and [2](http://www.hindawi.com/journals/jeph/2012/258981/tab2/)).

3.1.2. Temporality

Because of the ubiquitous nature of PCBs in the environment and the way in which they accumulate over time in the body, as well as the nature of NHL as a disease that has seen its largest increases in the population over the age of 55, aside from the youngest patients with NHL (often those with readily apparent explanations for the disease, such as immunosuppressive infections), temporality is assumed to be appropriately present in most cases of NHL in the presence of high PCB titers.

3.1.3. Strength of Association (Causal Contribution) via Meta-Analysis

Eleven published case-control studies reported on the association between NHL and PCB levels were considered for meta-analysis (Table [1](http://www.hindawi.com/journals/jeph/2012/258981/tab1/)). Of these publications, six articles described seven unique populations associating the influence of 10 congeners (28, 99, 118, 138, 153, 156, 170, 180, 183, and 187) on NHL incidence and which were deemed eligible under the meta-analysis inclusion criteria. Point-estimate odds ratio results for all studied congeners from each of the published case-control studies are described via horizontal forest plot as a summary of the previous published results (Figure [1](http://www.hindawi.com/journals/jeph/2012/258981/fig1/)). These results were then meta-analyzed according to the methods described previously (Figure [2](http://www.hindawi.com/journals/jeph/2012/258981/fig2/)).



Figure 1: Odds ratios and 95% confidence limits for all PCB blood-level congeners as associated with NHL and reported in six case-control studies.



Figure 2: Meta-analyzed congeners indicating Mantel-Haenszel-adjusted odds ratios and 95% confidence limits for all PCB blood-level congeners with two or more strata including the ORMH for all congeners combined. Congeners with single study analyses are also included (congeners 99, 156, 183, and 187). Statistically significant confidence intervals are indicated (\*). Meta-analyzed upper percentile cutoff PCB blood-level values are also included for each congener (ng/g lipid).

The weight-adjusted odds ratio (ORMH) for all 10 congeners collectively was 1.43 (95% CI 1.31–1.55). Each of the 10 congeners contributed to its own congener-specific meta-analysis as well as toward the all-congener ORMH. ORMH results for seven congeners (118, 138, 153, 156, 170, 180, and 187) were statistically significant, whereas the results for three congeners (28, 99, and 183) were not (Figure [2](http://www.hindawi.com/journals/jeph/2012/258981/fig2/) and Table [4](http://www.hindawi.com/journals/jeph/2012/258981/tab4/)). All of the seven congeners with significant meta-analysis results have been previously described as having immunotoxic characteristics, and one (118) is also considered to be dioxin like.



Table 4: List of contributing strata and OR metrics satisfying the meta-analysis criteria. Results of the Chi-square test for homogeneity (𝑃 values and degrees of freedom, DOF) are shown for each meta-analyzed congener. Note that congener 118 is statistically heterogeneous (𝑃<0.025). However, removal of the weighted outlier [[46](http://www.hindawi.com/journals/jeph/2012/258981/#B49)] indicated homogeneity in the remaining strata. A combined test of all congeners indicated overall homogeneity (𝑃>0.10 and 37 DOF).

3.2. Ecological Effects

The ecological data representing the incidence of NHL versus PCB accumulation over time indicated statistically strong correlations (𝑅2>0.94) regardless of the assumed accumulation models (Figure [3](http://www.hindawi.com/journals/jeph/2012/258981/fig3/)). A high degree of correlation (𝑅2>0.8) between NHL incidence and PCB accumulation was observed for several other cancers for one or two of the accumulation models, including breast, liver and bile duct, kidney, skin, and soft tissue and heart, however none of these other cancers consistently demonstrated high-correlation values in all three models (Table [5](http://www.hindawi.com/journals/jeph/2012/258981/tab5/)).



Table 5: Summary of the dose-response correlations between synchronized polychlorinated biphenyl (PCB) bioaccumulation and the incidence of cancer. Accumulation is represented as based on sales alone (sales growth), environmental exposure (static growth), and physiologic exposure (dynamic growth).



Figure 3: Ecological correlations between PCB accumulation and the national incidence of NHL compared over calendar years and relative year based on the assumptions of (a) sales-only exposure (sales model); (b) environmental exposure (static model); (c) physiologic exposure (dynamic model).

4. Discussion

The results of the (nonexhaustive) application of the Hill criteria to the current state of knowledge regarding the relationship between blood levels of PCBs and NHL risk indicate a plausible causal association. The multiple case-control studies described herein also consistently demonstrate a strong level of association between elevated PCB levels and NHL sufficient to conclude that a (general) causal relationship exists between the two, and that if PCBs were to be eliminated from the environment, a certain proportion of NHL cases would likewise be eliminated.

This conclusion is further supported by the results of the ecological analysis reported herein, in which a relationship between PCB levels in the environment over time appeared to be more uniquely and strongly correlated with NHL incidence than with other types of cancers. The multicause nature of NHL means that these data should be viewed with caution and even skepticism, but the observed relationships are at the very least consistent with other theories regarding the inordinately large increase in NHL incidence over the past approximately 40 years.

Based on these results and the multifactorial nature of NHL, it is reasonable to conclude that a certain proportion of individual cases of NHL occur only because of elevated PCB levels; in another proportion, elevated PCB levels have contributed to the cause of the NHL in conjunction with other causes but cannot be said to be solely necessary as a cause; in another proportion the body burden of PCBs is neither completely nor partially contributory to the NHL occurrence. We posit that if an individual with NHL is found to have a titer of PCB congeners 118, 138, 153, 156, 170, 180 or 187 that exceeds 75% of that of the comparable general population of the same age and era [[75](http://www.hindawi.com/journals/jeph/2012/258981/#B69)], then it can be concluded that the elevated body burden of PCBs causally contributed to the NHL occurrence.

Given this conclusion, the issue of the >2.0 relative risk specific causation threshold must be addressed. In a setting in which there is an identified unexposed comparison group, a relative risk of 1.43 (here defined by an OR with the lesser exposed) would mean that out of 143 hazard-exposed subjects with the disease of interest, 43 acquired the disease only because of the exposure, and 100 developed the disease independent of the exposure to the hazard. For the purposes of a specific causation evaluation, randomly selecting one of the exposed cases would result in a probability of causation of 30% (43/143), and thus the conclusion that the individual’s disease was not related to the exposure, on a more probable than not basis. Such an approach is potentially problematic because it will result in an erroneous determination of no causal relationship between the hazardous exposure and the disease in 30% of specific causation evaluations [[76](http://www.hindawi.com/journals/jeph/2012/258981/#B75)]. The 2.0 relative risk approach becomes problematic to a point of impracticality when evaluating specific causation for PCBs and NHL. When considering the 143 highest PCB titer percentile-exposed subjects with NHL (representative of the meta-analyzed 1.43 ORMH described herein), there will be 43 who have the disease only because of the PCB exposure, and 100 subjects in whom their elevated PCB levels may or may not have contributed to their NHL, since in reality all of the “unexposed” subjects are really just “lesser exposed” subjects. The fact that there are no unexposed comparison groups (zero PCB body burden) with which the cases could be compared in the meta-analyzed studies effectively lowered the resulting odds ratios to a largely unknown degree. Some indication of the magnitude of this effect can be inferred from the ecological data presented herein, as there was an approximate doubling of the incidence of NHL over a 30-year period of time that was temporally associated with the introduction of PCBs into the environment. It may be a reasonable supposition that some proportion of the cases resulted from the exponential increase in environmental PCBs that preceded the dramatic increase in the rate of NHL and which are represented in all percentiles of PCB exposure.

Additionally, it appears that there are a couple of factors that tend to decrease PCB levels in the body that may be associated with the presence or diagnosis of NHL, resulting in lower post-NHL-diagnosis titers than what may have been presented prior to diagnosis. Individuals with higher body mass index (BMI) levels metabolize and eliminate PCBs more slowly, and because weight loss is a common feature of NHL, this feature of the disease would tend to decrease the body burden of PCBs as the illness progressed [[77](http://www.hindawi.com/journals/jeph/2012/258981/#B76)]. Additionally, chemotherapy, a common medical treatment for NHL, has been observed to potentially decrease PCB levels in the body by nearly 30% [[78](http://www.hindawi.com/journals/jeph/2012/258981/#B77)].

Taken together, all of these factors indicate that the 2.0 relative risk or odds ratio threshold cannot be reasonably applied to PCB and NHL. It is for this reason that the use of upper percentile cutoff values associated with the maximum versus minimum ORMH to conclude that causal contribution is present is thought to be a reasonably practicable alternative to evaluating causation for an environmental toxin so ubiquitous that no unexposed group exists for comparison.

5. Conclusions

Application of the Hill criteria to the current state of knowledge regarding the association between environmental PCBs and NHL reveals convincing evidence of plausibility, as well as a strong general causal association, with meta-analyzed odds ratios indicating a 43% association of studied NHL cases in the literature with total PCB levels in the highest percentile, relative to comparison populations in the lowest percentiles of PCB levels. For evaluation of the causal contribution of PCBs to an individual case of NHL, the meta-analyzed values for seven immunotoxic congeners (118, 138, 153, 156, 170, 180, and 187) are presented and compared with relevant population survey data. When an individual case of NHL presents with one of these seven congener titers that fall into the highest quartile of their representative general population, it is reasonable to conclude a causal contributory relationship is present, on a more probable than not basis.

Disclosure

Both authors provide forensic consulting services for environmental toxin litigation.

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| Number of New Cases and Deaths Per 100,000 People (All Races, Males and Females), Age-Adjusted |
| --- |
| **Year** | **New Cases - SEER 9**  | **New Cases - SEER 13** | **Deaths - US** |
| 1975 | 7.9 | - | 2.1 |
| 1976 | 8.2 | - | 2.2 |
| 1977 | 8.9 | - | 2.3 |
| 1978 | 8.9 | - | 2.3 |
| 1979 | 9.5 | - | 2.4 |
| 1980 | 10.5 | - | 2.3 |
| 1981 | 11.1 | - | 2.4 |
| 1982 | 11.2 | - | 2.5 |
| 1983 | 11.1 | - | 2.5 |
| 1984 | 11.4 | - | 2.5 |
| 1985 | 12.8 | - | 2.6 |
| 1986 | 13.3 | - | 2.6 |
| 1987 | 13.7 | - | 2.6 |
| 1988 | 12.9 | - | 2.6 |
| 1989 | 13.7 | - | 2.7 |
| 1990 | 13.9 | - | 2.8 |
| 1991 | 14.6 | - | 2.7 |
| 1992 | 14.8 | 14.1 | 2.7 |
| 1993 | 14.6 | 13.8 | 2.7 |
| 1994 | 15.7 | 14.8 | 2.7 |
| 1995 | 16.5 | 15.8 | 2.7 |
| 1996 | 17.4 | 16.5 | 2.8 |
| 1997 | 17.7 | 16.8 | 2.7 |
| 1998 | 17.9 | 16.8 | 2.8 |
| 1999 | 18.3 | 17.3 | 2.6 |
| 2000 | 19.0 | 17.7 | 2.7 |
| 2001 | 19.7 | 18.5 | 2.7 |
| 2002 | 19.3 | 17.9 | 2.6 |
| 2003 | 19.5 | 18.0 | 2.7 |
| 2004 | 20.7 | 19.0 | 2.7 |
| 2005 | 22.5 | 20.4 | 2.8 |
| 2006 | 22.1 | 20.0 | 2.7 |
| 2007 | 21.8 | 20.1 | 2.7 |
| 2008 | 23.1 | 21.0 | 2.7 |
| 2009 | 23.0 | 20.5 | 2.8 |
| 2010 | 23.8 | 21.3 | 2.7 |
| 2011 | 22.7 | 20.3 | - |

[Expand All](http://seer.cancer.gov/statfacts/html/melan.html) [Collapse All](http://seer.cancer.gov/statfacts/html/melan.html)

Top of Form

**New Cases, Deaths and 5-Year Relative Survival** [**View Data Table**](http://seer.cancer.gov/statfacts/html/ld/melan.html)



| **Year** | **1975** | **1980** | **1985** | **1990** | **1994** | **1998** | **2002** | **2006** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 5-Year Relative Survival | 81.8% | 83.9% | 86.1% | 89.2% | 88.8% | 90.9% | 92.9% | 92.8% |

SEER 9 Incidence 1975-2011 & U.S. Mortality 1975-2010, All Races, Both Sexes. Rates are Age-Adjusted.





[Béatrice Lauby-Secretan](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=B%C3%A9atrice+Lauby-Secretan) , [Dana Loomis](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Dana+Loomis) , [Yann Grosse](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Yann+Grosse) , [Fatiha El Ghissassi](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Fatiha%20El+Ghissassi) , [Véronique Bouvard](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=V%C3%A9ronique+Bouvard) , [Lamia Benbrahim-Tallaa](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Lamia+Benbrahim-Tallaa) , [Neela Guha](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Neela+Guha) , [Robert Baan](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Robert+Baan) , [Heidi Mattock](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Heidi+Mattock) , [Kurt Straif](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Kurt+Straif) , on behalf of the International Agency for Research on Cancer Monograph Working Group IARC, Lyon, France

In February 2013, 26 experts from 12 countries met at the International Agency for Research on Cancer (IARC), Lyon, France, to reassess the carcinogenicity of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). These assessments will be published as volume 107 of the IARC Monographs.[1](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970104-9/fulltext?version=printerFriendly" \l "bib1" \o ")

PCBs are a class of aromatic compounds comprising 209 congeners, each containing one to ten chlorine atoms attached to a biphenyl nucleus. Technical PCB products, which were manufactured to obtain a specific level of chlorination, are mixtures of many PCB congeners. These products were widely used as dielectric fluid in capacitors and transformers, and to a lesser extent in building materials (eg, caulking, paints, and lighting ballasts). PCB production and new use were banned in most countries by the 1980s, but production has been reported recently in North Korea.

Earlier, occupational exposure was highest during manufacture of PCBs, transformers, and capacitors; today, exposure can come from demolition, dysfunction, or uncontrolled recycling of PCB-contaminated structures and equipment. PCBs are persistent and bioaccumulate; they have become ubiquitous environmental pollutants, including in polar regions and the deep ocean. Because of weathering and biotransformation, the PCB profiles noted in the environment or during biomonitoring differ from those of the commercial products. The general population is exposed mainly via food, mostly from contaminated animal fats; two major episodes of food poisoning took place in Japan and Taiwan, China, where cooking oil was accidentally contaminated with PCBs. Indoor air can also contribute to human exposure. Worldwide monitoring programmes have shown that PCBs are present in most samples of human milk.

PCB congeners can be categorised by their degree of chlorination, substitution pattern, and binding affinity to receptors. 12 congeners with a strong affinity for the aryl hydrocarbon receptor (AhR) are referred to as dioxin-like PCBs. PCBs are readily absorbed and distributed in the body, and accumulate in adipose tissue. Biotransformation of all PCB congeners starts with cytochrome P450-dependent mono-oxygenation. Low-chlorinated PCBs are readily metabolised into highly reactive electrophilic species (ie, arene oxides, quinones) which, in addition to producing DNA adducts and reactive oxygen species, are directly genotoxic and mutagenic.[2](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970104-9/fulltext?version=printerFriendly" \l "bib2" \o ") By contrast, highly chlorinated PCBs are poorly metabolised but, through induction of xenobiotic-metabolising enzymes, can also generate reactive oxygen species, lipid peroxidation, oxidative and alkylating DNA adducts, and can eventually cause genotoxic effects.

Individual PCBs activate numerous receptors, including AhR and the constitutive androstane and pregnane xenobiotic receptors (CAR/PXR). AhR activation is one of the key events linked to carcinogenesis mediated by dioxin-like PCBs. Sustained activation leads to deregulation of cell-cycle control and cell proliferation, inhibition of apoptosis, suppression of cell-to-cell communication and adhesion, and increased cell plasticity and invasiveness. Non-dioxin-like PCBs induce many of these effects via several AhR-independent mechanisms, including activation of the constitutive androstane and pregnane xenobiotic receptors, and perturbations in cell-to-cell communication and cell adhesion.

PCBs can compromise the immune surveillance mechanism. Highly chlorinated PCBs with a strong affinity for the AhR are potent immunotoxicants; less-chlorinated PCBs, which are less immunotoxic, act via AhR-independent mechanisms, including metabolic activation. Both low-chlorinated and high-chlorinated PCBs are associated with chronic inflammatory responses. Non-dioxin-like PCBs can stimulate the production of inflammatory mediators, whereas dioxin-like PCBs can inhibit such reaction. By contrast, some dioxin-like PCBs, but not non-dioxin-like PCBs, can compromise the normal function of the vascular endothelium.

PCBs target the endocrine system. Several models have shown direct modulation of nuclear steroid hormone-dependent gene expression by PCBs. Furthermore, depending on their structure, monohydroxylated PCB metabolites can act as oestrogen agonists or antagonists. These disruptions might have reproductive, toxic, and carcinogenic consequences.

The Working Group considered more than 70 independent epidemiological studies with informative data for carcinogenicity of PCBs in human beings. Excess risks for melanoma were reported in several studies, mainly cohort studies of workers in the manufacture of capacitors and transformers, and in electric power and equipment maintenance. A significant linear exposure—response trend was noted in the largest study.[3](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970104-9/fulltext?version=printerFriendly" \l "bib3" \o ") In a population-based case-control study that assessed exposure with PCB serum levels, the association persisted after control for sun sensitivity and exposure.[4](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970104-9/fulltext?version=printerFriendly" \l "bib4" \o ") The association of melanoma and PCBs was noted consistently in occupational studies in different industries in North America and Europe, in studies of the general population, and with cohort and case-control designs. Thus, the Working Group concluded that there is sufficient evidence in humans for the carcinogenicity of PCBs. Notably, AhR can modulate melanogenesis,[5](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970104-9/fulltext?version=printerFriendly" \l "bib5" \o ") which lends mechanistic plausibility to this association. Increased risks for non-Hodgkin lymphoma and breast cancer were also reported, both of which are biologically plausible. However, the associations were not consistent and were considered as providing limited evidence. Data for cancers at other sites were too sparse to draw any conclusions.

The carcinogenicity of PCBs in animals has been assessed for individual congeners; binary mixtures of congeners; technical mixtures containing various congeners; and simulated environmental mixtures, with 2 year bioassays; studies with perinatal and postnatal exposure; and studies that examined the initiating and promoting activities of PCBs. Individual congeners (PCB118, PCB126) and several commercial products with a high chlorine content induced benign and malignant tumours of the liver, lung, and oral mucosa in rats; these studies provided sufficient evidence of carcinogenicity in experimental animals.[6](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970104-9/fulltext?version=printerFriendly" \l "bib6), [7](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970104-9/fulltext?version=printerFriendly" \l "bib7) These congeners and mixtures include AhR agonists that exhibit dioxin-like activities, and CAR agonists.[8](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970104-9/fulltext?version=printerFriendly" \l "bib8" \o ") Other PCB congeners (PCB153) and low-chlorinated commercial products, which were less well studied than highly chlorinated products, showed limited evidence of carcinogenicity in experimental animals.[9](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970104-9/fulltext?version=printerFriendly" \l "bib9" \o ") The relative contributions of different PCB congeners to the carcinogenicity of the commercial mixtures are not known.

Overall, all PCBs can induce formation of reactive oxygen species, genotoxic effects, immune suppression, an inflammatory response, and endocrine effects to various extents and through different pathways. The dioxin-like PCBs exert their effects mainly through AhR activation and the downstream cascade of related events; less-chlorinated PCBs act more readily through metabolic activation and the downstream effects of these metabolites. Thus, mixtures might have more than additive effects.

On the basis of sufficient evidence of carcinogenicity in humans and experimental animals, the Working Group classified PCBs as carcinogenic to humans (Group 1). Additionally, dioxin-like PCBs were also classified in Group 1 on the basis of extensive evidence of an AhR-mediated mechanism of carcinogenesis that is identical to that of 2,3,7,8-tetrachlorodibenzo-para-dioxin, and sufficient evidence of carcinogenicity in experimental animals. However, the carcinogenicity of PCBs cannot be solely attributed to the carcinogenicity of the dioxin-like PCBs.

PBBs resemble PCBs, with bromine rather than chlorine atoms. PBBs were used mainly as flame retardants in the 1970s, but production has been discontinued in most countries for many years. One release of PBBs took place in Michigan, USA, where they were inadvertently distributed as cattle-feed supplement, contaminating many agricultural products. Similar to PCBs, PBBs are highly lipophilic, bioconcentrate and bioaccumulate, and are environmental contaminants worldwide. FireMaster FF-1, the most widely used commercial PBB product, consistently induced benign and malignant hepatocellular tumours in rats and mice, and cholangiocarcinomas in rats.[10](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2813%2970104-9/fulltext?version=printerFriendly" \l "bib10" \o ") PBBs, like their chlorinated analogues, are ligands to several cellular and nuclear receptors, including AhR. They are efficacious inducers of hepatic drug metabolism, accelerating the biotransformation of both endogenous and exogenous compounds. PBBs have various adverse effects including suppression of the immune system and disruption of normal hormone function. They are efficient promoters in two-stage rodent hepatocarcinogenesis bioassays. Although PBBs have received less attention and study, the available data indicate that PBB congeners exhibit their toxic effects and carcinogenic potential via many of the same pathways as their chlorinated counterparts. On the basis of these similarities with PCBs, and together with inadequate evidence for carcinogenicity in humans and sufficient evidence in experimental animals, PBBs were upgraded to Group 2A, probably carcinogenic to humans

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