

## THE RELATION OF POLYCHLORINATED BIPHENYLS TO BIRTH WEIGHT AND GESTATIONAL AGE IN THE OFFSPRING OF OCCUPATIONALLY EXPOSED MOTHERS

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The authors studied the relation of polychlorinated biphenyls (PCBs) to birth weight and gestational age among the live offspring of women occupationally exposed to PCBs during the manufacture of capacitors in Upstate New York. Interviews were conducted in 1982 with 200 women who had held jobs with direct exposure and 205 women who had never held a direct-exposure job in order to ascertain information on reproductive history and other factors influencing reproductive outcome. Exposure was assessed as high-homolog PCB (Aroclor 1254), a continuous exposure variable estimated from an independently derived prediction model. After adjustment for variables other than gestational age known to influence birth weight, a significant effect of high-homolog exposure is seen for birth weight (slope of the regression  $\beta = -33$  g/unit change in natural logarithm (ln) estimated serum PCB; 90% confidence interval (CI) -59 to -7;  $p_{(1)} = 0.02$ ). For gestational age, a small but significant decrease is also observed with an increase in estimated exposure ( $\beta = -1.1$  days/unit change in ln estimated serum PCB; 90% CI -2.0 to -0.1;  $p_{(1)} = 0.03$ ). When gestational age is accounted for in addition to other variables related to birth weight, estimated serum PCB is no longer a significant predictor of birth weight ( $\beta = -24$  g/unit change in ln estimated serum PCB; 90% CI -49 to 2;  $p_{(1)} = 0.06$ ). The authors conclude that these data indicate that there is a significant relation between increased estimated serum PCB level and decreased birth weight and gestational age, and that the decrease in birth weight is at least partially related to shortened gestational age. The magnitude of these effects was quite small compared with those of other known determinants of gestational age and birth weight, and the biologic importance of these effects is likely to be negligible except among already low birth weight or short gestation infants.

birth weight; gestational age; occupational diseases; polychlorobiphenyl compounds; reproduction

Polychlorinated biphenyls (PCBs) are chlorinated aromatic hydrocarbons con-

sisting of mixtures of 210 different isomers having varying degrees of chlorination.

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Originally formulated in 1867, they were commercially manufactured in the United States between 1929 and 1977. The chemical and thermal stability of these substances resulted in their wide use in capacitors, transformers, hydraulic fluids, heat transfer fluids, lubricants, plasticizers, and as components of surface coatings and inks. Retention of these lipophilic compounds in animals, humans, and the general environment has been well documented and is related to both the degree of chlorination and the position of the chlorine atoms in the molecular structure (1, 2). The PCBs with lower degrees of chlorination (low homologs) tend to be more rapidly excreted, while the more highly chlorinated compounds (high homologs) are retained in the body. Increasing concern about environmental contamination and potential health effects contributed to a ban in 1979 on their further distribution in this country.

Much information has been generated on PCBs in the past decade, but very little is known about their effects on human health in general. Even less information is available concerning their influence on human reproductive outcome. Although they are no longer produced or used in new products in this country, their long life in existing products and resistance to degradation continue to make the question of their safety an important one for occupational groups with high exposure to these products. Their widespread contamination of the environment makes this question important for general populations as well.

Human health studies on possible toxic effects of PCBs on fetuses of exposed mothers are limited to the Yusho incident in Japan (3-6), a similar although more recent

episode in Taiwan (6), infants of mothers in Michigan who consumed fish from Lake Michigan previously shown to be contaminated with PCBs (7), and our earlier evaluation at the same capacitor manufacturing facility in Upstate New York reported here (8). In Yusho in 1968, an epidemic of acneform eruption of the upper eyelids with increased eye discharge affected 1,291 persons who had ingested rice oil contaminated with PCBs (3, 4). Among the persons afflicted were 11 women who gave birth in the subsequent year (5). These 11 pregnancies resulted in nine live births and two stillborns. Although no infant demonstrated structural defects, evidence of fetotoxicity was found. Eight of the nine live births had increased eye discharge and grayish, dark brown staining of the skin, gingiva, or nails. Three of the nine infants were considered small for dates. The role of toxicity of PCBs in Yusho (and Taiwan) has been confused, however, by the finding of polychlorinated dibenzofurans in high concentrations in the ingested rice oil (4, 6). The Michigan study used three separate exposure categorizations in comparing birth weight with various gestational age measures (7). In the first comparison, birth weight in the 242 infants born to women with a history of frequent consumption of fish from Lake Michigan over the previous six years was an average of 190 g lower than that in 71 infants born to women who never ate fish from Lake Michigan. No significant difference in gestational age was observed between these two groups. In the second comparison, exposure was limited to fish consumption during pregnancy, and no difference in birth weight or gestational age was seen. For the third comparison, infants were dichotomized by cord blood PCB levels into detectable and undetectable. Those infants with detectable cord blood levels ( $n = 75$ ) weighed 160 g less and were born 1.2 weeks earlier on average than those with undetectable levels ( $n = 166$ ). In our previous study of live births to females employed in a capacitor manufacturing facility in New York (8), assessment was limited to

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information recorded on birth certificates. We found that 51 infants born to women in high-exposure jobs had an average birth weight that was 153 g lower than that of 337 infants born to women working in low-exposure jobs. This difference was due mainly to reduction in the gestational age in the high-exposure group.

This report includes the findings of a more detailed interview study of birth weight and gestational age of infants born to women occupationally exposed to PCBs and is based on the same cohort as that examined previously (8). The exposure reviewed here is limited to high-homolog PCBs, estimated as both a dichotomous and continuous variable.

## MATERIALS AND METHODS

### *Exposure estimates*

Between 1946 and 1977, two facilities of the same company located in Upstate New York manufactured capacitors using PCBs with Aroclors 1254, 1242, and 1016 (Monsanto Company, St. Louis, MO) as their primary dielectric fluid. Our study population consisted of the cohort of all employees who worked at either of these two facilities between the years 1946 and 1975 for a minimum of three months. Employees were first identified by personnel records for these years and later verified by obtaining copies of Social Security premium payment records for the years 1945–1965. A total of 6,292 persons, including 2,691 females and 3,601 males, were verified to have worked at least three months during the defined study period. With the Social Security premium reports as the reference, missing personnel records numbered only 41 after verification efforts were finished, indicating that the cohort was 99 per cent complete for the 4,129 (66 per cent of the total) persons starting work before 1965.

Information on the personnel records included a code, a description, and dates for each job at the two facilities. The job descriptions in combination with manufacturing process information and industrial

hygiene data were used to categorize all jobs into two broad exposure groups. Direct-exposure jobs were defined as those in which direct contact with PCBs occurred during the manufacturing process. These jobs were further characterized into subcategories as follows: low—air contact only; medium—air contact plus occasional dermal contact; and high—air contact plus frequent dermal contact. All other jobs within the two plants, including those performed in office and manufacturing areas where PCBs were not directly used, were termed indirect-exposure jobs. When PCBs were still in use at the facilities, environmental monitoring was performed in both direct- and indirect-exposure job areas during three industrial hygiene surveys. Results (summarized in table 1) showed that in 1977, concentrations in the indirect-exposure job areas were an order of magnitude below those in the direct-exposure job areas. The indirect-exposure job areas had much higher concentrations than did areas surrounding the plants, where values averaging  $6.2 \mu\text{g}/\text{m}^3$  were recorded prior to discontinuation of use. These concentrations exceed previously reported urban ambient air averages of  $0.1 \mu\text{g}/\text{m}^3$  (9). Serum total PCB determinations performed on workers in these facilities (summarized in table 2) demonstrated a geometric mean concentration for workers in direct-exposure

TABLE 1  
*Geometric mean PCB air levels ( $\mu\text{g}/\text{m}^3$ ) in a capacitor manufacturing plant in Upstate New York, by exposure status\**

Exposure status	Area air samples (October 1975)	Area air samples (April 1977)	Personal air samples† (April 1977)
Direct	679 ( <i>n</i> = 30)	310 ( <i>n</i> = 16)	168 ( <i>n</i> = 31)
Indirect	260 ( <i>n</i> = 1)	27 ( <i>n</i> = 16)	

\* Written personal communication, R. Lawton, 1980. (Note: Caution should be used in making direct comparisons between results from 1975 and 1977 because the sampling techniques and analytic procedures employed in these two surveys were different.)

† Time-weighted average.

TABLE 2  
*Serum PCB concentrations in capacitor workers, by  
 exposure status and type of homolog, 1979\**

Exposure status of workers	n	Geometric mean (ppb)		
		Low homologs	High homologs	Total PCBs
Direct	147	269	33	302
Indirect	18	50	11	61
Reference group†	16	7	9	16

\* Written personal communication, R. Lawton, 1980.

† Employees without occupational PCB exposure working for the same company at another facility.

jobs more than fourfold higher than for workers in indirect-exposure jobs, and almost 20-fold higher than for reference subjects without occupational exposure. These high relative exposures were primarily the result of exposure to low homologs. Exposure to high homologs was only three to four times greater for direct exposure than for indirect exposure or for nonexposed reference subjects, and there was only marginal difference between exposures of indirect exposure and reference groups. Exposure to chemicals at these facilities was limited to those used in the manufacture of capacitors, including PCBs, trichlorethylene, methyl isobutyl ketone, lead, zinc, tin, aluminum, iron, and epoxides (10, 11). Exposure was homogeneous compared with the highly mixed exposure found in most chemical work environments.

From among the 2,691 women in the total cohort, groups with high (direct) exposure and low (indirect) exposure were chosen for study in such a way as to attempt to maximize the differences in exposure within the study sample. Selection was limited to women for whom all job codes in their record were categorized as to exposure level. A total of 405 women including 10 surrogates were interviewed. The direct-exposure group consisted of 200 women less than 55 years of age as of 1982 who had worked in direct-exposure jobs. The 200 included all 140 women who had had more than one year in direct-exposure jobs and a random sample of 60 of the 258 with under

12 months in direct-exposure jobs. The 205 women in the indirect-exposure group were selected from among 909 women under 55 years of age as of 1982 who had *never* held a direct-exposure job (clerical jobs were excluded). Selection was stratified by age (five-year groups), year of first employment (five-year groups), and duration of employment (number of years) to be balanced with the direct-exposure group, but was otherwise random. It was necessary to select 219 women from the direct-exposure group in order to locate and complete interviews on 200 (including four surrogates), for an overall completion rate of 91 per cent. For the indirect-exposure group, 226 selections were necessary to accomplish 205 interviews (including six surrogates), for a completion rate in this group of 91 per cent as well.

Although the exposure status over all intervals was the basis for selection of women into ever direct- and never direct (indirect)-exposure groups, pregnancies and not mothers were the real focus of interest. Pregnancies to direct-exposure women were categorized into three groups with respect to time of exposure: before employment, after indirect exposure only, or after direct exposure. Pregnancies to women in the indirect-exposure group were categorized as occurring either before employment or after indirect exposure only. The evaluation reported here is limited to a comparison of events occurring after direct (for the direct-exposure group) and indirect (for the indirect-exposure group) exposure. Twins, nonwhite births, fetal losses, births before work at the facilities, and births with incomplete data were excluded from this analysis (see table 3).

The dichotomous direct- versus indirect-exposure categorization is one among a large variety of possible indices of exposure that can be drawn from the work history of a study subject. Other possible indices include duration of employment in direct-exposure jobs, years of total employment, a weighted combination of exposure that considers both intensity and duration of

TABLE 3

Number of potential events, exclusions, and number of actual events included in final analysis, by exposure status

	Exposure status	
	Direct	Indirect
Total no. of pregnancies	654	697
No. of singleton, white, live births	545	561
No. of live births after starting employment (i.e., after either direct or indirect exposure)	219	207
No. of live births after direct exposure	190	0
No. of live births with complete data used in analysis	172	184

exposure, and exposure within a specified number of preceding years. The dichotomous categorization was convenient for the selection of study subjects but has a number of potential deficiencies. For example, 60 of the subjects classified as exposed by this measure spent less than one year in a direct-exposure job. For this population, as with many occupational study populations, no clear rule regarding exposure can be derived from the work histories. Fortunately, for this study, both serum PCB levels and work histories were available for a sample of 194 employees at these plants, including serum PCB levels and work histories for six employees from the present study. Linear regression methods were used on these data to develop a model for the prediction of high-homolog serum PCB levels. The resulting empirically derived model formed the basis for our primary index of exposure. This model (described in detail in the Appendix) allowed us to estimate the high-homolog serum PCB level at the time of each pregnancy as a continuous variable. The model appears to estimate these levels quite well. Applying this model to the direct- and indirect-exposure groups yielded distributions for these two exposure groups that were neither normal nor natural logarithm (ln)-normal. Graphs of their empirical cumulative distribution functions (figure 1) showed a crossover with direct exposure having higher estimated serum

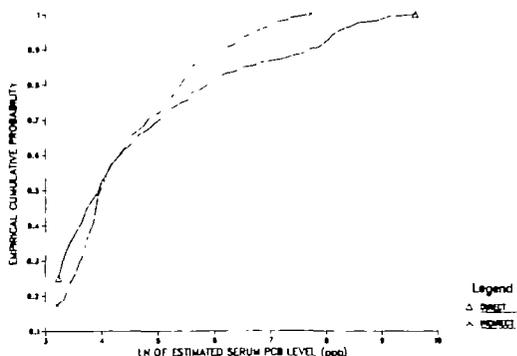


FIGURE 1. Cumulative distribution function of ln of estimated serum PCB level, by exposure group for female capacitor plant workers in Upstate New York, 1949-1983.

levels only in the upper 40 per cent of the distribution. The model, through incorporation of different kinetic assumptions, can be used to estimate serum levels at the time of each pregnancy, as average annual serum level prior to pregnancy, or as cumulative serum level or exposure prior to pregnancy. For the present study, the most relevant exposure to the fetus was that which occurred at the time of the pregnancy, and only this estimate was used. Maternal body burden results in direct fetal exposure as indicated by the detection of PCBs in cord blood (12). Transfer across the placental barrier has been demonstrated in other species as well, including cows and monkeys (13, 14).

In summary, high-homolog PCB exposure in this study was estimated in two ways. Our primary index was a continuous exposure variable estimated from an empirically derived model described in the Appendix. The second index was derived deductively and used the simple dichotomous exposure variable (direct vs. indirect) based on highest level ever exposed prior to the pregnancy.

Addresses and phone numbers were obtained for the 405 women (or their surrogates), and information was obtained on demographics, medical history, occupational history, environmental exposures, marital history, and a complete history of pregnancies and their outcomes. For each

pregnancy, information on specific exposures (such as tobacco, alcohol, medications, etc.) was obtained for the interval three months prior to conception until termination of the pregnancy.

For pregnancies that ended in live births, we verified birth weight and date of last menstrual period through medical or vital records. For those events occurring in 1968 or later, birth weights and dates of last menstrual period were taken directly from birth certificates. For those events occurring prior to 1968, birth weights were also taken directly from birth certificates with the exception of certificates for the years 1947, 1948, and 1951, which did not contain this information. In those cases, birth weights were obtained from hospital records. Prior to 1968, dates of last menstrual periods were obtained from hospital or physician records where available. For 31 pregnancies, the last menstrual period dates were unavailable, and gestational ages were taken as recorded in estimated weeks of gestation on the birth certificates.

#### *Statistical considerations*

In univariate analyses, groups of infants with different PCB exposures were compared with respect to mean outcomes, birth weights, and gestational ages. Differences between means were evaluated parametrically using the *t* test or, when parametric assumptions were not met, nonparametrically using the Wilcoxon rank sum test. Adjustment for potentially confounding variables was made by including the variables in forward linear regressions based on least squares for the continuous outcomes of birth weight and gestational age. A model predicting outcomes was found using a stepwise regression technique incorporating all of the explanatory variables except exposure. High-homolog PCB exposure was estimated using both a dichotomous (direct vs. indirect) and a continuous (serum PCB level estimate) variable. The serum variable was ln-transformed because of the wide range of the data (24–14,595 ppb). Exposure was then added to the model, and the

overall statistical significance of the reduction in residual variance was tested using the partial *F* statistic and the *t* test. The estimated serum PCB level was also examined using an indicator variable for each quarter of the distribution to search for a nonlinear or threshold effect. Although considerably more information was obtained during the interview, independent variables used in the analysis were limited to 20 having some known relation to outcome.

Because of our concern for the nonindependence of multiple pregnancies occurring to the same woman, the analyses for birth weight and gestational age were run using *all* post-direct (in the direct-exposure group) and post-indirect (in the indirect-exposure group) exposure pregnancies, and then were repeated to examine the results in only a *single* pregnancy per mother (birth of her last live child).

Confidence intervals of the regression coefficients were estimated under the assumption of normal distribution of the estimates of the coefficients.

## RESULTS

A total of 190 singleton, white, live births occurred to 95 women in the direct-exposure group following direct exposure, while 207 such events occurred to 96 women in the indirect-exposure group following indirect exposure. Twelve live births lacked information on either birth weight or gestational age, and an additional 29 births had a missing value for one of the explanatory variables, leaving for analysis 172 and 184 events, respectively, in the direct- and indirect-exposure groups (table 3). Tables 4 and 5 describe by dichotomous exposure status the explanatory and outcome variables considered in this analysis.

#### *All births—univariate analysis*

We could not reject the hypothesis that birth weights were normally distributed in both the direct- and indirect-exposure groups. The curve for the direct-exposure group is shifted to the left of that of the

TABLE 4

Description of dichotomous variables used in birth weight and gestational age analysis, by exposure group

Variable	Exposure group			
	Direct (n = 172)		Indirect (n = 184)	
	n	%	n	%
Alcohol consumption during pregnancy	84	49	82	45
Complication during pregnancy*	52	30	61	33
Low birth weight infant				
Prior to employment	11	6	8	4
After employment	1	1	6	3
Underlying medical condition before pregnancy	13	8	11	6
Previous miscarriage	38	22	50	27
Previous pre-term birth (<260 days gestation)	24	14	32	17
Sex (male)	76	44	96	52
Tobacco use	75	44	64	35

\* Includes history of hypertension, anemia, kidney conditions, spotting, or bleeding.

TABLE 5

Description of continuous variables used in birth weight and gestational age analysis, by exposure group

Variable	Exposure group	
	Direct (n = 172)	Indirect (n = 184)
	Mean $\pm$ SD*	Mean $\pm$ SD
Year of pregnancy	1968.5 $\pm$ 8.3	1967.3 $\pm$ 8.1
Gravidity	3.2 $\pm$ 1.7	3.5 $\pm$ 2.1
Age (years)	27.8 $\pm$ 4.7	27.2 $\pm$ 4.9
Education (years)	11.8 $\pm$ 0.8	11.9 $\pm$ 1.0
Height (inches)	63.3 $\pm$ 2.4	64.3 $\pm$ 2.3
Weight (pounds)	128.7 $\pm$ 20.7	129.1 $\pm$ 20.7
Weight gain during pregnancy (pounds)	25.5 $\pm$ 14.0	29.0 $\pm$ 14.7
Prenatal care (weeks)	8.4 $\pm$ 4.7	8.6 $\pm$ 4.4
Quetelet index ((pounds/inches <sup>2</sup> ) $\times$ 1,000)	32.1 $\pm$ 5.4	31.2 $\pm$ 4.8
Year first employed	1962.4 $\pm$ 8.4	1961.7 $\pm$ 8.2
Birth weight (g)	3,313 $\pm$ 456	3,417 $\pm$ 486
Gestational age (days)	279.0 $\pm$ 17.0	279.3 $\pm$ 13.5

\* SD, standard deviation.

indirect-exposure group, and the difference in the mean birth weights between groups is  $-104$  g (90 per cent confidence interval (CI)  $-163$  to  $-45$ ,  $p_{(1)} = 0.02$ ). Estimated serum PCB level is a significant predictor of birth weight in the univariate model ( $\beta = -30$  g/unit change in ln estimated serum PCB; 90 per cent CI  $-58$  to  $-1$ ;  $p_{(1)} = 0.05$ ). The relation between actual birth weight and estimated ln serum level is shown in figure 2.

Neither the direct- nor the indirect-exposure group of gestational ages is normally distributed. No significant difference in their distribution is detected by the Wilcoxon rank sum test ( $p = 0.95$ ). The plot of the residuals from the univariate regression predicting gestational age as a continuous variable is nearly normal. The dichotomous exposure variable (direct, indirect) in the univariate regression predicting gestational age is not significant ( $\beta = -0.3$  days; 90 per cent CI  $-3.0$  to  $2.3$ ;  $p_{(1)} = 0.42$ ), but the slope of the coefficient for estimated serum level is ( $\beta = -1.1$  days/unit change in ln estimated serum PCB; 90 per

cent CI  $-2.0$  to  $-0.1$ ;  $p_{(1)} = 0.03$ ). Point estimates (90 per cent CI) for the effect on gestational age by quarters are quarter 2 =  $-0.1$  days ( $-3.9$  to  $3.6$ ); quarter 3 =  $-3.3$  days ( $-7.0$  to  $0.5$ ); and quarter 4 =  $-3.3$  days ( $-7.0$  to  $0.5$ ).

#### All births—multivariate analysis

Seven covariables are found to be significantly associated with birth weight, including gestational age. However, because we had previously observed an effect of exposure on birth weight that was mediated through gestational age (8), we use only the six other significant variables in our primary model, excluding gestational age, so that we can later reexamine the specific effect of gestational age. The six remaining variables explaining the most variation about the birth weight mean for all births are shown in table 6 (model 1). When these six factors are accounted for, the mean birth weight in the direct-exposure group is only 60 g lower than that in the indirect-exposure group, and this exposure variable

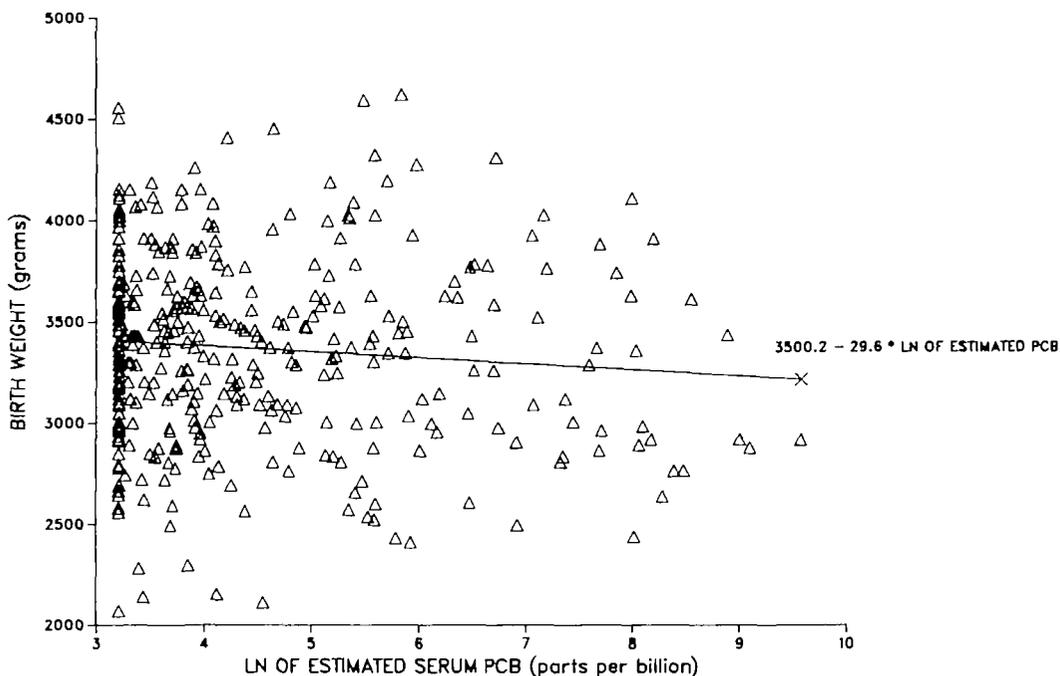


FIGURE 2. Birth weight versus ln of estimated serum PCB level among live births to female capacitor workers in Upstate New York, 1949-1983.

does not contribute significantly to the regression (90 per cent CI  $-138$  to  $19$ ;  $p_{(1)} = 0.11$ ). The ln high-homolog serum estimate for all births is a significant negative slope in the multivariate model ( $\beta = -33$  g/unit change in ln estimated serum PCB; 90 per cent CI  $-59$  to  $-7$ ;  $p_{(1)} = 0.02$ ). Point estimates (90 per cent CI) for an effect on birth weight when examined between quarters of the exposure distribution in the multivariate model (relative to the first quarter) are quarter 2 =  $-1$  g ( $-107$  to  $106$ ); quarter 3 =  $-45$  g ( $-152$  to  $62$ ); and quarter 4 =  $-65$  g ( $-172$  to  $43$ ).

The stepwise regression predicting gestational age without exposure fails to find a single predictive covariable.

#### *Last births*

We also examined the effect of exposure limited to a single birth per mother. The last birth to each mother, after adjustment for the six significant covariables, is not significantly higher in weight than other births ( $\beta = 47$  g; 90 per cent CI  $-28$  to  $123$ ;  $p_{(1)} = 0.15$ ). Significant effects for exposure

on birth weight are seen in univariate analysis for both the dichotomous ( $\beta = -182$  g; 90 per cent CI  $-296$  to  $-68$ ;  $p_{(1)} = 0.005$ ) and continuous exposure estimates ( $\beta = -49$  g/unit change in ln estimated serum PCB; 90 per cent CI  $-94$  to  $-3$ ;  $p_{(1)} = 0.04$ ), and both remain significant after accounting for the six factors influencing birth weight, for the dichotomous exposure variable ( $\beta = -135$  g; 90 per cent CI  $-242$  to  $-28$ ;  $p_{(1)} = 0.02$ ) and for the continuous exposure estimate ( $\beta = -60$  g/unit change in ln estimated serum PCB; 90 per cent CI  $-102$  to  $-19$ ;  $p_{(1)} = 0.01$ ).

Last births are not significantly longer in gestational age than other births ( $\beta = 0.4$  days; 90 per cent CI  $-2.5$  to  $3.1$ ;  $p_{(1)} = 0.40$ ). The estimate of the effect of exposure on gestational age in unadjusted analyses for last births is not significant for the dichotomous exposure variable ( $\beta = -1.6$  days; 90 per cent CI  $-5.3$  to  $2.1$ ;  $p_{(1)} = 0.24$ ), but is significant for the continuous exposure variable ( $\beta = -1.9$  days/unit change in ln estimated serum PCB; 90 per cent CI  $-3.3$  to  $-0.4$ ;  $p_{(1)} = 0.02$ ).

TABLE 6  
Multiple regression model predicting birth weight (grams) without gestational age \*

Variable	No exposure (Model 1)	Occupational exposure (Model 2)	PCB level exposure (Model 3)
	$\beta \dagger \pm SE \ddagger$	$\beta \pm SE$	$\beta \pm SE$
Intercept	945	1,119	1,091
Tobacco use (1 = yes, 0 = no)	-205 $\pm$ 48	-198 $\pm$ 48	-216 $\pm$ 48
Sex (1 = male, 0 = female)	168 $\pm$ 46	165 $\pm$ 46	166 $\pm$ 46
Low birth weight infant prior to employment (1 = yes, 0 = no)	-571 $\pm$ 165	-594 $\pm$ 166	-560 $\pm$ 164
Height (inches)	27.7 $\pm$ 9.8	25.4 $\pm$ 9.9	28.1 $\pm$ 9.8
Quetelet index ((pounds/inches <sup>2</sup> ) $\times$ 1,000)	16.0 $\pm$ 4.8	16.2 $\pm$ 4.8	15.6 $\pm$ 4.8
Weight gain (pounds)	5.7 $\pm$ 1.6	5.5 $\pm$ 1.6	5.6 $\pm$ 1.6
Occupational exposure (1 = direct, 0 = indirect)		-60 $\pm$ 48	
PCB level exposure estimate (g/unit change in ln estimated serum PCB)			-33 $\pm$ 16
	$R^2 = 0.19$	$R^2 = 0.19$	$R^2 = 0.20$

\*  $n = 356$ .

$\dagger \beta =$  grams change in birth weight per unit change in variable.

$\ddagger SE$ , standard error.

#### Control for gestational age

Additional regressions removing from the final models independent variables that are also potential measures of outcome (i.e., sex of infant, weight gain, and prior history of low birth weight after employment) were done for all births and last births only, but without effect. Addition of variables such as gravidity or year of birth is similarly found to be without influence. When gestational age is added to the model, the dichotomous exposure variable remains insignificant for all births ( $\beta = -51$  g; 90 per cent CI -125 to 24;  $p_{(1)} = 0.13$ ), and remains significant for last births ( $\beta = -114$  g; 90 per cent CI -216 to -12;  $p_{(1)} = 0.03$ ). The coefficient for estimated serum PCB in the model predicting birth weight for all births, which is significant without gestational age, is marginally insignificant with gestational age in the model ( $\beta = -24$  g/unit change in ln estimated serum PCB; 90 per cent CI -49 to 2;  $p_{(1)} = 0.06$ ), indicating that there is an influence of exposure on birth weight, and that this effect is in part mediated through a change in gestational age. For last births only, estimated serum level remains as significant with gestational age in

the model as it is without it ( $\beta = -45$  g/unit change in ln estimated serum PCB; 90 per cent CI -85 to -5;  $p_{(1)} = 0.03$ ). Summaries of the analyses relating exposure to birth weight and gestational age are found in tables 7 and 8.

#### Infant deaths

In the cohort of 356 live births analyzed here, two deaths under the age of five years were reported to us during the interviews and later verified using New York State records which match births and deaths. One death occurred in the direct-exposure group and one in the indirect-exposure group. Each was related to prematurity, and the ages at death were both under one day.

#### DISCUSSION

We studied the relation of PCB exposure to the continuous variables of birth weight and gestational age in the offspring of occupationally exposed women. The methods used to select participants and to ascertain both exposure and outcome are unlikely to have resulted in bias. Bias could have been present if mothers in either exposure group selectively failed to report the presence of

TABLE 7

Summary of analyses relating PCB exposure to birth weight in infants born to women working at a capacitor manufacturing facility in Upstate New York, 1949-1983

Model	$\beta^*$	90% confidence interval	p value
All births			
Dichotomy			
Univariate	-104	-163 to -45	0.02
7-Variate†	-60	-138 to 19	0.11
8-Variate‡	-51	-125 to 24	0.13
Continuous			
Univariate	-30	-58 to -1	0.05
7-Variate	-33	-59 to -7	0.02
8-Variate	-24	-49 to 2	0.06
Last births			
Dichotomy			
Univariate	-182	-296 to -68	0.005
7-Variate	-135	-242 to -28	0.02
8-Variate	-114	-216 to -12	0.03
Continuous			
Univariate	-49	-94 to -3	0.04
7-Variate	-60	-102 to -19	0.01
8-Variate	-45	-85 to -5	0.03

\*  $\beta$  = grams (dichotomy) or grams/unit change in ln estimated serum PCB (continuous).

† Model includes tobacco, sex, prior low birth weight, height, Quetelet index, weight gain, and exposure.

‡ Gestational age plus 7-variate model.

TABLE 8

Summary of analyses relating PCB exposure to gestational age in infants born to women working in a capacitor manufacturing plant in Upstate New York, 1949-1983

Model	$\beta^*$	90% confidence interval	p value
All births			
Dichotomy			
Wilcoxon rank sum test			0.95
Univariate	-0.3	-3.0 to 2.3	0.42
Continuous			
Univariate	-1.1	-2.0 to -0.1	0.03
Last births			
Dichotomy			
Univariate	-1.6	-5.3 to 2.1	0.24
Continuous			
Univariate	-1.6	-3.3 to -0.4	0.02

\*  $\beta$  = days (dichotomy) or days/unit change in ln estimated serum PCB (continuous).

infants of high or low birth weight or long or short gestation. However, when women were asked during the interview whether they had ever been directly exposed to PCBs, 29 per cent of the mothers in the direct-exposure group reported exposure versus 17 per cent in the indirect-exposure group, suggesting that neither group had a level of awareness about exposure that was likely to influence their response. Confounding was minimized in this study by collecting information in the interview on factors known to influence birth weight and by adjusting for them in the analysis. Unknown or unmeasured confounding factors could, of course, alter our results.

The current study was limited to women employed at common facilities where PCB contact occurred, at least to a limited extent, everywhere in the plants. The comparison of direct- versus indirect-exposure events within the plants resulted in less exposure extremes than a comparison of, say, direct exposure versus a reference group having no contact. Limiting this study to within-plant events was done purposely because women performing common types of jobs in common facilities, discriminated essentially only by degree of exposure, represented the most valid contrast available. Unmeasured and potentially important influencing factors, such as type of insurance, access to health care, etc., are almost certainly more homogeneous within workers of a given plant. An effect analogous to the well-known "healthy worker effect" on mortality likely exists for reproductive outcomes as well (15-17). This is apparent in both our record and interview studies. For example, infants with low birth weight ( $\leq 2,500$  g) constitute only 3 per cent of births in the interview study reported here, substantially below the 7 per cent observed in the two-county geographic area surrounding the capacitor facilities for the years 1968-1976 (P. R. Taylor, unpublished data). Finally, failure to maximize exposure differences between study groups does not alter the basic exposure-disease relation; it

simply reduces its efficiency. This means that our point estimates of effect per unit exposure should be valid although our confidence intervals may be widened.

Our examination of the relation of estimated high-homolog PCB exposure to birth weight and gestational age found a significant influence of exposure on both birth weight (in the absence of adjustment for gestational age) and gestational age. The magnitude of these associations, while statistically significant, is small compared with that seen here with other exposures (e.g., tobacco smoke).

The great majority of birth weights in this series were well above 2,500 g, the level generally designated as the upper boundary of "low birth weight" (18). For these higher birth weights, the magnitude of the exposure effects seen here would have a negligible effect on perinatal and infant mortality and morbidity (19). Because of the small number of low birth weights included here, it is uncertain whether the estimates of effect found are applicable in the low birth weight range. If it is assumed that these estimates are applicable, it would be predicted that the added effect of PCB exposure to women with other causes of low birth weight and the associated infant morbidity would be appreciable. For example, an increase in PCB level from 10 to 20 ppb, the range typically found in women in the general population, would be associated with a decrease in birth weight of 23 g (20). If an expected birth weight were in the range of 2,000 g, because of other factors an additional decrement of 23 g would be expected to increase perinatal mortality appreciably.

In conclusion, we examined in detail the relation of PCBs to birth weight and gestational age. A significant decrease in gestational age was seen with increasing serum level. A decrease in birth weight, at least partially mediated by the effect of PCBs on gestational age, was also seen. The magnitude of these effects was quite small compared with those of other known determi-

nants of gestational age and birth weight, and the biologic importance of these effects is likely to be negligible except among already low birth weight or short gestation infants.

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#### APPENDIX

A regression model approach was used to develop a high-homolog serum PCB estimation model based on data from a company survey. The survey collected blood from 194 persons including 152 males and 42 females in 1976 selected to be a census of those current employees whose job required direct contact in high-exposure zones, employees in the immediate periphery of the high-exposure zone, and employees having high but intermittent exposure. A follow-up survey was conducted in 1979 on 174 of the 194 directly exposed workers who were still available. Because of our interest in PCBs that are retained in the body longer, we focused our efforts on a model for high-homolog PCBs (Aroclor 1254). Because of concern over a systematic laboratory error in the 1976 data, only values from 1979 were used in this analysis. Complete job history records through 1976 and serum Aroclor 1254 measurements from 1979 were available on 157 employees.

Although additional information was gathered on these 157 persons, information used in the development of the prediction model was limited to items found in the company personnel records and the job exposure categorization (described under Materials and Methods). This was done to allow us to generalize use of the model to the entire cohort of 6,292 persons. Work history variables included the number of months at jobs from each of four exposure levels (described under Materials and Methods) for each of four time intervals. In 1954, the use of highly chlorinated Aroclor 1254 was phased out and replaced by Aroclor 1242; in 1965, major engineering changes occurred,

including closed process filling of capacitors and improvements in ventilation, which presumably resulted in substantial reduction in exposure to PCBs; and in 1971, Aroclor 1242 use was stopped in favor of Aroclor 1016. To account for the potential influence of these changes, we incorporated separate variables corresponding to the periods 1946-1954, 1955-1965, 1966-1971, and 1972-1976 into the model to indicate the era of exposure: era 1—1946-1954 (25-33 years before sampling); era 2—1955-1965 (14-24 years before sampling); era 3—1966-1971 (8-13 years before sampling); and era 4—1972-1976 (3-7 years before sampling).

Weighting of the independent variables was used to satisfy the regression assumptions of homoscedasticity, normal error distribution, and linearity.

The model assumes first-order kinetics with a half-life of 3.32 years determined empirically by application of simple linear regression to the difference in serum PCB estimates from 1979 and 1983 on a subset of 150 persons in this cohort.

Indicator variables for exposure levels by time intervals were created using data from all 157 persons. Running the full least squares regression model with 16 exposure-time categories, 10 influential outlier values (standardized residual  $\leq -2.5$  or  $\geq 2.5$ ) were identified, reviewed, and removed. Removal of the 10 outliers resulted in an improvement in the  $R^2$  from 0.56 to 0.71. The model was then simplified by removal of all four of the statistically insignificant variables from era 4 and a single insignificant variable for low exposure during era 2. The final, reduced model was

$$\begin{aligned} \text{Serum PCB} = & 24.7 \\ & + 75.3 \times (\text{No. months at indirect in era 1}) \\ & + 652.1 \times (\text{No. months at low in era 1}) \\ & + 882.7 \times (\text{No. months at medium in era 1}) \\ & + 77.5 \times (\text{No. months at high in era 1}) \\ & + 6.6 \times (\text{No. months at indirect in era 2}) \\ & + 39.4 \times (\text{No. months at medium in era 2}) \\ & + 95.8 \times (\text{No. months at high in era 2}) \\ & + 1.7 \times (\text{No. months at indirect in era 3}) \\ & + 0.7 \times (\text{No. months at low in era 3}) \\ & + 7.3 \times (\text{No. months at medium in era 3}) \\ & + 16.0 \times (\text{No. months at high in era 3}). \end{aligned}$$

Regression coefficients are equal to serum concentration per era-specific exposure category month. The  $R^2$  for this reduced model was 0.69 based on 147 observations.