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Evaluation of Cumulative PCB Exposure Estimated by a Job Exposure Matrix versus PCB Serum Concentrations

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Abstract

Although polychlorinated biphenyls (PCBs) have been banned in many countries for more than three decades, exposures to PCBs continue to be of concern due to their long half-lives and carcinogenic effects. In National Institute for Occupational Safety and Health studies, we are using semi-quantitative plant-specific job exposure matrices (JEMs) to estimate historical PCB exposures for workers (n=24,865) exposed to PCBs from 1938 to 1978 at three capacitor manufacturing plants. A sub-cohort of these workers (n=410) employed in two of these plants had serum PCB concentrations measured at up to four times between 1976 and 1989. Our objectives were to evaluate the strength of association between an individual worker's measured serum PCB levels and the same worker's cumulative exposure estimated through 1977 with the JEM (i) and duration of employment (ii); and to calculate the explained variance the JEM provides for serum PCB levels using simple linear regression (iii). Consistent strong and statistically significant associations were observed between the cumulative exposures estimated with the JEM and serum PCB concentrations for all years. The strength of association between duration of employment and serum PCBs was good for highly chlorinated (Aroclor 1254/HPCB) but not less chlorinated (Aroclor 1242/LPCB)PCBs. In the simple regression models cumulative occupational exposure estimated using the JEMs explained 14-24% of the variance of the Aroclor 1242/LPCB and 22-39% for Aroclor 1254/HPCB serum concentrations. We regard the cumulative exposure estimated with the JEM as a better estimate of PCB body burdens than serum concentrations quantified as Aroclor 1242/LPCB and Aroclor 1254/HPCB.

INTRODUCTION

Although polychlorinated biphenyls (PCBs) have been banned in many countries for more than three decades, and use of PCBs is being phased out, exposures to PCBs continue to be of general, regulatory, and epidemiologic concern due to their carcinogenic effects (Baan et al. 2009, IARC; 1997). In recent epidemiological studies (Prince et al. 2006, Ruder et al. 2006, Silver et al. 2009, Steenland et al. 2006), we used job exposure matrices (JEMs) to estimate historical PCB exposures for former workers (n=24,865) in the National Institute for Occupational Safety and Health capacitor manufacturing cohort exposed to PCB at three plants from 1938-1978 (Hopf et al. 2012 in review, Hopf et al. 2009b, Hopf et al. 2010). The JEMs ranked all jobs identified from detailed work histories through 1977 into exposure categories based on assessed dermal and inhalation PCB exposures. Plant-specific air concentrations were used to anchor PCB exposure ratings, making it possible to compare across plants. Cumulative exposures were estimated by multiplying the time spent in each job exposure category by the corresponding exposure value and summing over all jobs worked. In the mortality study of the two larger plants in New York and Massachusetts, both liver (trend *p-value* = 0.071) and prostate (trend *p-value* = 0.0001) mortality increased with cumulative exposures estimated with the JEM, showing strong exposure-response relationships (Prince et al. 2006).

Traditionally, duration of exposure has been a surrogate for estimating cumulative exposure in occupational epidemiological studies; however, duration doesn't distinguish between workers in high or low exposure jobs, which may bias the results. Cumulative

exposures estimated with specific JEMs distinguish exposure levels associated with each job. JEMs are usually based on job titles and air concentrations. Exposure-response trends may be further improved by estimating cumulative internal exposures using biological monitoring. This is especially true for compounds such as PCBs, which may enter the body by inhalation, oral, and dermal routes because biological monitoring accounts for all routes of exposures. As opposed to cumulative exposures estimated with JEMs, serum PCB levels indicate an individual worker's measured body burden at the time of the blood draw.

Historically, two methods to quantify PCBs in sera were commonly used (Lawton et al. 1985a) by using an "Aroclor standard" by summing the heights of selected peaks on the gas chromatogram with an electron capture detection (GC/ECD) which correlated with hallmark peaks of the commercial PCB products Aroclor 1242 (42% chlorinated product) and Aroclor 1254 (54% chlorination); or by quantifying lower- or higher-chlorinated PCBs (LPCBs or HPCBs) based on the sum of the GC peaks that occurred before or after the retention time of p,p'-dichlorodiphenyldichloroethylene (DDE) [universally detected in sera from people in the industrialized world] (Table 1).

The two methods for quantifying PCBs in sera are related, with 93% of Aroclor 1242 being LPCBs and 96% of Aroclor 1260 being HPCBs (Lawton et al. 1985a). These serum PCB levels are a "snapshot" integrating current and past exposures; where LPCBs and Aroclor 1242 indicate current exposures due to their shorter half-lives (months to a few years) and HPCBs and Aroclor 1254 represent past exposures with very long half-lives

(several decades) (Brown et al. , Hopf et al. 2012 in review, Phillips et al. 1989, Seegal et al. 2011, Wolff et al. 1982).

The cohort includes workers at capacitor manufacturing plants in Indiana, Massachusetts, and New York. Sera were collected by a subset of workers at the New York plant (n=192), and the Indiana plant (n=218) (Brown et al. 1991, Brown Jr 1988, Lawton et al. 1985a, Lawton et al. 1985b, Phillips et al. 1989, Smith 1982). For some of these workers, serum PCB concentrations were collected once during and three times after PCB exposures ceased. Here, we explore the relationships among three different measures of cumulative exposure: duration of exposure, cumulative exposure estimated with the JEM, and internal exposure measured as PCB in sera.

The objectives of this paper were to evaluate the strength of association between an individual worker's measured serum PCB levels and the same worker's cumulative exposure estimated with the JEMs (i) and duration of employment, which is a common proxy for exposure used in epidemiological studies (ii); and finally, (iii) calculate the explained variance the JEM provides for serum PCB levels using simple linear regression.

METHODS

Capacitor manufacturing

Capacitor manufacturing began with winding foil or paper film into bales, which were placed in a metal capacitor box. These pre-fabricated capacitors were placed in a vacuum

chamber for impregnation with the dielectric fluid (PCBs). Excess PCBs were drained after the filling cycle. At this time trays of wet capacitors on carts were manually transported to a sealing station where they were soldered shut. Finally, the capacitors were degreased, leak tested, and painted.

PCB air concentrations

PCB air concentrations for the Indiana plant were measured in 1977 by NIOSH investigators. Personal air concentrations (n = 40) were collected in 10 jobs with varying degree of PCB exposures and area air concentrations (n = 16) in 16 locations (Hopf et al 2009b). The total range of the air concentrations were n.d.–264 µg/m³. PCB air concentrations for the New York plant were measured in 1975 and 1977 by the company and in 1977 by NIOSH investigators. The NIOSH personal air concentrations were measured for jobs with considerable PCB exposure, and ranged from 24 to 396 µg/m³ (n=31); and area air concentrations were measured in areas considered to have low PCB exposures with a range 3-476 µg/m³ (n=13). The New York plant company collected area air samples in the capacitor production departments in 1975 which ranged from 260 to 2000 µg/m³ (n=30), and in 1977 other highly exposed areas were sampled with a range of 172-582 µg/m³ (n=16). The 1975 PCB air concentrations were much higher than those from the NIOSH 1977 survey. Two of these samples were collected in the same highly exposed area in both years (1975 and 1977), and showed a decline of 80%, while levels of samples from other workstations declined between 30-60%. The reason for this large reduction could have been new production techniques recently initiated as noted in the NIOSH survey.

PCB use over time

PCB use started in 1946 and 1954, at the two facilities of the New York plant, respectively, and in 1959 at the Indiana plant. PCB use gradually decreased and eventually ended in 1977 at both plants. In the U.S., PCBs for capacitor manufacturing were sold under the trade name Aroclor. Aroclor 1254 had a mean chlorination of 54%, and Aroclor 1242/1016 a mean chlorination of 41-42%. The New York plant used Aroclor 1254 from 1946 to 1954, Aroclor 1242 from 1954 to 1971, and Aroclor 1016 from 1971 to 1977 (Brown and Jones, 1981). The Indiana plant used Aroclor 1242 from 1959 through 1971 and Aroclor 1016 from 1971 until the PCB dielectric fluid was replaced in 1977.

Serum PCBs

During the time the Indiana plant manufactured PCB-filled capacitors (1957 - 1977), a total of 3,569 employees worked at the plant. In 1977, blood specimens were obtained from 218 workers (Smith 1982). The New York plant employed 6,941 workers during PCB-filled capacitor manufacturing (1946-1954) and blood specimens were collected from 192 of these workers (Brown et al. 1991, Brown et al. 1994, Lawton et al. 1985a, Lawton et al. 1985b). Among the 192 New York workers 78% were men and among the 218 Indiana plant workers 88% were men.

We are designating the serum concentrations as Aroclor 1242/LPCB to encompass LPCB and Aroclor 1242/1016 and as Aroclor 1254/HPCB to encompass HPCB and Aroclor

1254 determinations so that we can consider the two analytical laboratory methods used in 1970-89 with a packed column GC/ECD (Brown et al. 1994, Brown et al. 1991, Lawton et al. 1985a, Lawton et al. 1985b, Smith 1987) equally in the statistical analysis (Table 1). These methods differ significantly from today's method because they do not allow for PCB congener determination. Table 2 shows the correspondence between commercial PCB mixtures and serum PCB levels. Overall, the workers' serum PCB levels decreased over time, serum PCB levels were serially correlated over time, and Aroclor 1242 concentrations were higher than those of Aroclor 1254.

Development of the JEMs

The JEMs (Hopf et al. 2009a, Hopf et al. 2012 in review) were based on detailed plant specific exposure assessments. Here we briefly describe the approach we used to develop the plant specific JEMs. **First**, we defined the appropriate factors that could influence possible PCB exposures (exposure determinants) (Stewart 1999) within the plant and in a job. **Second**, jobs with similar PCB exposures as determined by the similarly rated exposure determinants were assigned to a common job exposure category. **Third**, each job exposure category was ranked according to PCB exposures. The major factors governing the differences across job exposure categories were the extent of dermal and inhalation PCB exposure, and exposure to other chemicals. Jobs with other chemical exposures with known or suspected carcinogenic properties such as trichloroethylene (TCE) were differentiated from jobs without TCE exposure but with otherwise similar PCB exposures to reduce exposure misclassification in the epidemiological studies. For both dermal and inhalation exposures exposure frequency and intensity were estimated.

Frequency of PCB exposures was either continuous (PCB tasks performed all day) or intermittent (sporadic throughout the day). Inhalation intensity depended on proximity to the PCB sources, degree of automation, ventilation, and processes temperatures. Dermal intensity considered degree of contact with PCBs such as handling open PCB-filled containers or touching PCB-contaminated surfaces. The lowest exposure category (salaried workers) was the baseline, with the other job exposure categories ranked relative to baseline, and in three groups: low, medium, or high intensity PCB exposures. **Fourth**, the qualitative PCB exposure rankings for each job exposure category were replaced by quantitative values. We assigned continuous exposure to be 1. Intermittent exposure could potentially be anything from the time it took to perform a task up to all day and was assigned ½. PCB air concentrations were collected in both plants in 1977 by NIOSH. For the New York plant only, area air samples were also collected in 1975 by the company. For each plant all available PCB air concentrations ($\mu\text{g}/\text{m}^3$) were used. The PCB concentration means for each qualitative inhalation intensity ranking (high, medium, low, and baseline) were calculated separately for each plant giving plant specific values for the qualitative inhalation intensity. By doing this, we circumvented the problem of job exposure categories without associated PCB air concentrations. We did not have any measurements for skin exposures; therefore the dermal intensity exposure ratings were given equivalent values as the corresponding inhalation values. When applying the inhalation PCB intensity values for the dermal exposure groups (high, medium, low, and baseline, respectively), they became unitless, representing a scale rather than actual numeric dermal exposure which is typically measured in $\mu\text{g}/\text{cm}^2$. A worker's cumulative inhalation exposure to PCBs was calculated by summing workday exposure for the entire

work history, except when combining the inhalation ($\mu\text{g year/m}^3$) and dermal (unitless) JEMs both routes were treated as relative scales and gave a JEM with no units, because of the unitless dermal JEM. In our assessment, equal weights were given for inhalation and dermal PCB intensity exposure, but this is not to say that absorbed dose from a dermal PCB exposure with a given numerical value would be equal to that of an inhalation exposure with the same value. The values assigned for the exposure categories high, medium, low, and baseline/background for the New York plant were 750, 300, 50, and 10 ($\mu\text{g/m}^3$ for inhalation and unitless for dermal exposures); and for the Indiana plant were 230, 140, 50, and 5, respectively. **Fifth**, the job exposure category *value* calculated for PCB exposure was frequency multiplied by intensity. For categories with intermittent (estimated half-day) exposure this was performed twice to account for the rest of the day (the half-day without the intermittent exposure level was rated as the next lower intensity). Each job exposure category was described with both dermal and inhalation exposure values. **Sixth**, production changes made over the years (lay-out, equipment, Aroclor type use, and the awareness of industrial hygiene) that influenced PCB exposures were incorporated into the JEM using a modification factor, which assumed higher exposure levels in earlier eras. The higher PCB concentrations in the earlier era were due to less restrictive work practices, spills, or higher volume of use, while saturation of porous surfaces offgassing PCBs increased over time. To reflect historical changes that would influence the PCB concentrations, we multiplied the estimates for the first production era (both plants) by 1.20 to reflect an estimated exposure level 20% higher than in the 1976-77 era; for the New York plant a second production era (1-1-1961 to 12-

31-1975) with the multiplier 1.10 was used, to reflect an exposure level estimated to have been 10% higher than in 1976-77.

Cumulative exposure estimates using the JEMs

Cumulative exposure at time t was calculated by summing the product of the duration of exposure in each job and the exposure level for the job as assigned by the plant-specific JEM over all jobs worked prior to time t . For each of the serum draws, cumulative exposure was computed as of the date of the serum draw.

Statistical analysis

Pearson correlations between workers' serum PCB levels and cumulative exposure estimated with the plant-specific JEMs were calculated. Log-transformed serum PCB levels at each time point were related to the cumulative exposure levels estimated by the JEM in simple regression models using SAS PROC REG, version 9.2 (SAS Institute Inc., Cary, NC). Cofactors such as body mass index (BMI) and age were not incorporated in the analysis as information was not available.

RESULTS

The descriptive statistics of the workers and serum PCB levels are given in Table 3. All serum PCB concentrations were naturally log-transformed before statistical analysis.

Pearson correlations between cumulative exposures estimated with the plant-specific JEMs and serum PCBs were calculated separately for higher and lower chlorinated PCBs, for all years with blood draws (Table 4). Overall, consistent strong and statistically

significant associations were observed between the cumulative exposures estimated with the JEM and serum PCB concentrations (both lower-and higher chlorinated PCBs) for both plants and all years.

The associations between duration of employment and serum PCBs were not as consistent. For the New York plant the strength of association with Aroclor 1254/HPCBs was statistically significant for all years and increased from earlier to later time periods (1977-88). The association of employment duration with Aroclor 1242/LPCBs was weak but statistically significant for all years except for 1976. For the Indiana plant, the association of employment duration with Aroclor 1254/HPCBs was significant but weak in 1977 and statistically significant and strong in 1985. No significant relationship was observed with Aroclor 1242/LPCB for either of the two years.

Comparing the two cumulative exposure matrices, we observed that for Aroclor 1242/LPCB , the strength of association with the cumulative exposures estimated with the JEM improved with time and was stronger than that of duration of employment. For Aroclor 1254/HPCB in later periods, the Pearson correlation coefficients were similar for cumulative exposures estimated using duration of employment and the JEM. For earlier time periods, the New York JEM produced similar correlation coefficients as duration of employment with Aroclor 1254/HPCB , while the Indiana JEM was by far better than duration of employment.

The simple regression models with log-transformed serum PCB levels (dependent variable) and cumulative occupational exposure estimated using the JEM (independent variable) explained 14-15% of the variance of the Aroclor 1242/LPCB serum concentrations in the earlier years (1976 ($\beta = 0.00008$, $p\text{-value} = 0.001$) and 1979 ($\beta = 0.00009$, $p\text{-value} = 0.001$), respectively) for the New York plant, while this increased to 23-24% in later years (1988 ($\beta = 0.0001$, $p\text{-value} = 0.001$) and 1983 ($\beta = 0.0001$, $p\text{-value} = 0.001$), respectively). Approximately 22% of the variance of the Aroclor 1254/HPCB serum concentrations was accounted for by cumulative occupational exposure estimated using the JEM in 1976 ($\beta = 0.0001$, $p\text{-value} = 0.001$) and this explained variance increased for later years 33% (1979) ($\beta = 0.0001$, $p\text{-value} = 0.001$), 39% (1983) ($\beta = 0.0001$, $p\text{-value} = 0.001$), and 32% (1988) ($\beta = 0.0004$, $p\text{-value} = 0.001$).

For the Indiana plant, only 7% of the variance in 1977 Aroclor 1242/LPCB serum concentrations was accounted for by the JEM (1977 ($\beta = 0.0004$, $p\text{-value} = 0.001$) while 31% of the 1985 Aroclor 1242/LPCB serum concentrations was accounted for by the JEM ($\beta = 0.0008$, $p\text{-value} = 0.001$). The same pattern was seen for the Aroclor 1254/HPCB serum concentrations with 9% ($\beta = 0.0003$, $p\text{-value} = 0.001$) and 37% ($\beta = 0.0007$, $p\text{-value} = 0.001$) explained variance for 1977 and 1985, respectively.

Gender differences were not observed except for the New York plant in 1976 and only for Aroclor 1254/HPCB values, where women had lower log-transformed PCB concentrations than men.

DISCUSSION

We observed strong statistically significant associations between cumulative exposure estimates calculated with the JEMs and Aroclor 1242/LPCB and Aroclor 1254/HPCB serum concentrations in former workers in capacitor manufacturing for both plants. These associations were similar to, but more robust than, those for duration of exposure and serum concentrations. Aroclor 1254/HPCB have generally very long half-lives (Hopf et al 2013, Shirai and Kissel, 1996; Ritter et al., 2011, Steele et al., 1986; Phillips et al., 1989; Taylor and Lawrence, 1992; Wolff et al., 1992; Seegal et al., 2011) in the human body, it is therefore not surprising that both duration of employment and cumulative exposure estimated with the JEM have similar correlation coefficients with the Aroclor 1254/HPCB serum concentrations.

The trouble with spot biological samples is that they only give a “snapshot” of the exposures; meaning compounds with short half-lives might already have been excreted resulting in an underestimate, while compounds with long half-lives might give a better long term exposure picture of cumulative exposures. Strength of association between the cumulative estimates depends on several factors including but not limited to chemical properties and half-lives. PCB congeners with few chlorine atoms are excreted faster than those with many chlorine atoms, and hence sera containing PCB congeners with few chlorine atoms present a more recent exposure rather than the total exposure over time, as has been observed in other studies (Wolff et al. 1982). Cumulative exposures estimated with the JEM consider the variation in PCB mixtures and job exposures the workers experienced over the time worked at the specific plants. By incorporating exposure

differences within a job the strength of association with Aroclor 1242/LPCB serum concentrations was rather good for all years at both plants. The strength of association between duration of employment often used as a surrogate for exposure and Aroclor 1242/LPCB was poor, and is probably due to the assumption that all workers no matter in which job and plant had an equal and constant PCB exposure.

Incorporating differences in PCB exposures in a systematic approach such as a JEM, may explain why our JEMs performed well in the epidemiological studies (Prince et al. 2006, Ruder et al. 2012 submitted, Ruder et al. 2006, Silver et al. 2009, Steenland et al. 2006) showing an exposure-response. In a recent study of some former workers at the New York plant (Seegal et al. 2011), congener specific PCB analyses were performed for the stored (Wolff et al. 1982) and the newly collected blood specimens from former PCB manufacturing workers. Workers' PCB exposures were given one of four qualitative ratings: definitively not exposed, possibly exposed, probably exposed, and definitively exposed. Even with this crude rating of workers' PCB exposures, an association was found between the serum PCB levels and cumulative PCB exposure (Seegal et al. 2011). Another study with an even more basic exposure assessment also found a significantly strong association (Spearman correlation coefficient 0.76) between serum PCB levels and PCB exposures classified as time of employment in each job weighted by exposure in each job category coded 1–4 depending on distance from the more highly exposed areas (Persky et al. 2011). As seen in our study and those of Seegal *et al.* (Seegal et al. 2011) and Persky *et al.* (Persky et al. 2011), exposure ratings are necessary when exposure variability among workers in the cohort is great.

Most of the researchers who have performed different studies at these capacitor manufacturing plants acknowledge the great difference in PCB exposures within each plant and the importance of dermal exposures. However, the categorization of PCB exposures by job differs, and might explain the difference in epidemiological outcomes and lack of exposure-response. Fischbein (Fischbein et al. 1979) and Wolff (Wolff et al. 1982) categorized the New York workers in four exposure categories according to air concentrations expressed in 8 hour time-weighted averages; “None”, “Low”, “Medium”, and “High” exposure categories with $0 < 0.07$, $0.007 < 0.41$, $0.41 < 0.60$, and $0.6 - 11 \mu\text{g}/\text{m}^3$, respectively. In addition dermal contact was required for the medium and high exposed categories. The qualitative ratings were similar to our ratings; however, the PCB air concentrations assigned to each were far lower than our assignments. Lawton *et al.* (Lawton et al. 1985a, Lawton et al. 1985b) classified the New York workers as having high, medium, or low exposure. Workers with dermal contact in high air level zones such as handling and sealing wet capacitors, and capacitor salvage and repair, were considered highly exposed. The medium exposure category was defined as brief high exposure and contact, such as maintenance. Low exposure did not involve dermal contact, but the worker was in or at the periphery of the high exposure zone. No values were given to these qualitative ratings. Taylor (Taylor 1988) categorized all New York jobs into two broad exposure groups and four specific categories. One exposure group was direct exposure, which was subdivided to low, medium and high based on PCB air concentrations and frequency of dermal exposure. The workers who did not fit this pattern were grouped into indirect exposure groups. Kimbrough *et al.* (Kimbrough et al.

1999) included salaried workers in the New York cohort because they were often involved in the manufacturing process and all personnel worked in the same building. Jobs with direct PCB contact (dermal contact and/or inhalation exposure to high PCB air levels) experienced while filling, impregnation, repairing, or moving PCB-filled capacitors were classified as high-exposure jobs. In the areas of filling and impregnation, air levels ranged from 227 to 1500 $\mu\text{g}/\text{m}^3$ in 1975, and in the spring of 1977, when PCB use had declined substantially, air levels ranged from 170 to 576 $\mu\text{g}/\text{m}^3$. Work operations in which no PCBs were used, such as the winding, can, and cover manufacture and the assembly and shipping department, were tested in the spring of 1977, and air levels ranged from 3 to 50 $\mu\text{g}/\text{m}^3$. These jobs were classified as low exposure, and workers in these areas primarily had inhalation exposure to the background levels of PCBs in the plant. Where insufficient information was provided in the work history records to determine job location, these jobs were deemed indefinable.

At the Indiana plant, a significant association between twenty workers' serum log (L-PCB) concentrations and personal PCB air concentrations in 10 different jobs was significant ($r = 0.66$, $p = 0.001$) (Smith 1987). The correlation with serum log (H-PCB) concentration was not ($r = 0.37$, $p = 0.11$) (Smith 1987). The authors attributed this low statistical power to the small sample size; however, the cumulative exposure estimates were probably too unrefined, considering that Aroclor 1254 was not used at the time of sample collection. In another study in the Indiana plant (Sinks et al. 1992), PCB exposure was assessed using weighting schemes for estimated cumulative exposure, assuming airborne and dermal exposures to PCBs to decrease farther from the PCB impregnation

area. The zone around the capacitor chamber was assigned an exposure score of 5 based on the environmental sampling results, the process area farthest from the ovens was assigned an exposure score of 2 (Zone 2), the area adjacent to the ovens a score of 3 (Zone 3), and maintenance (Zone 4). However, the serologic data did not support the weights for Zones 2-4. In our study, we kept the qualitative ratings across the two occupational routes (inhalation and dermal) of exposure equal. The inhalation PCB intensity values were in mg/m^3 because they were assigned based on air concentrations. Since no useful dermal exposure measurements were made, the dermal exposure values were unitless representing a scale rather than actual numeric dermal exposure typically measured in $\text{mg}\cdot\text{cm}^{-2}$. Inhalation, dermal, and oral routes of exposure contribute to the absorption of PCBs; however, the importance of each route is debated. Dermal absorption was limited in an *in-vitro* skin permeation study (Schmid et al. 1992), while dermal absorption accounted for up to 20% PCBs in adipose tissue and 80% due to inhalation in PCB exposed capacitor workers (Wolff 1985). A biological monitoring study of workers performing capacitor repairs with PCBs showed extensive dermal PCB exposures (Lees et al. 1987), as it did among transformer repair and salvage workers in China (Xing et al. 2011). In a recent study, PCBs penetrate skin, and the rate and metabolism depends on the degree of chlorination (Garner et al. 2006). Based on this knowledge, we decided that both routes of exposures – dermal and inhalation – were equally important. The scaling was therefore kept equal. We did not estimate dermal absorption based on exposed surface area and skin penetration rates, which is common in risk assessments, because sufficient information was not available. Pearson correlations did not change significantly if only the dermal JEM or inhalation JEM was used separately, as they were highly

correlated (data not shown). However, using plant-specific PCB air concentrations for each JEM incorporated plant-to-plant variability.

Some of the unexplained variability in the model could be due to the uncertainty regarding Aroclor uses, which are unconfirmed for the period 1956-59 at the New York plant. Taylor *et al.* (Taylor 1988); however, assumed Aroclor 1242 from 1954-65, and Aroclor 1016 from 1971-76, which is a longer period of Aroclor 1016 than Brown *et al.* (Brown et al. 1991) found. Fishbein *et al.* (Fischbein et al. 1985) listed the use of Aroclor 1254 and 1242 in 1959-70, and in 1971 and during 1973-74 Aroclor 1016 and 1242, in 1974-75 only Aroclor 1016. The use of several different Aroclors in both plants complicated the serum PCB congener and metabolite pattern. Specimens did not have the same congener pattern as the known Aroclor mixture due to metabolism in the body; their mixture changed and also contained metabolites. The distribution of PCB congeners in a serum specimen will also reflect the inter-worker differences due to previous exposures; high doses of PCBs are known to induce enzymes in the body and result in an increased elimination rate (Emmett et al. 1988, Seegal et al. 2011, Wolff et al. 1982). Workers in a low PCB-exposure working environment might therefore have a different pattern.

Correlations between the exposure estimate using the JEM and serum PCB concentrations could have been weakened if the worker continued working at the plants after the PCB ban. These workers would still be exposed to PCBs but at different concentrations than predicted by the JEM, therefore exposure misclassification of these workers could have occurred.

Another source of variability in our study was the apparent interlaboratory variations arising from work-up methods such as fat extraction, removal of pesticides (which leads to an overestimation of PCBs), and especially the single solvent extraction method that was used in earlier days and had large losses of PCBs (Lawton et al. 1985a). The accuracy and precision of PCB analysis in serum using a packed column GC/ECD method were in a collaborative study found to be 82.2% mean recovery (for Aroclor 1254); and inter-laboratory precision was <21% for specimens spiked at 10–100 ng/mL (Burse et al. 1989). Current analytical methods are not just more sensitive but are also congener specific, which give additional dimensions to interpreting past PCB exposures. For example Seegal et al (Seegal et al. 2011) found that most of the occupational exposure to Aroclor 1254 was significantly associated with only one congener (PCB-156).

In addition to non-congener specific data and high detection limits, other limiting factors in our study were the lack of information on workers' personal variables such as age and body mass index (BMI), which are known to impact PCB serum concentrations. Recent studies (Persky et al. 2011, Seegal et al. 2011) have included more predictors in their models accounting for biological variability such as metabolism, race, age, genetic make-up, etc. Multiple authors have observed that serum PCB levels increase with age (Chase et al. 1982, Kreiss 1985, Wolff et al. 1982) and BMI. A measure of biological monitoring data, in addition to demographics such as age, would probably have helped our correlations, which were already in the 0.3 to 0.62 range. Gender differences have also been observed of serum PCB levels greater among men than women (Kreiss et al. 1981,

Wolff et al. 1982) or of women having higher PCB concentrations than men (Seegal et al. 2011). We did not observe a gender difference. Non-lipid adjusted PCB serum concentrations could potentially mask a gender difference; however, the correlation coefficient between non-lipid and lipid adjusted serum PCB concentrations was 0.95 in a recent study using stored blood samples (Rylander et al. 2012).

Serum PCB levels can vary greatly from day to day depending on the nutritional or metabolic state of the workers sampled. This was especially true when serum PCB concentrations were lower and become more influenced by low PCB exposures (Burse et al. 1994). In the U.S. population excluding the areas of known PCB manufacturing and use, the background levels of higher-chlorinated PCBs (five or more chlorines) in sera increased before 1979 and decreased after 1979, as would be expected from the PCB ban. For lower-chlorinated serum PCBs, no increase or decrease was shown (1.7 ppb for all years) (Hopf et al. 2009a). The use of serum PCB levels (Aroclor 1242 and 1254) may impart substantial misclassification regarding participants' true body burdens. Therefore, we regard the cumulative exposure estimated with the JEM as a better predictor of PCB body burdens than serum levels measured as Aroclor 1242/LPCB and Aroclor 1254/HPCB. This statement might not hold true for PCBs quantified by newer methods such as high resolution capillary GC with mass spectroscopy detection (reviewed by (Muir &Sverko 2006), which give better congener resolution and low detection limits.

Conclusion

Strong positive associations were observed between serum PCB concentrations and cumulative exposure estimates using JEMs for each of the plants for all years. The association was greater for highly chlorinated PCB serum levels than for less chlorinated. This might be explained by the shorter half-life of less chlorinated PCBs allowing some PCB to be eliminated over the years.

The strength of association between serum PCB concentrations and the cumulative exposure estimated with the JEMs was better than the association between serum levels and duration of employment. This was probably because the JEMs accounted for variable PCB exposures over time, in addition to duration of exposure. Therefore, the cumulative exposure estimated with the JEM should be regarded as a better predictor of PCB body burdens than serum levels measured as Aroclor 1242/LPCB and Aroclor 1254/HPCB. In addition, the JEM allows estimation of relative body burden for those for whom we do not have serum measurements.

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Table 1 Naming, commercial mixtures, analytical method for serum PCB concentrations, correspondence between an Aroclor type and the serum categorization

	Commercial mixtures	Percent chlorination	Analytical Laboratory Method¹		Correspondence Aroclor type and the PCB serum	Tetrachloro or higher congener (%)	Plant
Aroclor 1254/HPCB²	Aroclor 1254	54%	Aroclor 1254	Sum of selected peak heights corresponding to the Aroclor 1254 standard.	96% higher chlorinated PCBs (HPCBs), 4% lower chlorinated PCBs (LPCBs)	90%	New York
			HPCB	Sum of PCB hallmark peak heights with retention times greater than DDE.			Indiana
Aroclor 1242/LPCB²	Aroclor 1242 / Aroclor 1016	41-42%	Aroclor 1242/ Aroclor 1016	Sum of selected peak heights corresponding to the Aroclor 1242 and Aroclor 1016 standards.	93% HPCBs, 7% LPCBs	30%	New York
			LPCB	Sum of PCB hallmark peak heights with retention times less than DDE.			Indiana

¹All analysis were performed with packed column gas chromatography with electron capture detection (GC/ECD)

² Aroclor 1242/LPCB = lower chlorinated PCBs, Aroclor 1254/HPCB = higher chlorinated PCBs

Table 2 Descriptive statistics for workers (duration employed, cumulative exposures estimated with the combined JEM, and the serum HPCB/Aroclor 1254 and LPCB/Aroclor 1242 concentrations (ppb)) included in the study.

Variable	New York plant					Indiana plant				
	year ¹	n	mean	stdev	min-max	year	n	mean	stdev	min-max
Duration (years)		192	14.00	8.45	1.1-30.3		218	12.8	4.8	2.4-19.5
Cumulative exposure (unitless)		192	4124.3	4679.4	45.8-23886.7		218	888.9	622.0	39.3-3332.0
Serum concentrations										
HPCB/Aroclor 1254 (ppb)	1976	185	137.68	190.40	10.0-1900.0	1977	218	31.39	27.79	1.0-250.0
	1979	173	92.02	102.70	3.0-639.0	1985	60	18.64	20.74	2.5-129.1
	1983	150	52.12	54.16	7.0-303.0					
	1988	138	50.86	65.39	2.4-482.1					
LPCB/Aroclor 1242 (ppb)	1976	185	2750.92	3511.82	100.0-21400.0	1977	218	197.0	341.8	1.0-3300.0
	1979	173	449.91	474.130	8.1-3133.0	1985	60	21.39	25.5	1.6-124.5
	1983	150	183.64	191.04	10.7-1228.0					
	1988	138	120.49	96.96	3.0-523.5					

1. Year of blood draw

Table 3 Pearson correlations (r^2) between natural log transformed serum PCB concentrations) and cumulative exposure calculated using the JEMs or duration of exposure.

PCB	Pearson correlations (r^2)	New York plant				Indiana plant	
		1976 (n=185)	1979 (n=173)	1983 (n=150)	1988 (n=138)	1977 (n=218)	1985 (n=60)
LPCB/ Aroclor 1242/1016	Cumulative exposure JEM	0.37**	0.39**	0.49**	0.49**	0.26**	0.56**
	Duration	0.07	0.18*	0.29*	0.34**	0.01	0.18
HPCB/ Aroclor 1254	Cumulative exposure JEM	0.47**	0.57**	0.62**	0.56**	0.30**	0.61**
	Duration	0.44**	0.55**	0.61**	0.62**	0.15*	0.58**

*p-value <0.05; **p-value <0.0001