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Prenatal exposure to polychlorinated biphenyls and asthma, eczema/hay fever, and frequent ear infections

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ABSTRACT

Objectives: The effects of prenatal exposure to Polychlorinated biphenyls (PCBs) on the development of asthma, frequent ear infections, and eczema/hay fever are not well understood. We aim to investigate associations between prenatal PCB exposure and these health outcomes in the offspring of women who worked at the LaSalle Electrical Utilities Company (EUC). *Methods:* A retrospective cohort with at least one live birth and known employment time at EUC was eligible for this analysis. Exposure was defined and categorized by the number of fiscal quarters worked during the PCB era (1952–1981). A total of 288 women with 800 live births were included. A Chi-Square test was used to compare maternal and child characteristics across exposure groups and repeated measures logistic regression, controlling for clustering among siblings, was used to assess the associations between prenatal PCB exposure and these outcomes. *Results:* After adjustment for confounding and independent maternal predictors, 1–4 quarters of prenatal exposure to PCBs increased the odds for asthma (OR 3.24[1.30–8.09]), eczema/hay fever (OR 3.29[1.54–7.04]), and frequent ear infections (OR 2.24[1.19–4.22]) when compared with persons unexposed/exposed only to naphthalenes. The significance of the associations varied by exposure period and level of exposure, with the strongest associations in those employed exclusively after 1952 when PCBs were introduced. *Conclusions:* These results support previous findings of associations of prenatal exposure to PCBs with asthma, eczema/hay fever, and frequent ear infections. Additional prospective studies are needed to confirm these findings. Also required are more precise PCB exposures to separate them from other exposures in occupational settings.

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Epidemiology; morbidity; mortality

Abbreviations

PCB	Polychlorinated biphenyl
POP	Persistent organic pollutant
IgE	Immunoglobulin E
IL-8	Interleukin 8
DDE	1,1-dichloro-2,2-bis(chlorophenyl)ethylene
DDT	1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane
HCB	Hexachlorobenzene
EUC	Electrical Utilities Company
SD	Standard deviation
IgG	Immunoglobulin G

1. Introduction

Prenatal exposures to persistent organic pollutants (POPs) have been shown to have immunomodulating effects but the results are inconclusive. Prenatal exposure to polychlorinated biphenyls (PCBs), compounds historically used in dielectric material and coolant fluids, has been associated with increased cord blood Immunoglobulin E (IgE) (1), smaller indices of thymus size (2,3), decreased naïve T helper cell subsets (4), increased lymphocytes (5,6) and T cells (6), and decreased antibody response to selected vaccines in children (6–9). Maternal concentrations of POPs have also been associated with airway obstruction in offspring and higher maternal dioxin-like PCB concentrations have been positively associated with offspring airway obstruction compared with lower maternal exposure levels (10). Postnatal exposure has been associated with increased IgE (11), decreased polymorphic neutrophils in adolescents (12), and decreased IgG levels (13). Mixed exposures of PCBs with dioxins and/or pesticides in Japan have also been associated with altered percentages of T cell subgroups (14,15) but not with immunoglobulins (16).

There is also evidence that prenatal exposures to PCBs are associated with an increased risk for clinical diseases, such as middle ear (17,18), respiratory infections (5,17,18), and gastrointestinal infections (17), with

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varying immune responses in those with clinical disease, such as recently reported associations of serum PCB levels with IL-8 mRNA expression among children with asthma in Japan (19–21). Current PCB burden has been associated with recurrent ear infections and chicken pox (6), asthma in 3–6- year-old children (22), and postnatal exposure with recurrent ear infections (23). Related compounds, such as 1,1-dichloro-2,2-bis(chlorophenyl)ethylene (DDE), which is a downstream metabolite of the insecticide 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), have also demonstrated associations with higher prevalence of asthma and risk of wheezing at 4 years of age (24), otitis media (25), and lower respiratory tract infections (26,27). In a recent analysis, DDE was found to be associated only with wheeze at 4 years but hexachlorobenzene (HCB) was associated also with chest infections at 10 years (28). Similarly, exposures to dioxins and dioxin-like PCBs have been associated with increased risk of wheeze (9,29), frequent upper respiratory tract infections (9), and asthma medication use (30). Other studies, however, have found inverse associations of prenatal PCB exposure with shortness of breath with wheeze (6,23) or have found no association between prenatal or early postnatal PCB exposure and antibody concentrations (31,32), prenatal PCB exposure and respiratory infections (27), or prenatal organochlorine exposure and eczema during childhood (33). Results for other organochlorines have been similarly negative or weak (34,35). The results of a recent systematic review were also mixed, with associations between PCB and/or dioxin exposure and asthma, allergy symptoms, and ear infections varying based on the age of the child, the time of exposure, congener type, and study sample size (36).

Many current studies lack power to make definitive conclusions and have very different samples and research questions, making comparisons between them difficult. Furthermore, much of the literature focuses on dietary PCB exposures and therefore includes infants with comparatively lower exposure levels as opposed to the higher levels seen in a typical occupational situation. Thus, we focus on occupational exposures to PCBs.

The objective of this study was to examine the association between in-utero exposure to PCBs at a capacitor manufacturing plant, the LaSalle Electrical Utilities Company (EUC), and asthma, eczema/hay fever, and frequent ear infections. We hypothesized that in-utero PCB exposure would be positively associated with asthma, eczema/hay fever, and frequent ear infections.

2. Methods

2.1. Subjects and sample selection

Participant selection was described in detail previously as a part of the Final Report published by The Illinois Department of Public Health and The University of Illinois at Chicago School of Public Health (37). To summarize, participants were ascertained from the LaSalle EUC Retrospective Mortality Cohort and were eligible for the current study if they were alive at the time of the phone interview, had a confirmed vital status within 6 months of initiation of the LaSalle EUC Morbidity Study II in 2001, had a confirmed last known address, and provided written consent to participate. This study was monitored by the Institutional Review Board at Illinois Department of Public Health through Single Project Assurance with The University of Illinois at Chicago.

Due to budgetary constraints, it was not possible to interview all members of the entire cohort. Because tracing was ongoing, eligible members were sampled in two batches 3 months apart: The first batch selected all persons >65 years of age (69% of the workforce). For those less than 65 years, a relatively small number worked >3 years. For that reason, all those, but only 50% of those who worked <3 years were included (37). For the second batch, those who worked less than one quarter (3 months) and 50% of those <65 years working 2–11 quarters were excluded. The final sample consisted of all those who reported or whose records indicated working 3 or more years or were ≥65 during data collection and a random sample of people <65 who had worked less than 3 years. Overall, 47.8% of men and women sampled completed an interview – a total of 26% refused, while most of the other non-participants were unable to be reached or were unavailable. As this analysis focused on outcomes in offspring, participants were eligible if they were female, had at least one live birth, and had information on the total years worked at the plant. In total, 288 former female workers and 966 pregnancies resulting in 800 live births were considered here. Figure 1 diagrams the population sampling.

2.2. Outcome and exposure measurement

Mothers from the original EUC cohort were interviewed to assess the outcomes of their pregnancies. Questions included those about a child's developmental progress, diagnoses of respiratory infections, frequent ear infections, asthma, thyroid disorders, reproductive disorders, birth weight, and birth defects, as well as those assessing conditions of pregnancy such as toxemia, maternal high blood pressure, maternal exposures to X-Rays, tobacco and alcohol use, medication use during pregnancy, and postnatal environmental questions such as duration of breastfeeding. All outcomes and exposure estimates were assessed by self-report. Exposures, defined as working at EUC during its known time of operation and use of PCBs, were also verified using social security records. Additional exposures, such as known exposure to specific

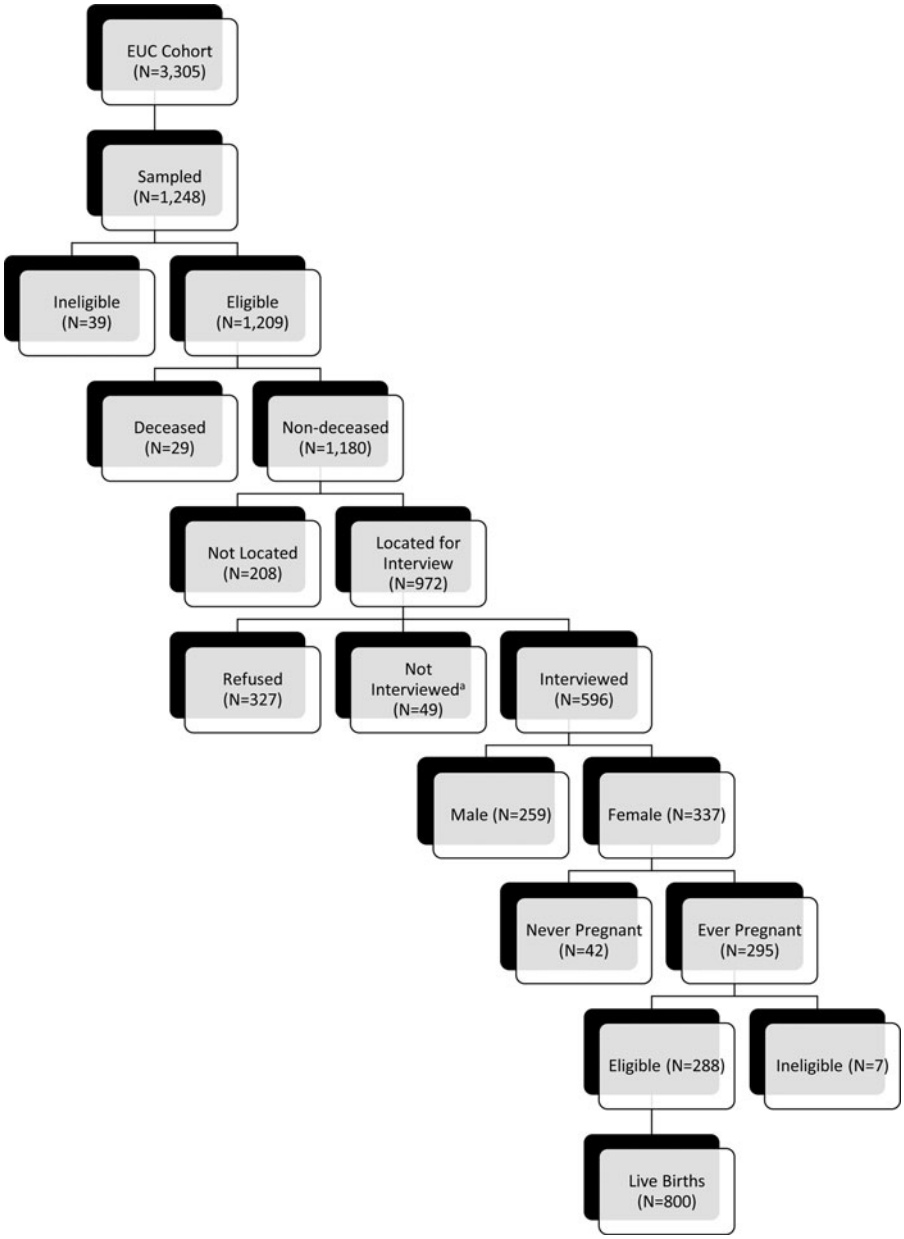

Figure 1. Sampling schema for interviewing former female employees of the LaSalle Electrical Utilities Company.
[a]Reasons participants were unable to complete an interview include: denying working at EUC, unavailability, or being ineligible for other reasons.

compounds and work at other jobs that may have produced chemical exposure to volatile organic compounds or heavy metals, were assessed as well, but sample sizes were too small to analyze separately.

The capacitor manufacturing plant was open between 1943 and 1981. Chlorinated naphthalenes were used at the plant throughout its existence, but, after 1952, PCBs were used as well and naphthalene use decreased. Both PCBs and chlorinated naphthalenes were used as dielectric material in the creation of capacitors, and although naphthalene use decreased once PCBs were introduced, the plant continued to use them on a small scale. Children of women who worked at EUC after 1952 and before or during the pregnancy were assumed to be exposed to PCBs. Although the primary exposure of interest in this study was PCBs, because of a small literature showing health effects from chlorinated naphthalenes, primarily in animal models (38,39), the exposure was broken down into four main groups: unexposed, exposed to naphthalenes only (employed only pre-1952), 1–4 quarters worked prior to or during pregnancy after 1952, when PCBs were used, or greater than four quarters worked prior to or during pregnancy after 1952. There were two different exposure variables created based upon these outlined groups: a three-category cumulative exposure variable with the referent group including both those exposed

just to naphthalenes but not PCBs and those whose pregnancies occurred before employment, or unexposed (Model 1) and a four-category cumulative exposure variable which separated no exposure to PCBs as the referent group (pregnancy occurring before employment) from exposure to naphthalenes only (employed only before 1952: Model 2). Since the primary focus of this report is on PCBs, the three-category variable, with the referent group including those who were unexposed and those with exposure to naphthalenes only, was the main exposure variable for the analyses. Associations were additionally examined in the final models for a smaller cohort of women who only worked at the plant after PCBs were introduced in 1952.

Frequent ear infections was defined as having four or more ear infections annually, asthma was defined as ever having a diagnosis of asthma, while eczema/hay fever was a composite category from two questions addressing the diagnosis of eczema and hay fever separately. These conditions were combined due to low subject counts and because they are frequently related conditions. All outcomes were reported by the mother at the time of interview. Reported outcomes were considered for persons of all ages because we were unable to verify the age of diagnosis for many subjects and there was enough missing data to cause a considerable reduction in power if only outcomes reported as diagnosed during early childhood (<10 years of age) were used.

2.3. Statistical methods

Collected maternal and child characteristics were compared between each exposure category in relation to the unexposed using a Chi-Square test. Birth order, as it was the only continuous variable, was compared between exposure categories using a *t*-test. The associations between prenatal exposure to PCBs and asthma, allergies, and frequent ear infections were assessed using logistic regression with generalized estimating equations (GEE) and an exchangeable correlation structure to account for clustering due to some women having multiple pregnancies using SAS version 9.2 (SAS Institute, North Carolina). These methods were chosen because all outcomes were binary and the relationship between siblings needed to be appropriately accounted for. An exchangeable correlation structure was selected because the within-mother observations were believed to be correlated equally, i.e. siblings were related to one another evenly. Collected variables were considered potential confounders if they were associated with one of the three outcome measures ($p < 0.20$), associated with the exposure variable of interest, and not likely to be found on the causal pathway between exposure and outcome or downstream of the outcome. Possible confounders meeting these criteria were then added to unadjusted models and considered confounders if the odds ratio changed by greater than 10%. Therefore, the final models for each health outcome could contain different variables. Possible covariates were assessed for evidence of multiplicative effect modification by adding the interaction term to a model and were considered significant indicators of an interaction with the main exposure at $p < 0.20$. Models were built in a forward step-wise fashion with covariates left in the model at $p < 0.20$. Covariates and/or effect modifiers were considered significant at $p < 0.05$.

Variables considered in model building included breastfeeding (binary and categorical), alcohol use during pregnancy (binary and categorical), tobacco smoking during pregnancy (binary and categorical), low birth weight (<2500 g), and binary variables: maternal age, mother 18 or younger at conception, mother 35 or older at conception, history of urinary tract infection (UTI), diabetes, maternal high blood pressure, maternal exposures X-Rays during pregnancy, toxemia (preeclampsia) during pregnancy, history of oral contraceptive use, other prescription medication during pregnancy, use of natural or folk remedies, mother ever having a still born or a miscarriage, child having any birth defect, any diagnosed thyroid disorder, any hearing problems, unusual head size, birth on time (early, early but on time, or late vs. on time), and child's gender. All categorical binary (yes/no) variables were used in the model building process with "no" as the reference category.

3. Results

3.1. Description of the sample

Of the 800 live births included in the analysis, the mean pregnancy number was 2.53 (s.d. 1.52) and the mean birth order was 2.27 (s.d. 1.34). Women reported breastfeeding in 80.98% of children and reported using other drugs/medications during 10.83% of pregnancies, toxemia during 3.01%, and high blood pressure during 5.56% of pregnancies. A total of 10.13% of pregnancies occurred in mothers 35 and older while 3.00% occurred in mothers 18 and younger. Mothers reported other medical problems in 4.76% of pregnancies and 14.25% reported ever having miscarried while only 2.63% reported ever having a stillborn. The average birth weight of children in the cohort was 3301.61 g with 8.93% being considered low birth weight and 3.90% of infants reported as being born prematurely. In 327 live births (40.88%), the infant was considered unexposed, with exposure to only chlorinated naphthalenes occurring in an additional 230 (28.75%) births. The remaining births were considered exposed,

Table 1. Characteristics of female employees of a capacitor manufacturing plant and their children by maternal exposure status, LaSalle Electrical Utilities Company, 1952–1981 ($N = 800$).

	Unexposed ($N = 327$) % *(N)*	Naphthalenes only ($N = 230$) % *(N)*	1–4 quarters PCBs ($N = 131$) % *(N)*	>4 quarters PCBs ($N = 112$) % *(N)*
Child Characteristics				
Asthma	3.47 (*317*)	4.00 (*225*)	10.85 [a] (*129*)	7.14 (*112*)
Eczema/hay fever	4.44 (*315*)	4.05 (*222*)	11.02 [a] (*127*)	4.50 (*111*)
Frequent ear infections	6.67 (*315*)	9.33 (*225*)	19.38 [a] (*129*)	14.55 [a] (*110*)
Any thyroid problem	3.29 (*304*)	4.07 (*221*)	3.10 (*129*)	5.50 (*109*)
Low birth weight	9.84 (*305*)	9.78 (*225*)	8.40 (*131*)	5.36 (*112*)
Singleton	9.88 (*327*)	99.57 (*230*)	100.00 (*131*)	96.43 (*112*)
Birth defect	4.63 (*324*)	6.61 (*227*)	4.62 (*130*)	8.11 (*111*)
Unusual head size	0.31 (*323*)	1.32 (*227*)	0.00 (*130*)	1.79 (*112*)
Breastfeeding (any)	77.78 (*324*)	86.34[a] (227)	81.68 (*131*)	*78.57* (*112*)
Maternal characteristics				
Mom 35+	2.75 (*327*)	16.96 [a] (*230*)	7.63 [a] (*131*)	20.54 [a] (*112*)
Mom ≤ 18	2.76 [a] (326)	2.62 [a] (229)	5.34 [a] (131)	1.79 [a] (112)
Smoking during pregnancy	2.32 (*327*)	26.52 (*230*)	3.82 [a] (*131*)	33.33 [a] (*111*)
UTI	0.93 (*321*)	2.17 (*230*)	0.78 (*130*)	0.89 (*112*)
X-rays	10.44 (*316*)	13.24 (*219*)	20.31 [a] (*128*)	11.01 (*109*)
Other meds (other than oral contraceptives)	10.15 (*325*)	10.09 (*228*)	10.77 (*130*)	14.41 (*111*)
Medical problems	3.69 (*325*)	5.65 (*230*)	3.82 (*131*)	7.14 (*112*)
Toxemia (preeclampsia)	7.34 (327)	0.00 (230)	0.00 (131)	0.00 (112)
Ever stillborn	3.08 (*327*)	0.87 (*230*)	4.58 (*131*)	2.68 (*112*)
Ever miscarry	7.03 (*327*)	12.17 [a] (*230*)	26.72 [a] (*131*)	25.00 [a] (*112*)
High blood pressure	6.46 (*325*)	6.61 (*227*)	3.85 (*130*)	2.75 (*109*)
Alcohol during pregnancy	17.13 (*327*)	2.12 (*226*)	28.24 [a] (*131*)	31.25 [a] (*112*)

[a] $p < 0.05$ from a Chi-Square test of exposure category vs. unexposed.

with 131 (16.38%) having reported exposure of four fiscal quarters or less and 112 (14.00%) reporting more than four quarters of PCB exposure. There were 42 offspring considered to have asthma, 42 with eczema/hay fever, and 83 with frequent ear infections (data not shown).

Table 1 reports the distribution of key covariates by exposure category. To summarize the differences, only maternal age greater than or equal to 35 years ($p < 0.0001$) or less than or equal to 18 years ($p < 0.0001$), ever having a miscarriage ($p < 0.0384$), and breastfeeding ($p < 0.0111$) differed significantly between the naphthalene only group and the unexposed group. In the 1–4 quarters PCB exposed group, the proportions of asthma ($p < 0.0021$), eczema/hay fever ($p < 0.0102$), and frequent ear infections were significantly greater ($p < 0.0001$), in addition to maternal smoking ($p < 0.0012$), maternal exposure to X-Rays ($p < 0.0055$), ever having a miscarriage ($p < 0.0001$), maternal age greater than or equal to 35 years ($p < 0.0179$) or less than or equal to 18 years ($p < 0.0014$), and drinking during pregnancy ($p < 0.0075$), compared with the unexposed group. In the >4 quarters PCB exposed group, only frequent ear infections ($p < 0.0116$), maternal age 35 plus ($p < 0.0001$) and 18 and under ($p < 0.0032$), smoking ($p < 0.0358$), ever miscarrying ($p < 0.0001$), and drinking ($p < 0.0015$) differed significantly when compared to the unexposed group. Increasing birth order was not included in the tables but differed significantly between the unexposed group each with the naphthalene only group ($p < 0.0466$), the 1–4 quarters PCB exposure group ($p < 0.0066$), and the >4 quarters PCB exposure group ($p < 0.0439$).

3.2. Regression analyses

Unadjusted: In the unadjusted analysis, exposure to PCBs before or during pregnancy was directly associated with asthma (OR 2.91[1.23,6.88], $p < 0.0152$), eczema/hay fever (OR 3.09[1.49,6.41], $p < 0.0025$), and frequent ear infections (OR 2.54[1.40,4.61], $p < 0.0022$) in those with 1–4 quarters PCB exposure, and with frequent ear infections (OR 2.09[1.10,3.95], $p < 0.0235$) in those with >4 quarters PCB exposure when naphthalenes were included in the unexposed referent group (Table 2-Model 1). When exposure to naphthalenes was analyzed separately, the relationships with PCB exposure compared with the referent group of unexposed remained the same (Table 2-Model 2).

Asthma: Results from the final models on asthma show that exposures to PCBs for 1–4 quarters are associated with approximately a three-fold increase in odds of asthma (model 1: OR 3.24[1.30,8.09], $p < 0.0118$; model 2: OR 3.23[1.18,8.85], $p < 0.0223$) after adjustment for maternal smoking, prenatal exposure to X-Rays, maternal UTI during pregnancy, other medical problems during pregnancy, and the mother ever having a still born (Table 3-Models 1 and 2). Exposure to PCBs for >4

Table 2. Unadjusted associations of PCB exposure category with asthma, eczema/hay fever, and frequent ear infections[a1,a2].

	OR (95% CI)	*p*-value
Asthma ($N = 783$)[b]		
Model 1		
Unexposed/exposed to only naphthalenes	REF	
1–4 quarters exposed to PCBs	2.91 (1.23–6.88)	0.0152
>4 quarters exposed to PCBs	2.00 (0.81–4.93)	0.1312
Model 2		
Unexposed	REF	
Exposed only to naphthalenes	1.20 (0.52–2.79)	0.6638
1–4 quarters exposed to PCBs	3.14 (1.21–8.19)	0.0191
>4 quarters exposed to PCBs	2.17 (0.80–5.84)	0.1272
Eczema/hay fever ($N = 775$)[c]		
Model 1		
Unexposed/exposed to only naphthalenes	REF	
1–4 quarters exposed to PCBs	3.09 (1.49–6.41)	0.0025
>4 quarters exposed to PCBs	1.02 (0.41–2.51)	0.9672
Model 2		
Unexposed	REF	
Exposed only to naphthalenes	0.94 (0.37–2.36)	0.8975
1–4 quarters exposed to PCBs	3.01 (1.35–6.69)	0.0070
>4 quarters exposed to PCBs	1.00 (0.39–2.54)	0.9921
Frequent ear infections ($N = 779$)[d]		
Model 1		
Unexposed/exposed to only naphthalenes	REF	
1–4 quarters exposed to PCBs	2.54 (1.40–4.61)	0.0022
>4 quarters exposed to PCBs	2.09 (1.10–3.95)	0.0235
Model 2		
Unexposed	REF	
Exposed only to naphthalenes	1.42 (0.73–2.74)	0.3013
1–4 quarters exposed to PCBs	2.96 (1.53–5.75)	0.0013
>4 quarters exposed to PCBs	2.44 (1.20–4.95)	0.0138

[a1]logistic regression with generalized estimating equations (GEE) used to generate models.
[a2]model 1- naphthalenes included in the referent group; model 2- naphthalenes considered separately.
[b]42 participants reported asthma.
[c]42 participants reported eczema and/or hay fever.
[d]83 reported frequent ear infections.

quarters also showed a significant association at nearly a three-fold increase with asthma (OR 2.76[1.08,7.03], $p < 0.0336$) when naphthalenes were included in the reference group (Table 3-Model 1). The association with >4 quarters PCB exposure when naphthalenes was removed from the reference group (OR 2.75[0.99,7.65], $p < 0.0524$) suggested a trend toward a positive association, but was only of borderline significance (Table 3-Model 2).

Eczema/hay fever: Results from final models on eczema/hay fever indicated that after adjustment for maternal age 35 years and older, maternal high blood pressure, and infant low birth weight (<2500 g), exposure to 1–4 quarters of PCBs as compared to the referent group including both unexposed and those exposed only to naphthalenes was associated with a three times the odds of experiencing eczema/hay fever (OR 3.29[1.54–7.04], $p < 0.0022$; Table 4-Model 1) later in life. This relationship remained for the 1–4 quarters PCB exposure group once exposure to naphthalenes only was removed from the unexposed group (OR 3.47[1.50,8.01], $p < 0.0035$; Table 4-Model 2). Eczema/hay fever was not significantly

Table 3. Fully adjusted models on PCB exposure category and asthma[a1,a2] ($N = 736$)[b].

	OR (95% CI)	*p*-value
MODEL 1		
Exposure group		
Unexposed/exposed to only naphthalenes	REF	
1–4 quarters exposed to PCBs	3.24 (1.30–8.09)	0.0118
>4 quarters exposed to PCBs	2.76 (1.08–7.03)	0.0336
Smoking group		
1–8 cigs/day	0.65 (0.16–2.73)	0.5608
9–16 cigs/day	0.56 (0.17–1.77)	0.3223
>16 cigs/day	2.57 (1.11–5.97)	0.0281
X-rays	2.35 (0.89–6.23)	0.0847
UTI during pregnancy	6.17 (0.99–38.60)	0.0516
Other medical problems during pregnancy	2.53 (0.88–7.30)	0.0861
Ever had a stillborn	3.56 (0.82–15.38)	0.0894
MODEL 2[c]		
Exposure group with naphthalenes separated		
Unexposed	REF	
Exposed only to naphthalenes	1.00 (0.40–2.48)	0.9922
1–4 quarters exposed to PCBs	3.23 (1.18–8.85)	0.0223
>4 quarters exposed to PCBs	2.75 (0.99–7.65)	0.0524

[a1]logistic regression with generalized estimating equations (GEE) used to generate models.
[a2]model 1- naphthalenes included in the referent group; model 2- naphthalenes considered separately.
[b]39 of the 736 participants in this analysis reported asthma.
[c]all models adjusted for the variables tabulated under Model 1 (variables listed above).

associated with working >4 quarters during the PCB era in either model (Table 4).

Frequent ear infections: With frequent ear infections, exposure to 1–4 quarters of PCBs was associated with approximately twice the odds of frequent ear infections, both before (OR 2.24[1.19,4.22], $p < 0.0123$) and after

Table 4. Fully adjusted models on PCB exposure category and eczema/hay fever[a1,a2] ($N = 745$)[b]

	OR (95% CI)	*p*-value
MODEL 1		
Exposure group		
Unexposed/exposed to only naphthalenes	REF	
1–4 quarters exposed to PCBs	3.29 (1.54–7.04)	0.0022
>4 quarters exposed to PCBs	1.32 (0.52–3.36)	0.5559
High blood pressure (mother)	2.95 (1.06–8.16)	0.0377
Mother 35+	0.26 (0.06–1.11)	0.0683
Low birth weight (<2500 g)	2.38 (0.99–5.74)	0.0529
MODEL 2[c]		
Exposure group with naphthalenes separated		
Unexposed	REF	
Exposed only to naphthalenes	1.14 (0.44–2.92)	0.7891
1–4 quarters exposed to PCBs	3.47 (1.50–8.01)	0.0035
>4 quarters exposed to PCBs	1.39 (0.53–3.60)	0.4983

[a1]logistic regression with generalized estimating equations (GEE) used to generate models.
[a2]model 1- naphthalenes included in the referent group; model 2- naphthalenes considered separately.
[b]41 of the 745 participants in this analysis reported eczema and/or hay fever.
[c]all models adjusted for the variables tabulated under Model 1 (variables listed above).

Table 5. Fully adjusted models on PCB exposure category and frequent ear infections[a1, a2] ($N = 736$)[b].

	OR (95% CI)	*p*-value
MODEL 1		
Exposure group		
Unexposed/exposed to only naphthalenes	REF	
1–4 quarters exposed to PCBs	2.24 (1.19–4.22)	0.0123
>4 quarters exposed to PCBs	1.74 (0.81–3.74)	0.1582
Ever had a miscarriage	2.32 (1.17–4.58)	0.0157
Toxemia	4.05 (1.54–10.63)	0.0046
Low birth weight (<2500 g)	1.94 (1.00–3.77)	0.0492
Ever had a stillborn	6.01 (1.64–22.00)	0.0068
Thyroid disorder (Child)	2.05 (0.74–5.73)	0.1690
Singleton pregnancy	0.15 (0.03–0.77)	0.0227
Any other birth defect	3.51 (1.61–7.65)	0.0016
Unusual head size	8.25 (1.85–36.83)	0.0057
MODEL 2[c]		
Exposure group with naphthalenes separated		
Unexposed	REF	
Exposed only to naphthalenes	1.22 (0.61–2.45)	0.5730
1–4 quarters exposed to PCBs	2.44 (1.20–4.96)	0.0139
>4 quarters exposed to PCBs	1.89 (0.81–4.41)	0.1384

[a1]logistic regression with generalized estimating equations (GEE) used to generate models.
[a2]model 1- naphthalenes included in the referent group; model 2- naphthalenes considered separately.
[b]79 of the 736 participants included in this model reported frequent ear infections.
[c]all models adjusted for the variables tabulated under Model 1(variables listed above).

(OR 2.44[1.20,4.96], $p < 0.0139$) exposure to naphthalenes was removed from the referent group and after adjustment for the mother ever having a miscarriage or stillborn, experiencing toxemia during pregnancy, infant low birth weight, a singleton pregnancy, and the child having a diagnosed thyroid disorder, an unusual head size, or any other birth defect (Table 5-Models 1 and 2). Frequent ear infections were not significantly associated with the >4 quarters PCB exposure groups (Table 5).

When only cohort members exposed predominantly to PCBs were included in the models (women who began working at the EUC after the introduction of PCBs in 1952), the associations between exposure and each of the outcomes increased in all cases except for the >4 quarters PCB exposure group and eczema/hay fever (Table 6).

4. Discussion

The results suggest that exposure to PCBs, dioxins, and other chemicals present at the EUC during its operation is associated with increased odds for eczema/hay fever, asthma, and frequent ear infections after controlling for confounders and independent predictors of the outcome and maternal clustering among siblings, thereby confirming the hypothesis that a direct relationship exists between PCB levels during pregnancy and the outcomes of interest. The significance of the associations vary by definition and level of exposures, with associations strongest in the

Table 6. Associations of PCB exposure categories with asthma, eczema/hay fever, and frequent ear infections: fully adjusted models[a] using a post 1952 cohort ($N = 398$)[b1, b2]

	OR (95% CI)	*p*-value
Asthma[c]		
Model 1		
Unexposed/exposed to only naphthalenes	REF	
1–4 quarters exposed to PCBs	5.09 (1.83–14.11)	0.0018
>4 quarters exposed to PCBs	4.99 (1.48–16.87)	0.0096
Eczema/hay fever[d]		
Model 1		
Unexposed/exposed to only naphthalenes	REF	
1–4 quarters exposed to PCBs	4.28 (1.74–10.55)	0.0016
>4 quarters exposed to PCBs	1.08 (0.29–4.02)	0.9125
Frequent ear infections[e]		
Model 1		
Unexposed/exposed to only naphthalenes	REF	
1–4 quarters exposed to PCBs	2.74 (1.23–6.11)	0.0137
>4 quarters exposed to PCBs	3.58 (1.35–9.51)	0.0104

[a]all models adjusted identically as in the preceding tables.
[b1]logistic regression with generalized estimating equations (GEE) used to generate models.
[b2]model 1- naphthalenes included in the referent group.
[c]28 experienced asthma.
[d]25 experienced eczema and/or hay fever.
[e]44 experienced frequent ear infections.

cohort of women employed after 1952 suggesting PCBs, rather than other exposures, are most important.

These results are biologically plausible and are cohesive with previously published literature. Exposure to PCBs has been associated with recurrent ear infections (23) and allergic sensitization (1). Maternal concentrations of dioxin-like PCBs have been associated with an increased risk of asthma (30) and children with asthma have been shown to have higher serum-PCB (non-dioxin-like congeners) levels, using IL-8 expression as a biologic marker (19–21). Associations between PCB exposure and alterations in the immune system are also consistent with findings in this study. Higher levels of total IgE were noted in placentas of mothers living in industrial compared with rural regions (1), and higher IgE levels were found in children exposed to PCBs through prenatal and postnatal dietary exposure (11). Other immune responses, while not specific for allergic diseases such as decreased cellular responses to vaccines (6–8), decreased IgG levels (13), decreased thymus size (2), and altered T cell subsets and proliferation (4), may predispose to risk of infections and immune-related diseases.

Results are not consistent with other studies (36). Gascon et al. (27) found an association between lower respiratory tract infection/wheeze and DDE but failed to see one for PCBs in 12–14-month olds. Jusko et al. (31,32) similarly did not see a correlation between prenatal and early postnatal PCB exposure and total serum immunoglobulin concentrations in 6-month olds (32) or between PCBs

and post-vaccination antibody response at 6 months (31). One meta-analysis found no associations between prenatal exposure to 16 different maternal contaminants, including PCB-153 and DDE, to childhood asthma or wheeze, but found a negative association with eczema (33). These studies examined environmental exposures and not occupational exposures which tend to have higher levels of contaminants. Also, these studies focused on only on infants or young children who, particularly in the case of asthma, may not be old enough to exhibit symptoms or be diagnosed by a physician. Further differences could be due to the PCB congeners common at this plant versus environmental exposure (40) as well as the mixture of other compounds which here included chlorinated naphthalenes and lead.

Our results suggest a non-linear relationship between PCB exposure levels and all three outcomes with stronger associations in the 1–4 quarters PCB exposure group when compared with the >4 quarters PCB exposure group (Tables 2–5). In the post-1952 subset, a non-linear relationship was seen for asthma and eczema/hay fever, but not for frequent ear infections (Table 6). A similar trend with stronger positive associations at lower levels of exposure has been noted in other studies examining the relationship between PCB levels and other POPs with diabetes and endogenous hormones (41–43).

As previously mentioned, a mother ever having a stillborn or a miscarriage placed a child at greater odds of frequent ear infections (Table 5). It is important to note that this is a cluster-level variable which means that it controlled for both previous and subsequent miscarriages and did not differ by timing of pregnancies in the same mother (i.e. if a mother had a miscarriage following a live birth, it was analyzed as equivalent to a mother having a miscarriage prior to a live birth). Therefore, it could be a measure of randomness (the more pregnancies, the higher the probability for a miscarriage) or genetic/reproductive fitness. We could find no evidence in the literature of an association between exposure to PCBs and miscarriage or miscarriage and frequent ear infections. More research is necessary to test the validity of this finding.

Models built using only those women working 1952 and later indicated stronger associations between exposure and outcomes (Table 6). Prior to 1952, EUC was known to use greater amounts of chlorinated naphthalenes, which have largely unknown health effects, but not PCBs (37). We can consider the subgroup who worked after 1952 to represent a population with predominantly PCB exposures. These models, however, were fairly imprecise with wide confidence intervals due to smaller sample size and thus further research is warranted to determine any threshold effects that may exist.

In this analysis, cumulative quarters worked during the PCB era was found to be highly correlated with both birth order and maternal age and was much higher in mothers with PCB exposure during pregnancy compared to PCB exposures prior to pregnancy (18.87 and 8.16 quarters, respectively – results not shown in tables). The stronger effects in women exposed 1–4 quarters to PCBs versus more than four quarters to PCBs is therefore counterintuitive. This could be related to larger numbers of women in the prior and 1–4 quarters PCB exposure groups. Alternatively, women working during pregnancy or for more quarters could be healthier than the general working population, a phenomenon often referred to as the healthy worker effect, or the reverse dose response could be a true trend.

This study had a number of limitations. First, both recall and reporting bias could have influenced the results. That is to say, women may have underreported tobacco and alcohol use during pregnancy intentionally due to the negative social connotations these activities hold and case parents may be more likely to remember certain exposures compared to control parents. Because this sample was not part of a birth cohort and pregnancies occurred over many years, there could also be cohort effects unrelated to the exposure of interest.

Second, the only verification that took place of subject information was the duration of work history. Therefore, all medical outcomes were self-reported and thus misclassification of the disease could be present but is likely non-differential. An earlier analysis of this cohort performed testing on biologic samples to verify PCB exposure. Levels had a high correlation with quarters worked ($\rho = 0.71$) and with calculated job score ($\rho = 0.70$) (44).

Third, it has been documented that certain areas of the facilities contained higher levels of one compound versus another, but there was too much missing data to analyze by job category (37). As previously discussed, maternal exposure through other jobs prior to or during pregnancy was not factored into the exposure calculation. Also, these women most likely had multiple exposures and thus these findings may be not just from exposure to PCBs, but from concurrent exposure to interacting heavy metals and naphthalenes. Fourth, the survey administered to study participants did not include questions pertaining to other environmental exposures the children may have faced that could have changed their risk profiles apart from in-utero exposures faced by the mother. While the fetal stage is undoubtedly an important period for programming development, pathways continue to be programmed throughout early childhood. Therefore, early childhood exposures, whether environmental, dietary, or otherwise, could be important contributors to the development of

asthma, eczema/hay fever, and frequent ear infections and should be measured. Breastfeeding could be a significant additional exposure that the children of these mothers may have faced. The results remained the same when the models were examined in those 81% who were breastfed but the data were too sparse to assess the exposure among those who were not breastfed (results not shown).

The most obvious limitation to this study is the omission of age at diagnosis in the models. Ideally, these outcomes should be examined only in young children as diagnoses later in life are less likely to be caused by exposures before birth. Because the data were collected retrospectively from parents we opted to include all reported outcomes in the models regardless of reported age of diagnosis. When the age of diagnosis was not missing, many were reported as under the age 10, with some reported later in childhood (<18), and a few reported during adulthood. One should be mindful that when the mothers were interviewed, many were in their 60s and 70s making recall limitation quite likely.

Although there were numerous limitations, this study also had a number of strengths. Due to the retrospective cohort design, cases and controls were obtained from the same source population. This could attenuate a possible selection bias and increase the generalizability of these results to occupational cohorts under similar exposure conditions. Additionally, self-report was used for most outcome measures, but employment history was verified with social security records which, on a very basic level, strengthened the measurement of the main exposure variable.

5. Conclusions

These results support previous findings that exposure to PCBs is associated with clinical measures reflective of immunologic changes, though further research examining the effects of heavy metals, PCBs, chlorinated naphthalenes, and dioxins on the developing immune system is needed in order to suggest causality of these findings. Because it is feasible that exposures experienced postnatally could have also contributed to the development of asthma, eczema/hay fever, or frequent ear infections, temporality of this relationship cannot be determined. Although PCBs were outlawed in the United States in 1979, their persistence in the environment supports the importance of further research to examine these associations and with lower levels of exposure in order to assess possible dangers to unborn children presently. Furthermore, because these findings could suggest stronger associations at presumably lower exposure levels, future studies will be particularly important for guideline development to identify individuals at high risk for these outcomes and others. In future studies, it will also be necessary to tease out the associations with mixed exposures through biologically measuring POP levels in mothers so that each chemical may be examined separately and in conjunction with others found for interacting effects.

Declaration of interest

No potential conflicts of interest exist with any organizations whose products may be discussed in this article. The writing and content of this paper was solely the responsibility of the named authors.

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