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THE LA SALLE ELECTRICAL UTILITIES COMPANY MORBIDITY STUDY II LA SALLE, IL

SUBMITTED BY

THE ILLINOIS DEPARTMENT OF PUBLIC HEALTH AND
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The La Salle Electrical Utilities Company
Morbidity II Study

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ABSTRACT

The Illinois Department of Public Health (IDPH) in conjunction with the University of Illinois at Chicago, School of Public Health, conducted a multi-year exposure/health study of former workers of the La Salle Electrical Utilities Company (EUC) Superfund site in La Salle, Illinois. This study was conducted with funding from the Agency for Toxic Substances and Disease Registry (ATSDR). The overall study consisted of three parts: a retrospective cohort mortality study of 3,305 persons who had worked at the plant; a cross-sectional morbidity study (Morbidity I) of 191 former employees and 26 community residents examining the relationship of EUC exposure and PCB levels with history of selected diseases, reproductive factors, and biologic markers; and the current Morbidity II study. The Morbidity II study reported here was a telephone interview of 596 former employees relating years of working at the plant with health outcomes in these former employees and their children. Among the children, exposure of their mothers at the plant was associated with ear infections, having attention problems, being in special education classes and endometriosis (girls only). Only the association with ear infections, however, remained significant after control for confounders and clustering within families. Among the former employees, the only association that was significant after control for confounders was breast cancer in women. The association with breast cancer was not seen in our mortality study and should be interpreted with caution.

SITE BACKGROUND

The La Salle Electrical Utilities Company (EUC) manufactured electrical equipment in the city of La Salle, La Salle County, Illinois (106,913 population), on a 9.6-acre tract of land. The EUC manufactured electrical capacitors at the plant from July 1943 until May 28, 1981. By the early 1950s, EUC had begun utilizing polychlorinated biphenyls (PCBs) and various volatile organic compounds (VOCs), including trichloroethylene (TCE), in manufacturing processes. PCBs were used as a dielectric material and TCE as a degreasing/cleaning agent. In addition, chlorinated naphthalenes were used as dielectrics prior to the use of PCBs, as well as in the manufacture of smaller capacitors after PCBs were introduced in 1952-1953. Oils containing PCBs were reportedly used for dust control on and off the site property until 1969. PCBs and VOCs were also spilled at various on-site locations, roadways, and in nearby residential areas. Although more than 3,000 persons were employed at the plant between 1944 and the time of its closing in 1981, at any given time no more than 410 persons worked at the plant.

The original facility included a two-story brick building used for offices and employee lockers and a one story production area extending west from the two-story structure. The production area had a catwalk running the length of the building with areas used for document storage. The production area housed a separate room used for making the internal components of the capacitors or windings. The winding room needed to be separated to reduce dust contamination of the windings (layers of foil and paper) in order to prevent short circuiting of the capacitors. This room was located in the northeast corner of the original production building. The southeast corner of the production building included offices and laboratory space used for engineering, production planning, purchasing, and quality assurance/quality control (QA/QC) laboratories. The main portion of the production area was used for the assembly of the capacitors and the southwest corner of the production area was used for adding the Halowax (chlorinated naphthalenes), a dielectric material that was used at the plant from its inception.

In 1950, a Quonset hut building was added to the southwest corner of the production building. The Halowax and maintenance operations were moved into this new building. In 1952-1953, PCB use as a dielectric began in addition to the Halowax. This was determined through interviews with a former purchasing agent and the former foreman of the Cook department, the department where the PCBs and Halowax were used. In the cooking process, the assembled capacitors were placed into heated ovens where a vacuum was drawn to remove air from the capacitors and the oil or wax was impregnated into them. This area of the plant is thought to have the highest exposures to PCBs and Halowax. Soldering of the capacitors was performed in this area to seal the lids to the cans of the capacitors. Lead exposures were also prominent in this area according to an interview with an OSHA Compliance Officer who performed investigations at EUC.

In 1962 or 1963, a metal building was added to the north side of the brick production building. This new building housed an assembly area, the larger kilovolt capacitor manufacturing area, a stock room, and a loading dock. In addition, there was a second story to the metal building in the dock area which housed offices for industrial engineering, computing, shipping and stocking, and quality control. In 1971, an addition was made to the metal building to accommodate manufacturing needs. North and west of the new metal building was the metalizing shed where a zinc coating was applied to the metal cans of the capacitors to prevent rusting. Production continued at the facility until 1981, when plant operations were relocated to North Carolina. The United States Environmental Protection Agency (USEPA) declared EUC a Superfund site in 1982 and the buildings were subsequently dismantled and destroyed. Most company records were lost in the move or destroyed. All information regarding process flow and chemical use were obtained from interviews with former employees of the company.

EUC used Halowax as a dielectric in the manufacturing of capacitors from its inception at La Salle in 1943 until the plant closed in 1981. In 1952-1953, the use of PCB oil began with Aroclor 1254 used until 1956. Aroclor 1242 use began in 1954 and continued until 1970. At that time, EUC began using Aroclor 1016. PCB oil was delivered to the plant in a tank car and consumption was estimated at 45,000 pounds per month. This continued until 1979 when EUC switched to di-(2)-ethylhexyl phthalate (DEHP) as the dielectric to replace PCBs. In addition, the facility used TCE as a degreasing solvent to clean the outside of capacitors after filling with dielectric, or after fabricating the cans to remove any oil. Another VOC, 1,1,1-trichloroethane, was used for only a short period of time at the facility (the exact dates, unknown). Mineral oil, lacquer paint, paint thinner and epoxies were also used throughout the plant's history. Methyl ethyl ketone was used for limited cleaning purposes and was ordered as one fifty-five-gallon drum when needed.

Through interviews with project personnel from USEPA, it was established that there was PCB contamination throughout the facility. In addition, employee interviews stated that all employees of the company entered into production areas of the plant and at times of a strike or high production, office staff often worked in the production areas. For these reasons, it was assumed that the entire population within the plant was exposed. Since there are no records of exposure, or any other records to indicate potential exposure, areas of the plant were delineated based on job title and activity performed in those areas. These areas were then ranked 1-4 based on the likelihood of airborne or dermal contact with PCB oil; 1 indicating areas of low potential exposure and 4 indicating areas of high potential exposure.

Measurements of on-site contamination were made during a 1985 remedial investigation. On-site PCB contamination of the top 12 inches of soil ranged from 0.22 to 17,000 micrograms per gram (cg/g). Below the 12-inch level, PCB concentrations dropped off below the 0.2 cg/g detection limit. Immediate off-site residential soil PCB concentrations ranged from 0.2 to 2,600 cg/g. Polychlorinated dioxins and furans were

also detected in both on- and off-site soil samples. On-site total soil dioxin concentrations based on toxicity equivalency factors (TEFs) ranged from 0.001 to 3.4 micrograms toxicity equivalency quotient (TEQ) per kilogram (cg TEQ/kg) and total furan concentrations ranged from 3.80 to 31.70 cg TEQ/kg. Dioxin concentrations in off-site residential soil samples ranged from 0.0002 to 0.0033 cg TEQ/kg with furan concentrations ranging from 0.0095 to 0.1138 cg TEQ/kg. No 2,3,7,8-tetrachlorodibenzo-p-dioxin was detected in any on- or off-site soil samples. PCB contamination was detected in 18 of 20 monitoring wells on-site, with levels ranging from 0.13 to 440,000 micrograms per liter (cg/l). Groundwater contamination with VOCs was less wide spread but also detected in both on- and off-site monitoring wells.

The EUC became a National Priorities List site (NPL or Superfund) in 1982. Since then, more than $50 million has been spent remediating the site. The entire complex of EUC offices and various storage and industrial buildings occupied approximately 67,000 square feet of floor space. All on-site buildings have been destroyed, and PCB contaminated soils from both on- and off-site were incinerated on-site from 1988-1992 under supervision of USEPA and the Illinois Environmental Protection Agency (IEPA). All remedial activities are now complete with the exception of an on-site groundwater treatment facility.

COMMUNITY HEALTH CONCERNS AND HEALTH ASSESSMENTS

Former employees of the EUC have voiced concern about possible adverse health effects resulting from their exposure to PCBs and other toxic substances while employed by EUC. In addition, area residents have expressed similar concerns about possible adverse health effects resulting from exposure to PCBs, dioxins, and other toxic substances present in contaminated residential soils, well water, and from the clean up incineration activities.

The Illinois Department of Public Health (IDPH), in cooperation with the Division of Health Assessment and Consultation, Agency for Toxic Substances and Disease Registry (ATSDR), completed a Public Health Assessment of the EUC Superfund Site (CERCLIS NO. ILD98074333) in October 1993[1]. This document reviews data pertaining to the extent and toxicity of the environmental contamination caused by EUC, as well as a summary and interpretation of results of three preliminary health outcome studies conducted by IDPH.

1. In 1985, the IDPH conducted a questionnaire survey of 262 former EUC employees[1]. PCB exposure for each participant was estimated based on self-reported job activities and duration and job exposure ratings derived from interviews with workers and a review of the literature. Health outcome data were based upon study participant self-reporting.

Non-specific health conditions of persistent or severe headache, cough, and runny nose were significantly associated with high exposure to PCBs. Among women, high levels of exposure were significantly associated with elevated risk of gallbladder disease/stones compared with low levels of exposure. Uncertainty about the dates of these self-reported conditions in relation to the dates of exposure limits interpretation of these associations. Other similar non-specific conditions were not significantly associated with exposure in this study.

2. In 1985, the IDPH also examined cancer mortality data for La Salle County residents during 1969-1983[1]. La Salle County cancer site-specific mortality rates for each year were compared with rates obtained from other non-metropolitan counties. Malignant melanoma, pancreatic cancer, liver cancer, and soft tissue sarcoma were studied. The rate of pancreatic cancer in white males, but not females, was found to be significantly elevated.

3. In 1991, the IDPH used Illinois State Cancer Registry data to assess the incidence of site-specific cancer in La Salle (defined by zip code) from 1985 through 1988 [2]. Cases of cancer diagnosed in the study period were identified. This included cases diagnosed or treated in the neighboring states of Missouri, Iowa, Michigan, and Wisconsin. Ascertainment of cancer cases for the Illinois Cancer Registry is estimated to be 94 percent complete. Overall, there were fewer combined cancers reported for La Salle residents than would have been expected based upon registry rates for all cancers. The

only statistically significant difference observed was for prostate cancer. Twenty-five cases of prostate cancer were expected in La Salle for the period, but only ten cases were observed.

In 1994, a pilot study was conducted to determine serum PCB concentrations in former workers and residents who lived near the site. In addition, exposure and health information was collected to identify other sources of PCB exposure and potential health implications that should be investigated during future study activities. Serum samples were collected from 60 former EUC workers and 32 area residents. PCB serum concentrations in former EUC workers (mean=14.3 ppb) were significantly elevated compared with area residents (mean=3.6 ppb). Lipid-adjusted PCB concentrations maintained the same statistically significant relationship with former EUC workers' levels significantly elevated (mean=1,883 ppb) compared with those of residents (mean = 491 ppb). Self-reported length of employment was significantly correlated with PCB serum concentrations ($r=0.53$ $p < 0.001$, $n=60$). Because the majority of workers at this facility routinely rotated between jobs, and recall regarding length of time at each position was low, the researchers were unable to relate job classification with PCB exposure. The average length of employment in pilot study participants was 12.25 years and total years worked ranged from 0.5 to 36.3 years. There was a positive correlation between length of residence near the site and serum PCB concentrations ($r=0.54$, $p<0.05$, $n=32$). The average length of residence near the site was 19.8 years. Serum PCBs were also significantly correlated with triglycerides and age. Lipid-adjusted PCBs were significantly correlated with age, length of employment, and length of residence.

While these studies provide a mixed picture of possible health effects in former EUC workers and La Salle residents, the interpretation of these data is far from certain. Reliance on self selection of study subjects and a lack of objective exposure and outcome data in the survey study raise the possibility that observed associations may be due to selection and recall bias. While the cancer mortality study is not subject to these possible influences, neither is it able to relate specific exposures to health outcomes. Many former EUC workers no longer live in La Salle County and almost 1/3 of the cohort is deceased. The observation of an increased risk for one of the main study endpoints, pancreatic cancer, is a concern. However, this increase is not directly linked to PCB exposure and could be entirely unrelated to exposure to EUC contaminants. The observation that cancer incidence rates were not found to be elevated in La Salle residents for the period 1985-1988 is not very persuasive either. This is a rather short time period, with relatively few cancers expected in the small population of La Salle (population = 9,087 in the 1980 census -- 9,717 in the 1990 census). Overall exposure in residents was considerably lower than exposure in workers. Except for the pilot study, these studies also lack objective PCB exposure data, and consequently they do not provide a strong test of possible exposure related health effects.

This multi-phase health study was undertaken in response to community concerns. It included a retrospective cohort mortality study of 3,305 persons who had worked at the

plant; a cross-sectional morbidity study in 191 former employees and 26 community residents examining the relationship of EUC exposure and PCB levels with history of selected diseases, reproductive factors, serum lipids, liver enzyme tests, hormonal balance and immune function (Morbidity I); and a telephone interview of 596 former employees examining associations of exposure at EUC with the health of themselves and their children. Both the mortality and first part of the morbidity study have been published by ATSDR previously[3,4]. Preliminary results from the mortality study suggested that, in highly exposed persons, working at EUC was associated with thyroid and stomach cancer in men and liver/biliary cancer in women. Associations with non-Hodgkin's lymphoma in women were not consistently related to degree of exposure. In the Morbidity I study, PCB levels were highly correlated with total quarters worked at the plant (r=0.71). History of diabetes was significantly associated with selected measures of exposure in men and women after control for age and body mass index. Exposure was also significantly associated in women with increased triglycerides, decreased HDL-cholesterol, decreased sex hormone binding globulin (SHBG) and decreased follicle stimulating hormone (FSH) and in men with decreased thyroid stimulating hormone and increased percent natural killer cells. Pregnancy outcomes were also compared for 115 pregnancies occurring during or after employment at the plant vs. 248 pregnancies occurring prior to exposure. Women who worked at EUC before or during the pregnancies had higher percentages of children with learning difficulties, chronic respiratory illnesses and ear infections than those whose pregnancies occurred before employment. Because the numbers of persons examined were relatively small, this Morbidity II study was undertaken to evaluate in more depth, associations of exposure at the plant with the development of selected diseases in the former employees and their children.

LITERATURE REVIEW

Health Effects of PCBs

Liver

PCBs and related compounds are hepatotoxic in animal studies, with abnormalities seen for hepatic enzymes, microsomal induction, and liver pathology in a wide variety of models[5]. Human studies have been less consistent, with acute hepatotoxic effects[6], as well as less severe changes in liver[7-13] enzymes noted. Several reports have noted positive associations of serum PCBs with serum GGT [7-12] and serum SGOT[9,10,12,13] and negative associations with serum bilirubin[7] levels after occupational and environmental exposures. Most of these reports are in cohorts examined either during or shortly after exposure, with few reports including long term follow-up[9,10].

Urinary porphyrins have also been shown to be elevated in persons exposed to PCBs and to combinations of PCBs and related compounds [7,14-17], although results have not always been consistent. Effects of PCBs on porphyrins vary by type of congener [18], with the relative effects of mono-ortho congeners compared to dioxin like congeners on increases in porphyrins greater than the relative effects of mono-ortho congeners on cytochrome 1A1 and 1A2 induction. Two mechanisms of action have been postulated: increase in hepatic cytochrome 1A2 (mediated by the Ah receptor) and increase in aminolevulonic acid synthetase (phenobarbital-type effect), with mono-ortho PCBs having both mechanisms of action [18]. Interactive effects have also been found in animals [19] and humans [17] with greater effects seen in rats exposed to dioxins and PCBs than in those exposed to either alone [19] and greater effects seen in persons with chloracne and occupational exposure to both pentachlorophenols and PCBs than in persons with chloracne and exposed to pentachlorophenols alone [17].

Lipids

PCBs and related compounds are associated with increased serum lipids in experimental animal models [5]. Human studies have also found consistent positive associations of serum PCBs with serum triglyceride levels [8-10,20-23]. Less consistent positive associations have been seen with serum cholesterol [8,11] and negative associations with HDL cholesterol [10]. In these observational studies, however, the causal pathway is not well delineated. Thus, the relationships, rather than being due to hepatotoxic effects of PCBs could be secondary to partitioning of PCBs within fatty compartments of the blood [8].

Cancer

Despite a large amount of animal data suggesting that PCBs and related compounds are carcinogens, effects in humans are not as clear, in part because the relatively small numbers of exposed individuals often are not followed for an adequate latency period. Animal studies of PCBs have shown effects that differ by gender and Aroclor mixture [24]. Liver cancer has been noted more frequently in female than male rats and thyroid

cancer has been noted more in males[24]. Most human studies of exposure to PCBs have been cohort studies of persons exposed in transformer and capacitor manufacturing plants. These exposures have been to mixtures: not only to mixtures of dioxin and non-dioxin like PCBs, but also to other chemicals such as chlorinated solvents which are also thought to be carcinogens. Previous studies include six cohort studies of workers exposed to PCBs in capacitor or transformer manufacturing plants. Brown [25] reported on cancer mortality among 2,588 workers at two capacitor manufacturing plants and noted increased risk of liver, gallbladder and biliary cancer, with most of the excess in women at one of the plants. In a recent study of two cohorts, including those originally analyzed by Brown, Kimbrough et al[26], in general, did not find elevated risks of cancer. The cohort was young, however, and numbers of workers in the highly exposed group was small. There was a significant increase in intestinal cancer among women with more than 20 years latency. Sinks [27], however, also reporting cancer mortality among 3,588 persons (2,742 men and 846 women), noted increased risk of melanoma with a suggestion of increased risk of brain cancer and no increased risk of liver/biliary cancer. Gustavsson [28] in a much smaller study of capacitor manufacturing workers, also found a suggested increase in risk of cancer of the liver/bile ducts. Bertazzi et al [29] and Tironi at al [30] studied 544 males and 1,556 females in a capacitor manufacturing plant and found significantly increased deaths from total cancers and GI cancers among male workers and significantly increased deaths from total cancers and hematologic cancers in women. Yassi et al[31] also found a significant increase in pancreatic cancer deaths in a cohort of 2,222 men working in a capacitor manufacturing plant. In probably the largest cohort study to date of 138,905 electric utility workers, Loomis et al [32] noted a statistically significant association of PCB exposure with melanoma after control for solvent exposure. The association was particularly pronounced in those with high exposure after a 20-year lag. An association with liver cancer was no longer significant after control for solvents, while associations with brain cancer were inconsistent. Two studies have followed the Yu-Cheng and Yusho cohorts that had mixed PCB/furan exposure. Hsieh, in a study of acute mixed PCB/furan exposure in Taiwan, found an increased risk of death from liver disease [33]. Kuratsune et al [34] followed the Yusho cohort and noted significant increased risks for total cancer and liver cancer in males. In a nested case-control study in Maryland, Rothman et al [35] found a strong dose-response relation between quartiles of total lipid-corrected PCB levels and risk of non-Hodgkins lymphoma, with evidence suggesting an interactive effect with seropositivity for Epstein-Barr virus.

Previous occupational studies have, in general, failed to find associations of PCB exposure with breast cancer [25,26,36]. Case control and nested case control studies of breast cancer and PCB exposure in normal populations have also, generally, found no associations [37-44] with total PCB level, although there have been some exceptions [45-46]. Some studies have noted associations with specific congeners [39,41,43] , as well as associations in high risk populations, such as parous women who never lactated [47] or women with the CYP1A1 genotype with at least one valine allele [48].

Endocrine System

Animal data suggest that PCBs affect thyroid function. The effects, however, may be congener and dose specific. Desauliniers et al [49] noted a paradoxical increase in T_4 at lower doses and a decrease in T_4 at higher doses of PCBs, with the effect primarily present with the dioxin like congener PCB 77 and only in female animals. At these doses there was no effect on testosterone, gonadotropins, or thyroid stimulating hormone (TSH). The effect of individual congeners on thyroid is related to the laterality of chlorine substitution and the relation of the chlorines to hydroxylated metabolites [50]. The mechanisms by which PCBs are thought to reduce T_4 levels include increased glucuronidation, displacement of thyroxine through decreased binding to transthryretin, and increased conversion of T_4 to T_3 by 5'diodinases [51-54].

Human studies have, in general, found associations of PCB exposure with alterations in thyroid function [55]. Murai et al [56] found elevated T_3 and T_4, but not Free Thyroxine Index (FTI) or TSH, after exposure to PCBs and furans in the Yusho outbreak. Two recent studies of pregnant women and their infants with low level exposure to PCBs and dioxins showed associations of maternal PCB exposure with infant thyroid levels [57-58]. One of the studies [57], however, showed lower T_4 levels at 2 weeks, with higher TSH levels at 2 weeks and 3 months, while the other study [58] found higher, not lower, T_4 levels at 1 week and 11 weeks, with higher TSH at 11 weeks. Nagayama et al [59] also found inverse associations of T_4 and positive associations of TSH with levels of breast milk dioxins and dioxin-like PCBs in breastfed babies. However, a more recent report among 160 North Carolina children found no relationship of PCB exposure during pregnancy with thyroid levels in their infants [60]. Osius et al [61] noted inverse associations of non-coplanar PCBs with free T_3, a positive association of PCB 118 with TSH and no association with T4 among second grade children living near an industrial waste site in Germany. Langer [62] noted increased thyroid volume in 238 employees of a factory that had previously produced PCBs and 454 adolescents in the surrounding area, and Guo [63] noted increased prevalence of goiter in the YuCheng cohort. Among women who miscarried, PCB was inversely associated with TSH and positively associated with FSH, LH, and prolactin [64].Hagmar et al [65] also found inverse associations of PCB153 with total T_3, but not T_4, FTI or TSH among 182 wives of fishermen in Sweden. These findings are consistent with our results in Great Lakes fishermen and their wives, in which we noted significant inverse associations of PCB levels with thyroxine that were stronger in women than in men. In that study effects on TSH were inconsistent, with positive associations with fish consumption in women and negative associations in men [66]. The concern over in utero effects of low level PCB exposure relates to known neurotoxic effects of hypothyroidism on developing organisms [67], with potential effects being delayed neurodevelopment, decreased intelligence, and hearing deficits.

Animal studies have also shown decreases in testosterone from PCB exposure, although, in general, the effects are less impressive than on thyroid hormones Aroclor 1254 reduced serum T_4 at doses 250 fold lower than the dose that altered testicular function [68]. PCBs act, in part, on testosterone through changes in its metabolism [69], although effects are not consistent [70-72].

There also appears to be congener specificity for PCBs estrogenic activity. In general, the dioxin like congeners are thought to be more antiestrogenic and the ortho-substituted, non-dioxin like congeners more estrogenic [50,73-74], although there is now some evidence that coplanar PCBs may also act as estrogens through increased binding to estrogen receptors [75] and that metabolites of selected ortho-substituted PCBs may act as antiestrogens [76]. Increased estrogenicity may be related to shortened menstrual cycles in women eating PCB-contaminated fish [77], with the decreased levels of FSH seen in the Morbidity I La Salle Report [4].

Immune System

Several studies have examined the effects of PCB mixtures on immune function in animals, with conflicting results. Exposure to doses varying from 5-80 cg/kg body weight of Aroclor
1254 was associated with increases in serum hemolytic complement activity, thymosin alpha 1 levels and natural killer cell activity in rhesus monkeys and significantly reduced antibody titers to sheep red blood cells [78,79]. Subsequent examination of the infants of these monkeys revealed reductions in titres to sheep red blood cells as well as a decreased lymphocyte proliferation response to concavalin A [80]. However, exposure to Arochlor 1254 PCB levels of 4-500 mg/kg twice a week for 5 weeks (a dose which was sufficient to cause changes in the thyroid gland and liver) in mallards failed to have any effect on antibody titres to sheep erythrocytes, natural killer cell activity, or lymphocyte mitogenesis [81]. *In vitro* studies, in addition, have failed to find effects of individual PCB congeners [82] or mixtures of PCBs with dioxins and furans [83] on various parameters of immune function.

Human studies of immunotoxicity of PCB exposure are sparse. Weisglas-Kuperus et al [84] found that higher prenatal PCB/dioxin exposure was associated with an increase in the number of T cell receptor cc^+ cells at birth and with an increase in the total number of T cells and number of $CD8^+$ T cell receptor cc^+ and T cell receptor cc^+ T cells at 18 months of age. Higher prenatal and postnatal PCB/dioxin exposure was associated with lower monocyte and granulocyte counts at 3 months of age. In a follow-up study of 207 healthy mother-infant pairs, Weisglas-Kuperus et al[85] reported that in presechool children, prenatal PCB exposure was associated with increased T cell numbers and lower antibody levels to mumps and rubella, whereas current PCB burden was associated with higher prevalence of recurrent middle rear infections and chickenpox. Two of the most severe acute exposures were in Yu-Cheng and Yusho after accidental ingestion of PCB and furan contaminated rice oil [86-87]. In both of those studies, decreased concentrations of IgM and IgA, but not IgG were seen 1-2 years after exposure. These changes reversed after 3-4 years [87]. In Yu-Cheng transient decreases were also seen in the percentages of total T cells, active T cells and helper T cells, as well as in delayed respond to skin testing for allergens [86]. Nagayama et al [88] noted significant inverse associations of breast milk dioxins and dioxin-like PCBs with CD8 cells and non-significant positive associations with CD4/CD8 cells among 69 breastfed babies. A study of fish eaters from the Baltic Sea noted lower proportions and numbers

of natural killer (NK) cells, identified by the CD 56 marker, in peripheral blood than in the non-fish consumers. Significant negative associations were seen with non-ortho and mono-ortho congeners [89].

Overall results from animal, *in vitro,* and human studies of PCBs are inconclusive. More functional measures, such as primary immune response to vaccines, which have not in general, been applied to epidemiologic studies, may yield results more consistent with animal studies of sheep red blood cells [90]. Tryphonas, in a comprehensive review [91] of the field suggested that some of the differences among studies could also be due to differential effects among species and gender. Variations among studies could reflect the complexity of PCB mixtures, the short term nature of the studies, and the possibility of interactions with other contaminants limiting precise determination of specific immune effects. Harper et al [92] found that TEFs calculated from mixtures of lower chlorinated congeners, such as Aroclors 1254, 1248, and 1242, may somewhat overestimate immune effects, in part, they postulate, due to antagonistic effects with other halogenated hydrocarbons. Others [93] have noted that competitive effects of dioxins and non-dioxin like PCBs may be due to functional antagonism rather than competitive binding to the Ah receptor or to dispositional antagonism. In addition, there is evidence that lower doses may be more toxic than higher doses [78], effects consistent with inverted u shaped responses seen in other models.

Reproductive and Developmental

Although animal studies have shown a wide variety of reproductive effects of PCB and dioxin exposure [5,94], again, human data are sparse. Rylander et al [95], in an ecologic study of persons exposed to varying levels of PCBs in Sweden, noted lower birthweight and proportionately more girls with higher parental PCB exposure. Taylor et al [96] noted lower birthweights and gestational ages in infants of women with higher PCB levels from occupational exposure at a capacitor manufacturing plant. Similarly, after the Sevsco explosion relatively more girls were born [97] . Grandjean, however, found significant inverse associations of the fish oil eicosopentaenoic acid, but not of PCBs, with birth weight in the Faroe Islands [98].Vartiainen et al [99], also found significant inverse associations of birth weight with dioxins and furans, but not with PCBs in Finland. Associations of exposure to PCBs through fish consumption in utero with low birth weight have been seen by the Jacobsons in the Michigan cohort [100], and in the Netherlands [101], but not in cohorts near Lake Ontario [102], in North Carolina [103] or in Green Bay Wisconsin [104].

Studies of in utero PCB exposure have also produced a variety of effects on neurodevelopment. The Jacobsons found reduced visual recognition memory at seven months with relatively low level of in utero PCB exposure [100]. At four years [105], these children had poorer short term memory function and, at 11 years, lower IQs [106]. A similar North Carolina cohort [107] showed developmental delays in motor function during infancy with no differences in McCarthy scores at 3,4 or 5 years of age [108]. In a more recent study from the Netherlands [109] higher levels of cord blood and maternal PCBs, but not postnatal exposure to PCBs, were associated with lower early growth rates.

Higher levels of PCBs, PCDDs and PCDFs in breast milk were related to reduced neonatal neurological optimality and higher levels of planar PCBs were associated with higher incidence rates of hypotonia. Subsequent follow-up in 42-month-old children showed lower cognitive and simultaneous processing scores on the Kaufman assessment battery [110]. Another study in the Netherlands [111], however, showed no neurological differences in the first half year of life. A recent study of Lake Ontario fish eaters [102,112,113] showed no differences in fecundity or fetal deaths. They did find poorer scores on reflex, autonomic and habituation clusters of the Neonatal Behavioral Assessment Scale, but no difference in orientation, range of state, regulation of state, or motor activity in children of mothers who were high vs. low fish eaters. A German study of 171 healthy 7-month-old infants found negative associations of PCBs in mild with the Bayley II mental (MDI), but no significant association with the psychomotor development index or the Fagan Test of Infant Intelligence [114]. A wide variety of growth and developmental abnormalities have been seen in children born after high exposure to PCBs and furans in Yu-Cheng [115,116]. Those children had lower birth weights, hyperpigmentation, deformed nails, acne, swollen gums, delayed cognitive development, increased respiratory infections, increased middle ear disease, increased porphyrin excretion, and, as they entered puberty, decreased penile length.

Thus, there are now several studies showing alterations in neurodevelopment in children exposed to fairly low levels of PCBs in utero or early in life. These studies are consistent with a fairly extensive body of data in the animal literature [94]. Several investigators have suggested that decreased thyroid hormones may account for at least some of these neurodevelopmental effects. The transient lower levels of thyroxine in the Netherlands study support this hypothesis [111.] Controlled animal studies, however, examining the effects of individual congeners do not yield coherent results [94]. For instance, similar effects of PCB 28,118, and 153 have been seen on spatial learning, with markedly different effects on thyroid hormones. Alternatively, there is an increasing body of literature suggesting that altered cellular calcium homeostasis, with PCBs interacting directly with the ryanodine sensitive calcium release channels, may be the mechanism by which PCBs affect development in children [117].

Infections in children exposed in utero and early in life

In addition to effects on neurodevelopment in children, there is evidence that exposure to PCBs and related compounds in utero or early in life may be related to increased incidence of infections and allergic diseases in children. Dewailly [118] et al noted significant associations of prenatal exposure to DDE and hexachlorobenzene, but not of PCBs, with risk of otitis media in the first year of life in Inuit infants. Similarly, children exposed to PCBs/furans in Yucheng were subsequently found to have higher frequencies of bronchitis, influenza, and otitis media in the six year follow-up [119]. More recently, Karamus et al [120] found associations of exposure with DDE with risk of asthma and of exposure to PCBs and hexachlorobenzene with prevalence of otitis media among children with the highest DDE exposure. Weisglas-Kuperus et al [84], however, found no relationship of pre-or post-natal PCB/dioxin exposure with rhinitis, bronchitis,

tonsillitis, or otitis media in the first 18 months of life among 207 Dutch infants whose mothers were exposed to PCBs/dioxins from environmental sources.

Nervous System

There is an increasing amount of data suggesting that depletion of brain dopamine may be an additional effect of PCBs which could impact on neurologic function, not only in young, but also aging populations. Schantz et al [121] noted impairment of memory and learning, but not of executive or visual spacial function, with PCB exposure among 101 fish eaters and 79 non-fish eaters age 49-86. Older people may be at particular risk of neurological dysfunction from exposure to PCBs, because many aspects of nervous system function decline with advancing age[122]. Individuals who suffer a greater than normal loss of substantia nigra dopamine cells develop the neurological syndrome known as Parkinson's disease and suffer a characteristic pattern of motor deficits. The etiology of Parkinsons disease is unknown, but there is evidence to suggest that environmental and occupational exposures may play a role [123].

Laboratory studies in both rodents and primates have shown that exposure to PCBs during adulthood produces long-term reductions in brain dopamine content [124]. The findings in primates are particularly striking. Six months after PCB exposure ended, serum and brain PCB concentrations had declined by 50-60%, but brain dopamine concentrations were still depressed to the same extent as they were immediately following exposure. This suggests that occupational PCB exposure could produce long-term reductions in brain dopamine levels in humans. If so, capacitor workers may be at increased risk for developing Parkinson-like motor symptoms as they grow older.

Health Effects of Trichloroethylene

Occupational exposures to TCE can affect some of the same target organs as PCBs and must be considered as an exposure that could interact with PCBs on health outcomes. Since TCE is rapidly metabolized there is no biomarker that can measure it 15 years or more after exposure. There is some, but not consistent, evidence, however, that it may affect endpoints that require a long lag period before clinical manifestation.

Cancer

High levels of TCE exposure have been associated with liver and lung tumors in mice and renal and testicular tumors in rats [125], Historical cohort mortality studies of TCE exposed-workers, however, have yielded inconsistent results. One cohort study of 2,117 workers with a latency of only 6-13 years showed no increase in cancer deaths [126]. The only cancer associated with low TCE exposure in another cohort of 1,670 persons was nonmelanotic skin cancer [127]. A larger cohort of 2,050 male and 1,924 female workers in Finland exposed to TCE and other solvents, showed significant increases in stomach, liver, prostate and lymphohematopoietic cancers in persons followed more than 20 years [128]. An additional study of 4,733 aerospace workers found a significantly elevated risk for ovarian cancer in women with high cumulative exposure (RR=7.09, 95% CI=2.14-23.54)[129]. Slightly elevated risks were noted for kidney, bladder and prostate cancers. Another cohort of 14,457 aircraft maintenance workers found increased risk for multiple myeloma in white women (SMR 236, 95% CI=87-514), non-Hodgkin's lymphoma in white women (SMR 212, 95% CI=102-390), and cancer of the biliary tract and liver in white men (SMR 358, 95% CI=116-836) [130]. Reanalysis of the cohort with extended follow-up, however, showed non-significantly increased risk for non-Hodgkin's lymphoma, esophagus, colon, liver, breast, cervix, kidney and bone cancers, with no dose response relationship found [131]. There were no elevated risks for respiratory cancer, liver cancer or leukemia. A recent study [32] of capacitor manufacturing workers found that the association of liver cancer with PCBs was no longer significant after control for exposure to solvents. Examination of rates of renal cell cancer in the Danish Cancer Registry found a significantly increased risk for exposure to TCE (OR 10.80, 95% CI=3.36-34.75), while environmental exposure to TCE-contaminated drinking water has been associated with leukemia in two other studies [132,133].

Other Health Effects

Additional effects that have been noted include neurobehavioral disturbances, trigeminal neuralgia, and increased blink reflex latency [134], systemic lupus erythematosus [135], and cardiac malformations in children of mother exposed in utero [136-138]. The one study of hormonal effects of TCE exposure in 85 male workers exposed to TCE in an electronics factory found that years of exposure were significantly associated with dehydroepiandrosterone sulfate and negatively associated with SHBG, insulin and testosterone[139-140]. Insulin levels showed a triphasic response with level of exposure. Initial exposure was associated with a rise in insulin followed by a fall to normal levels 2-4 years after exposure and then a rise after 6 years. In their papers the authors postulate that the decreased SHBG is secondary to the hepatotoxic effects of TCE.

Health Effects of Chlorinated Naphthalenes

Chlorinated naphthalenes have been associated with acute and chronic liver disease. These effects have been well recognized since 1937 when the first of several case reports describing deaths from acute liver toxicity was presented [6]. A recent retrospective mortality study of workers exposed to chlorinated naphthalenes, as well as asbestos, manufacturing cables during World War II documented an excess of deaths from cirrhosis (both alcoholic and non-alcoholic) (SMR=1.84; 95% CI =1.56-2.16) [141]. They noted an increase in deaths from all cancers, which was statistically significant for men SMR=1.18 (95% CI=1.10-1.26). An excess of cancer of the connective tissue was suggested for workers with over 1 year of exposure and 25 years of latency (SMR=3.54 (95% CI=0.97-9.07) [142]. Among other cancer sites, increased risks were seen in both men and women for stomach, rectum and lung cancers, with associations diminished by the use of county, rather than the US population, as reference.

Summary

Overall, previous studies have suggested a wide variety of health effects of PCBs and related compounds. There remain a number of inconsistencies in human studies, including the variety of effects seen on the hormonal system, immunologic system and neurodevelopment of children exposed in utero. The La Salle cohort offered a unique opportunity to explore long term developmental and health effects, not previously explored, of exposure to PCBs and related other compounds. This group is unusual in the high percentage of women employees (58%), the long lag period between exposure and examination (up to 56 years) and the exposure to, not only solvents such as trichloroethylene, but also chlorinated naphthalenes, which may have interacted with PCBs on health parameters in ways that have not been previously examined.

SPECIFIC AIMS

1) To examine the relationships of exposure at EUC with birth outcomes and health and behavior problems in the children of former workers.

2) To examine the relationships of exposure at EUC with self-reported health outcomes in former employees.

METHODS

This study was a cross-sectional examination of a sample of 596 persons previously employed at EUC. It included an in-depth telephone survey concerning work exposures; medical and reproductive outcomes; the development and health of their children; and potential confounders, such as medication use, smoking and alcohol intake.

Sample selection

Those eligible to participate in the morbidity study were non-deceased members of the EUC cohort for whom we had confirmed vital status in the previous six months and for whom we had a last known address. Since tracing was ongoing, eligible members were selected in two batches, approximately three months apart. Budget constraints precluded interviewing all those who were potentially eligible. The total population was, therefore, stratified by age and time worked at the plant. For the first batch, all persons $\geq$ 65 years of age (69% of the workforce) were selected. For those less than 65 years, a relatively small number worked three or more years (n=90) compared with those who worked less than three years (n=315). For that reason, all those who worked three or more years, but only 50% of those who worked less than 3 years were included.

A different approach was used for the second batch of eligibles. There were a relatively large number of individuals with only one quarter of employment and many of these did not remember working at the plant at all. Hence, those whose social security record stated that they had worked one quarter (63 people less than 65 years of age and 174 people $\geq$ 65) were excluded from the second batch. In addition, a 50% sample of individuals less than 65 years with 2-11 quarters of employment (less than 3 years, excluding one quarter only) were included. Thus, all persons $\geq$ 65 of age or who had worked more than 3 years, but only a random sample of those who were < 65 and had worked less than 3 years, were selected. The distribution of eligibles and percent interviewed by age group and quarters worked is shown in Table 1. In general, a greater percent of those who were < 65 and had worked for a short period of time agreed to participate.

Analysis

Pregnancy/Children Analysis

Multiple logistic regression

Multiple logistic regression models were used to test the significance of the effect of the exposure variable (working at EUC prior to or during pregnancy) on each pregnancy and live birth outcome. A forward stepwise selection procedure was used to determine which confounders to include for each outcome variable. The following confounders were considered in the initial pool of independent variables: age of mother less than 18 years old when became pregnant (dichotomous, yes/no), age of mother greater than or equal to 35 when she became pregnant (dichotomous, yes/no), mother's exposure to lead at EUC via soldering, painting, or the 'lead dip process' before or during pregnancy (dichotomous, yes/no), number of cigarettes smoked per day during pregnancy (ordinal codes: 0=none, 1=1-8 cigarettes per day, 2=9-19 cigarettes per day, 3=20 or more cigarettes per day), number of alcoholic drinks per week during

pregnancy (ordinal codes: 0=none, 1=1-2 drinks per week, 2=3 or more drinks per week), breastfeeding (ordinal codes: 0=never breastfed, 1=breastfed less than 3 months, 2=breastfed 3-5 months, 3=breastfed 6 or more months), mother's use of oral contraceptives during pregnancy (dichotomous, yes/no), mother's exposure to x-rays during pregnancy (dichotomous, yes/no), and gender of child. Confounders were included in logistic stepwise regression at p<.10 and retained in the model at p<.10. The multiple logistic regression model was then rerun using only those relevant confounders for each outcome, helping to minimize exclusions based on missing values for those confounders not retained in the stepwise function.

Mixed effects regression models for the effect of exposure before pregnancy on health outcomes in children

Because events in children within families were not independent of each other, mixed effects regression models, or regression models with both fixed and random independent variables, were also used to evaluate the effect of female worker's exposure to PCBs on health outcomes in their children. Random intercept terms were used to account for the clustering or autocorrelation amongst children of the same mother. Each mother has her own random intercept that is common for all her children. Fixed effects in each model include an indicator of exposure, equal to 1 if the mother worked at EUC before the pregnancy and 0 if not, and any relevant confounders. Consider for example the outcome of asthma in children. If an evaluation of potential confounders identified one relevant confounder, an indicator for the mother's age less than or equal to 18 at the time of pregnancy, the mixed effects logistic regression model predicting asthma would be

$$log\{p_{ij}/(1-p_{ij})\} = c_0 + c_j + c_1 EXP_{ij} + c_2 Z_{ij}$$

where p_{ij} is the probability that the j^{th} child of the i^{th} mother will be diagnosed with asthma; c_0 is the fixed intercept term; $c_j \sim N(0, c^2)$ is the random intercept term for the j^{th} mother; c_1 is the exposure effect, or the increase in the log-odds of the child having asthma for mothers who worked at EUC prior to pregnancy versus mothers who did not work at EUC prior to pregnancy; EXP_{ij} is equal to 1 if the i^{th} mother worked at EUC before being pregnant with her j^{th} child and 0 otherwise; c_2 is the effect of the mother being 18 years old or less at pregnancy; and Z_{ij} is equal to 1 if the i^{th} mother was 18 years old or less when pregnant with her j^{th} child and zero otherwise. The parameter values and standard errors were estimated using the software program MIXOR. The resulting estimate of the odds ratio $exp(c_1)$ can be interpreted as the effect of working prior to pregnancy on the odds of the child being diagnosed with asthma, adjusting for whether or not the mother is 18 years old or less, and properly accounting for correlation within children of the same mother.

Health outcomes in former employees

Proportional hazards regression models for the effect of amount of cumulative exposure on health outcomes in workers

The Cox proportional hazards regression model with time-dependent covariates was used to evaluate the effect of the amount of exposure to PCBs on health outcomes in workers. For each worker, the outcome was defined as time from his/her start date at EUC until diagnosis of a particular disease or other health outcome. The unit of time for the analysis was quarters. For each number of quarters since the start date for each worker, a time-dependent covariate was defined as the cumulative number of quarters worked at EUC so far. Suppose for example that a particular worker started at EUC in January of 1960 and quit in December of 1961. In the first quarter, quarters worked so far is equal to 1; in the second quarter, quarters worked so far is equal to 2; and so on through the eighth quarter, in which quarters worked so far is equal to 8. Then starting with quarter 9, number of quarters worked at EUC remains equal to 8, and will remain 8 until that person starts another episode of working at EUC or until the time of the survey. Also included in the model were any relevant covariates. Consider the example of diagnosis of bladder cancer as an outcome. The proportional hazards model would be

$$log\{h_i(t)/h_0(t)\} = c_1 EXP_i(t) + c_2 Z2_i + ... + c_k Zk_i$$

where $h_i(t)$ is the hazard of being diagnosed with bladder cancer t quarters after starting work at EUC for individual i; $h_0(t)$ is the baseline hazard at quarter t; c_1 is the increase in the hazard associated with each additional quarter worked at EUC so far at quarter t; $EXP_i(t)$ is the cumulative number of quarters worked so far for individual i, t quarters after their start date; c_2 through c_k are the effects of relevant confounders; and $Z2_i$ through Zk_i are the values of relevant confounders for individual i. Estimates of parameters and standard errors were obtained using PROC PHREG in SAS. The resulting estimate of the hazard ratio $exp(c_1)$ can be interpreted as the increase in hazard of bladder cancer at any particular time associated with each additional cumulative quarter worked so far at EUC, adjusting for confounders Z2 through Zk.

Multiple logistic regression for the effect of total quarters worked on symptoms of Parkinson's Disease

Multiple logistic regression models were used to test the significance of the effect of total quarters worked at EUC on each of 8 self-reported symptoms of Parkinson's [143] and on the presence of 4 or more of the symptoms. The few individuals who stated that they had Parkinson's were included. Age at interview and body mass index (BMI) at 40 years of age were included in the model as possible confounders,

RESULTS

A total of 1,248 names and addresses were initially provided to the Survey Research Laboratory for interviewing. The total number of those assumed to be eligible was 1,209. Of those, 29 were subsequently found to be deceased, leaving 1,180 persons. A total of 972 were located and, of those, 327, or 27%, refused to be interviewed. Thus, 596 (337 females and 259 males), or 49.4% of the eligibles and 64% of those contacted, completed the interview. The final disposition of the sample is shown in Table 2.

Exposure Assessment for Children of Former Employees

In the analyses for this portion of the study, overall exposure was assessed by whether the mother was pregnant with the child during or after working at the plant. Exposure to lead during or before pregnancy was defined by self-reported history of soldering, dipping, or painting at EUC.

Outcomes in Children of Former Female Employees

A total of 295 out of 337 women interviewed had ever been pregnant. These 295 women had a total of 1,004 pregnancies of which 819 were live births. Thirty-eight of these were excluded for the reasons presented in Table 3.

Analyses of pregnancy outcome were based on a total of 966 pregnancies (of which 575, or 59.52%, occurred during or after exposure at the plant), while analyses of children's outcomes were based on a total of 800 live births (of which 476, or 59.50%, occurred during or after exposure at the plant). Presence of each of the outcomes was defined as a positive response to the questions given in Table 4.

Potential confounders were also determined by self-report. Frequency of potential confounders for both sets of analyses are given in Table 5.

Tables 6a-g examines associations of possible confounders with selected outcomes in the children. Significant associations were seen for maternal age < 18 with being retained in grade and other physical or mental handicaps; for maternal age $\geq$ 35 with mother having a miscarriage, and problems with attention deficit disorder; for lead exposure during pregnancy with abnormal head size at pregnancy, thyroid problems, hearing problems, ear infections, eczema, problems with balance, and reversal of letters; for previous lead exposure with thyroid problems, ear infections, hay fever, being in special education, having problems with drawing, having developmental problems and endometriosis (female children only); for smoking during pregnancy with having a premature baby, with having a baby with low birth weight, with asthma and with endometriosis (female children); for drinking during pregnancy with ear infections and reversal of letters; for exposure to x-rays during pregnancy with miscarriage, asthma, other respiratory infections, being in special education for speech, problems with speech, attention, impulsivity or hyperactivity, and undescended testicles (male children); for birth control pills with problems with balance and endometriosis (female

children); for breastfeeding with hearing problems and problems drawing; and for being a girl with being premature, having low birth weight, having low thyroid, not being in special education for reading or having attention problems, having problems with infertility and being less likely to die.

Table 7 presents the confounders that remained in the multivariate analysis with a $p<0.10$. Lead exposure before or during pregnancy rather than lead exposure during pregnancy was used in these analyses. Table 8 presents the results for each of the endpoints of interest in univariate analyses, in logistic multivariate regression analyses with control for each of the confounders that were significant in the logistic stepwise function, and in MIXOR multivariate models with control for clustering within families. Exposure at the plant was significantly associated in the children with ear infections, being in special education, with having attention problems, and with endometriosis (females). The association with ear infections remained significant, and associations with having asthma and being retained in a grade were of borderline significance, after control for confounders and after control for clustering. These associations were unchanged by the addition of birth order to the models (not shown in the tables).

History of Selected Diseases in Former Workers

History of selected diseases and the date of onset of these diseases were determined by self-report. Numbers of events are given in Table 9. Only those diseases with at least 5 events were analyzed. In addition, symptoms which have been related to Parkinson's [143] were assessed by positive responses to each of the following questions individually or positive responses to 4 or more of the 8 questions presented in Table 10.

The results of Cox regression analyses relating years of exposure to time of onset of selected diseases are shown in Tables 11a and 11b. Model 1 did not include any confounders; model 2 controlled for age at interview and BMI at 40 years of age. Models also including age at first employment (not shown) yielded results similar to those in model 2. The hazards ratios presented reflect the proportional increase in the hazard rate at any particular time associated with each additional 5 years worked at EUC (computed using continuous quarters worked data adjusting for a change in 20 quarters (exp (20*beta-hat)). The means $\pm$ standard deviations for age for men and women respectively were 63.3 $\pm$ 9.7 and 70.2 $\pm$ 10.6. The means $\pm$ standard deviations for BMI for men and women were 26.1 $\pm$ 3.6 and 24.1 $\pm$ 5.0. Inverse associations of high blood pressure and high cholesterol in men did not remain significant after control for age at interview and BMI. The only significant association after control for age at interview and BMI was a positive association with breast cancer in women. This association remained significant after additional control for number of pregnancies, age at first live birth, history of breastfeeding, age at menarche, age at menopause, and use of postmenopausal estrogens (not shown) ($p=0.0175$).

Results of multiple logistic regression analyses relating total quarters worked at EUC with symptoms previously related to Parkinson's are shown in Tables 12a and 12b. As above, Model 1 did not include any confounders; model 2 also controlled for age at

interview and BMI. Difficulty opening jars was significant in model 1, but was of only borderline significance after control for age at interview and BMI in men. Writing becoming smaller was significant after control for age at interview and BMI in women. There were no other significant associations.

DISCUSSION

The results of this study are consistent with those of our first La Salle Morbidity Study in showing higher rates of ear infections and learning problems in children born after or during exposure at EUC. The only association that remained significant, however, after control for all potential confounders and clustering within families was with ear infections. Previous literature on the effects of PCBs on ear infections has been sparse and inconsistent, with significant associations seen after a high mixed PCB/furan exposure in Yucheng [119] and in children exposed to high levels of both PCBs and DDE [120]. Others, however [118, 84], have not seen significant associations with PCBs or mixed PCB/dioxin exposures. Other infections have not been consistently associated with PCB exposure and the mechanism by which otitis would be selectively affected has not been elucidated. One possibility could relate to the decrease in hair cells in rats after PCB exposure noted by Crofton et al[144], but the biologic pathway by which this could affect otitis is not clear.

The suggestion of associations of exposure at EUC with selected learning problems that were of only borderline significance after control for confounders and/or clustering is consistent with previous animal [94] and human [100,105,106,115,116] literature. Of interest is the fact that no associations were seen with low birth weight, prematurity, miscarriage or mild hypothyroidism, some of which have been seen in previous studies [95, 96,100,115,116].

The association with breast cancer in females, the only significant association for former employees, is somewhat surprising, especially in light of the negative findings in our mortality study in the same cohort and the generally negative findings in previous studies [25,26,36-44]. Given the number of endpoints examined, the relatively small number of potential confounders for which data were available, and the potential prevalence and selection biases in persons interviewed, this finding must be viewed with caution. Nevertheless, the fact that this association has been noted before [45-46] in a few studies and the coherence with animal literature suggesting estrogenic etiologies for breast cancer, implies that the finding perhaps should not be completely discounted. The lack of association with diabetes in women is not consistent with our previous report and, again, suggests possible selection biases in either one or both samples from this cohort.

The numbers of persons with Parkinson's were too small to allow for analysis. Examination of individual symptoms, however, did not yield consistent findings. It is possible that the numbers of persons in this study were not sufficient to address this endpoint adequately.

The major limitations of this study are the prevalence and selection biases inherent in any study of survivors. The 596 persons interviewed are only 1/5 of the original cohort, half of

whom are already deceased. Thus, associations found in this group may not be generalizable to the entire cohort. Another limitation to this study is the fact that health endpoints were determined by self-report. This could bias towards positive findings, although the lack of precision inherent in self-report might also bias towards the null hypothesis. The fact that the significant associations are consistent with previous literature and that there are not associations with many other variables suggests that self-reporting bias is not operative here. Another limitation is the number of endpoints examined. Five percent of these would be expected to be significant by chance alone. Again, the fact that the associations with otitis media and neurodevelopmental problems have been noted in previous literature supports the possibility that they reflect real phenomena.

The lack of individual PCB measurement and precision in exposure measurement is another limitation to the study. The high correlation between years of exposure and serum PCB level seen in Morbidity I supports the validity of our exposure measures. Nonetheless, these were mixed exposures involving solvents, chlorinated naphthalenes, and other substances for which there is little previous data on effects seen in this study. There is a great deal of data indicating that lead affects neurodevelopment and this is born out in this study in which lead was significantly association with many of the endpoints examined (ear infections, hayfever, being in special education, having problems with balance and reversal of letters). Control for confounders, including lead, did affect the significance of some of the neurodevelopmental endpoints, but not history of otitis media. Our estimate of lead exposure, however, was very gross and control for it, therefore, may have been inadequate. In general associations of other confounders with endpoints studied were consistent with previous literature as well, also supporting the general validity of the study. Finally, although the number of births examined here is larger than many other studies, the relatively small numbers inherent in any study of this type may limit the power of the study and bias towards the null hypothesis.

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TABLES

Table 1 - **Disposition of Eligible Persons by Age and Quarters Worked**[1]

Quarters worked	Less Than 65 Years of Age	65 Years or Older
	No. Eligible (% interviewed)	No. Eligible (% interviewed)
One	41 (63.4%)	84 (56.0%)
2-11	226 (58.8%)	483 (43.7%)
12 or more	90 (53.3%)	256 (51.2%)
[1] Excludes individuals initially eligible but subsequently found to be deceased		

Table 2 - Final Disposition of Sample

Status	Number	Percent of Total
Completed interview	596	47.8
Unavailable	79	6.3
Refused	327	26.2
Not able to interview	95	7.6
Unable to locate	118	9.5
Respondent denies working at EUC	8	1.6
Deceased	24	1.9
Other ineligible	1	0.1

Table 3 - Reasons for Exclusion in Analyses

n Excluded	Reason for Exclusion
13	Pregnancies with missing outcomes
4	Pregnancies with missing mother's age
3	Mother given diethylstilbesterol (DES) when pregnant
2	Mother had German Measles when pregnant
16	Missing information regarding DES or German Measles

Table 4 - Definition of Variables

Variable	Pertaining to Question #:
miscarriage	What was the outcome of your (first) pregnancy? Live birth? Miscarriage (before 12 weeks)? Miscarriage (after 12 weeks)? Abortion? Stillbirth? Other?
gender (boy)	Was the baby a boy or a girl?
premature	Was he/she premature, early but term, on time, or overdue?
low birthweight	How much did the child weigh at birth? (low birth weight then defined as < 2500 gms)
abnormal head size	Did a doctor or other medical specialist ever tell you our child had an unusually small or unusually large head?
birth defect	Did the child have any birth defects diagnosed either at birth or at a later time?
slow thyroid	Has the child ever been diagnosed by a doctor as having a slow thyroid?
hypothyroidism	Has the child ever been diagnosed by a doctor as having hypothyroidism?
hyperthyroidism	Has the child ever been diagnosed by a doctor as having hyperthyroidism?
other thyroid	Has the child ever been diagnosed by a doctor as having some other thyroid problem?
any thyroid	Defined as any of the above (slow, hypo, hyper, or other thyroid problem)
hearing	Has this child ever been diagnosed by a doctor as having a hearing problem?
ear infections	Has the child ever been diagnosed by a doctor as having frequent ear infections occurring 4 or more time in any given year?
asthma	Has the child ever been diagnosed by a doctor as having asthma?
other respiratory	Has the child ever been diagnosed by a doctor as having any other chronic respiratory illness?
hay fever	Has the child ever been diagnosed by a doctor as having hay fever?
eczema	Has the child ever been diagnosed by a doctor as having eczema?
diabetes	Has the child ever been diagnosed by a doctor as having diabetes?
other hormone	Has the child ever been diagnosed as having any

Variable	Pertaining to Question #:
	hormonal problems other than diabetes or thyroid problem?
retained in grade	Has this child ever been retained in a grade at school?
special ed	Has the child ever received special education for such things as: reading & writing, math, speech, or behavioral/emotional problems?
special ed-reading	Has the child ever received special education services for reading & writing?
special ed-math	Has the child ever received special education services for math?
special ed-speech	Has the child ever received special education services for speech?
special ed-behavioral	Has the child ever received special education services for behavioral/emotional problems?
learning disability	Has your child ever been diagnosed by a doctor, psychologist, or psychiatrist as having a learning disability?
mental retardation	Has your child ever been diagnosed by a doctor, psychologist, or psychiatrist as having mental retardation?
add	Has your child ever been diagnosed by a doctor, psychologist, or psychiatrist as having attention deficit disorder (ADD)?
adhd	Has your child ever been diagnosed by a doctor, psychologist, or psychiatrist as having attention deficit hyperactive disorder (ADHD)?
dyslexia	Has your child ever been diagnosed by a doctor, psychologist, or psychiatrist as having dyslexia?
speech	Has a professional, such as a teacher, psychologist or doctor ever told you your child had a speech or language problem?
hand/eye coordination	Has a professional, such as a teacher, psychologist or doctor ever told you your child had a problem with hand/eye coordination?
drawing	Has a professional, such as a teacher, psychologist or doctor ever told you your child had a drawing or copying problem?
balance	Has a professional, such as a teacher, psychologist or doctor ever told you your child had a balance or coordination problem?

Variable	Pertaining to Question #:
reversal of letters	Has a professional, such as a teacher, psychologist or doctor ever told you your child had a problem with reversing of letters?
attention	Has a professional, such as a teacher, psychologist or doctor ever told you your child had an attention problem?
impulsivity	Has a professional, such as a teacher, psychologist or doctor ever told you your child had impulsivity?
hyperactivity	Has a professional, such as a teacher, psychologist or doctor ever told you your child had hyperactivity?
attention or impulsivity or hyperactivity	Defined as any of the above (attention, impulsivity, or hyperactivity)?
other learning	Has a professional, such as a teacher, psychologist or doctor ever told you your child had any other learning problem?
other developmental	Has a professional, such as a teacher, psychologist or doctor ever told you your child had any other developmental problem?
any developmental	Defined as any of the above developmental problems? (speech, hand/eye coordination, drawing, balance, or other developmental problems)
other problem	Has your child ever had any other physical or mental handicap that we haven't asked about?
endometriosis (female only)	Has your daughter ever been told by a physician that she had endometriosis?
uterus	Has your daughter ever had abnormalities of the uterus?
ovary	Has your daughter ever had abnormalities of the ovaries?
undescended testes (males only)	Has your son ever had one or both undescended testicle(s)?
infertility	Has he/she ever tried for at least a year to conceive a child without succeeding?
cancer	Was the child ever diagnosed as having cancer?
death	Is the child still alive?

Table 5 - Frequency of Potential Confounders

Confounder	Pregnancy Outcome		Outcomes in Live Births	
	n	%	n	%
Mother < 18 years	31	3.21	24	3.00
Mother ≥ 35 years	107	11.08	81	10.12
Prior exposure to lead	211	23.34	170	22.67
Exposure to lead in pregnancy	21	2.18	17	2.13
Birth control pills	22	2.28	17	2.13
Smoking in pregnancy				
None	681	71.76	575	73.06
1-8/day	90	9.48	75	9.53
9-19/day	85	8.96	65	8.26
≥ 20/day	93	9.80	72	9.15
Drinking in pregnancy				
None	746	77.87	620	78.09
<1 drink/week	82	8.56	70	8.82
1-2 drinks/week	74	7.72	62	7.81
≥3 drinks/week	56	5.85	42	5.29
Exposure to x-rays	108	11.56	100	12.95
Gender (boy)			398	49.81
Breastfeeding				
None			643	82.02
< 3 months			47	5.99

3-5 months			40	5.10
≥ 6 months			54	6.89

Table 6a - Associations of Possible Confounders With Selected Outcomes in Children

	Mother age < 18			Mother age 35+		
Outcome*	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
miscarriage	17.2%	15.0	.7404	**22.1%**	**14.2%**	**.0334**
gender (boy)	45.8	49.9	.6922	51.9	49.6	.6985
premature	8.7	3.8	.2286	6.2	3.7	.2660
low birthweight	16.7	8.7	.1767	11.3	8.7	.4414
abnormal head size	0.0	0.8	-	1.3	0.7	.5912
birth defect	8.3	5.6	.5688	5.0	5.8	.7811
slow thyroid	0.0	1.9	-	0.0	2.0	-
hypothyroidism	0.0	0.8	-	0.0	0.9	-
other thyroid	0.0	1.5	-	0.0	1.6	-
any thyroid	0.0	3.9	-	0.0	4.2	-
hearing	4.2	3.3	.8122	1.3	3.5	.2911
ear infections	8.3	10.7	.7081	10.4	10.7	.9367
asthma	12.5	5.1	.1150	6.4	5.3	.6656
other resp	**12.5**	**4.5**	**.0687**	5.1	4.7	.8619
hayfever	4.4	4.6	.9473	1.3	5.0	.1377
eczema	0.0	1.1	.6141	0.0	1.1	-
diabetes	4.2	2.0	.4536	1.3	2.1	.6185
other hormone	4.2	0.9	.1235	0.0	1.2	-
retained in grade	**16.7**	**3.8**	**.0020**	0.0	4.7	-
special ed	8.7	6.3	.6487	5.3	6.5	.6683
special ed - reading	4.4	3.4	.7987	2.6	3.5	.6973
special ed - math	0.0	1.2	-	0.0	1.3	-
special ed - speech	4.4	3.4	.7987	5.0	3.3	.7809
special ed - behavioral	0.0	1.5	-	1.3	1.5	.9238
learning disability	4.2	2.9	.7132	2.5	3.0	.8279
mental retardation	0.0	0.8	-	1.3	0.7	.5792
add	0.0	1.2	-	**3.9**	**0.9**	**.0183**
adhd	0.0	0.9	-	**2.6**	**0.7**	**.0978**
dyslexia	4.2	1.3	.2424	2.6	1.3	.3582
speech	4.2	3.7	.8987	2.5	3.8	.5660
hand/eye coord	0.0	1.8	-	0.0	2.0	-
drawing	0.0	0.9	-	0.0	1.0	-
balance	0.0	1.1	-	0.0	1.1	-
reversal of letters	0.0	2.0	-	2.5	1.8	.6722
attention	0.0	2.8	-	2.5	2.7	.9351
impulsivity	0.0	0.9	-	0.0	1.0	-

	Mother age < 18			Mother age 35+		
Outcome*	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
hyperactivity	4.2	1.8	.4107	1.3	2.0	.6609
att or impu or hyper	4.2	3.9	.9557	2.5	4.1	.4952
other learning	0.0	0.8	-	0.0	0.9	-
other developmental	0.0	0.8	-	0.0	0.9	-
any developmental	4.4	5.4	.8273	2.5	5.7	.2395
other problem	12.5	3.7	**.0287**	2.5	4.1	.4965
endometriosis	0.0	6.9	-	7.9	6.6	.7567
uterus	15.4	10.8	.5985	5.6	11.5	.2792
ovary	15.4	7.2	.2743	2.7	8.1	.2412
undescended testes	40.0	21.6	.1652	17.5	22.6	.4634
infertility	12.5	7.5	.3615	4.4	8.0	.2921
cancer	4.4	3.4	.8063	1.3	3.7	.2650
death	4.2	4.9	.8659	3.7	5.0	.5988

*Outcomes defined in Table 4

Table 6b - Associations of Possible Confounders With Selected Outcomes in Children

	Lead Exposure During Pregnancy			Lead Exposure Before Pregnancy's End		
Outcome*	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
miscarriage	15%	15.0%	.9984	16.3%	14.8%	.6192
gender (boy)	58.8	49.7	.4589	52.4	49.2	.4730
premature	0.0	4.0	-	2.9	4.3	.4146
low birthweight	6.3	9.0	.7023	10.7	9.0	.4940
abnormal head size	**5.9**	**0.7**	**.0138**	1.2	0.5	.3350
birth defect	11.8	5.4	.2602	7.7	4.9	.1159
slow thyroid	0.0	1.9	-	1.8	1.8	.9823
hypothyroidism	0.0	0.8	-	0.6	0.7	.8754
other thyroid	**11.8**	**1.2**	**.0003**	**4.2**	**0.7**	**.0013**
any thyroid	**11.8**	**3.6**	**.0828**	**6.0**	**3.1**	**.0814**
hearing	**11.8**	**3.1**	**.0495**	4.7	2.8	.2194
ear infections	**31.3**	**10.3**	**.0071**	**16.9**	**9.0**	**.0043**
asthma	5.9	5.4	.9257	5.4	5.3	.9603
other resp	5.9	4.7	.8233	3.6	4.8	.5076
hayfever	11.8	4.5	.1574	**9.2**	**3.6**	**.0032**
eczema	**5.9**	**0.9**	**.0435**	0.6	1.2	.4815
diabetes	0.0	2.1	-	2.4	1.6	.4912
other hormone	0.0	1.1	-	1.2	0.9	.7195
retained in grade	5.9	4.2	.7303	5.9	3.9	.2524
special ed	11.8	6.3	.3635	**10.7**	**5.1**	**.0095**
special ed - reading	5.9	3.4	.5695	5.4	2.9	.1322
special ed - math	0.0	1.2	-	1.2	1.3	.9295
special ed - speech	0.0	3.5	-	3.6	3.3	.8566
special ed - behavioral	5.9	1.3	.1207	**3.0**	**0.9**	**.0465**
learning disability	5.9	2.9	.4655	3.6	2.5	.4340
mental retardation	0.0	0.8	.7143	0.0	0.7	.2740
add	**5.9**	**1.0**	**.0642**	1.8	0.7	.2086
adhd	0.0	0.9	-	1.2	0.5	.3623
dyslexia	0.0	1.4	-	0.6	1.6	.3265
speech	**11.8**	**3.5**	**.0745**	**5.9**	**2.8**	**.0545**
hand/eye coord	0.0	1.8	-	1.2	1.6	.7058
drawing	0.0	0.9	-	**2.4**	**0.4**	**.0104**
balance	**5.9**	**0.9**	**.0437**	0.6	1.1	.5846
reversal of letters	**11.8**	**1.7**	**.0028**	1.8	1.8	.9659

	Lead Exposure During Pregnancy			Lead Exposure Before Pregnancy's End		
Outcome*	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
attention	5.9	2.6	.4081	3.0	2.3	.6099
impulsivity	0.0	0.9	-	0.6	1.1	.5846
hyperactivity	5.9	1.8	.2266	3.0	1.2	.1188
att or impu or hyper	5.8	3.9	.6810	5.4	3.4	.2311
other learning	0.0	0.8	-	0.6	0.7	.8769
other developmental	0.0	0.8	-	1.2	0.5	.3612
any developmental	11.8	5.2	.2371	**8.3**	**4.2**	**.0350**
other problem	**11.8**	**3.4**	**.0948**	4.8	3.7	.5303
endometriosis	14.3	6.6	.4212	**17.1**	**3.8**	**<.0001**
uterus	16.7	10.6	.6340	11.7	10.6	.7930
ovary	0.0	7.6	.5656	10.0	6.9	.3725
undescended testes	40.0	21.6	.1652	21.8	22.5	.8961
infertility	6.3	7.5	.8469	9.2	6.8	.3192
cancer	0.0	3.5	-	1.8	3.7	.2228
death	5.9	4.9	.8518	4.7	4.3	.8352

*Outcomes defined in Table 4

Table 6c - Associations of Possible Confounders With Selected Outcomes in Children

	# Cigarettes Per Day During Pregnancy				
Outcome*	**none**	**1 to 8**	**9 to 19**	**>20**	**p-value**
miscarriage	13.9%	12.8%	22.6%	17.2%	.1120
gender (boy)	49.1	49.3	58.5	50.0	.5623
premature	**2.6**	**4.0**	**10.8**	**8.5**	**.0006**
low birthweight	**7.3**	**13.5**	**10.8**	**16.9**	**.0048**
abnormal head size	0.9	0.0	0.0	1.4	.9357
birth defect	6.3	4.0	0.0	5.7	.2104
slow thyroid	1.6	2.7	1.7	3.0	.4413
hypothyroidism	0.7	1.4	0.0	1.5	.7144
other thyroid	1.1	4.2	1.6	1.5	.4729
any thyroid	3.6	6.9	3.4	3.0	.9967
hearing	3.4	6.8	0.0	2.9	.5669
ear infections	9.6	14.7	14.5	10.6	.3285
asthma	**5.0**	**2.7**	**4.8**	**13.0**	**.0360**
other resp	4.5	5.3	1.6	10.0	.2141
hayfever	**4.1**	**2.7**	**9.5**	**7.3**	**.0846**
eczema	0.7	2.7	1.6	1.5	.3056
diabetes	2.3	0.0	0.0	4.4	.8746
other hormone	0.9	2.7	1.6	0.0	.9537
retained in grade	4.3	4.0	4.8	4.3	.9283
special ed	6.0	6.8	6.4	10.5	.2334
special ed - reading	2.9	6.8	3.2	4.5	.3976
special ed - math	1.1	1.4	0.0	3.0	.4495
special ed - speech	3.7	1.4	3.2	4.5	.9779
special ed - behavioral	**1.1**	**1.4**	**1.6**	**4.5**	**.0566**
learning disability	3.0	4.0	1.6	2.9	.7928
mental retardation	0.7	1.3	0.0	1.4	.7343
add	1.1	1.3	3.2	0.0	.9430
adhd	0.9	1.3	1.6	0.0	.7831
dyslexia	1.6	1.3	0.0	0.0	.1632
speech	3.7	1.3	4.8	5.7	.4857
hand/eye coord	1.8	2.7	1.6	1.4	.9026
drawing	1.1	1.3	0.0	0.0	.2888
balance	0.9	1.3	0.0	2.9	.3183
reveral of letters	1.8	2.7	1.6	1.5	.9237
attention	3.0	1.3	1.6	2.9	.6242
impulsivity	1.1	1.3	0.0	0.0	.2907

	# Cigarettes Per Day During Pregnancy				
Outcome*	**none**	**1 to 8**	**9 to 19**	**>20**	**p-value**
hyperactivity	1.9	2.7	3.2	0.0	.6002
att or impu or hyper	4.4	2.7	3.2	2.9	.3988
other learning	0.7	0.0	0.0	2.9	.2358
other developmental	0.7	0.0	0.0	2.9	.2381
any developmental	5.3	4.0	4.8	8.6	.4548
other problem	4.4	4.0	0.0	4.3	.3951
endometriosis	**5.3**	**0.0**	**14.8**	**15.2**	**.0153**
uterus	11.1	16.7	7.4	8.6	.6477
ovary	8.7	8.8	0.0	3.3	.1290
undescended testes	22.9	36.1	14.3	11.8	.1512
infertility	7.0	13.2	7.4	8.2	.5428
cancer	3.4	4.1	1.6	5.7	.5888
death	4.9	2.7	4.7	7.1	.6140

*Outcomes defined in Table 4

Table 6d - Associations of Possible Confounders With Selected Outcomes in Children

	Drinks Per Week During Pregnancy				
Outcome*	**none**	**<1**	**1 to 2**	**3+**	**p-value**
miscarriage	14.7%	11.4%	13.9%	25.0%	.1920
premature	3.4	8.6	3.2	4.8	.4611
low birthweight	8.2	14.9	6.7	14.3	.2459
birth defect	5.4	7.1	3.2	7.3	.9027
abnormal head size	0.8	0.0	1.6	0.0	.8395
slow thyroid	1.7	4.5	1.7	0.0	.8669
hypothyroidism	0.8	0.0	1.7	0.0	.8600
other thyroid	1.2	6.0	0.0	0.0	.9161
any thyroid	3.6	10.3	1.7	0.0	.5719
hearing	3.5	1.4	6.6	0.0	.7209
ear infections	**9.1**	**15.7**	**18.3**	**15.8**	**.0113**
asthma	5.1	7.3	6.6	2.5	.9375
other resp	4.3	12.9	1.6	2.4	.8392
hayfever	4.8	6.3	1.6	2.4	.3048
eczema	0.8	1.5	3.3	0.0	.4422
diabetes	1.8	2.9	3.3	2.6	.4221
other hormone	0.8	3.0	1.6	0.0	.7206
retained in grade	4.5	2.9	6.6	0.0	.4795
special ed	7.0	2.9	8.3	2.4	.3666
special ed - reading	3.4	1.4	6.7	2.4	.7646
special ed - math	1.0	1.4	1.7	2.4	.3676
special ed - speech	4.1	0.0	3.3	0.0	.1153
special ed - behavioral	1.7	1.4	0.0	0.0	.2068
learning disability	3.1	0.0	3.3	4.9	.8561
mental retardation	0.8	0.0	1.6	0.0	.8374
add	1.1	0.0	3.3	0.0	.8862
adhd	0.7	0.0	4.9	0.0	.1545
dyslexia	1.2	0.0	4.9	0.0	.4512
speech	4.4	0.0	0.0	4.9	.2016
hand/eye coord	1.6	0.0	3.3	2.4	.5540
drawing	0.8	0.0	3.3	0.0	.5955
balance	1.0	1.4	1.6	0.0	.9227
reversal of letters	**1.3**	**0.0**	**9.8**	**0.0**	**.0428**
attention	2.3	2.9	6.6	2.4	.2366
impulsivity	0.7	2.9	1.6	0.0	.5980
hyperactivity	1.6	2.9	4.9	0.0	.5470
att or impu or hyper	3.3	5.7	9.4	2.4	.1609

	Drinks Per Week During Pregnancy				
Outcome*	**none**	**<1**	**1 to 2**	**3+**	**p-value**
other learning	0.8	0.0	0.0	2.4	.7795
other developmental	1.0	0.0	0.0	0.0	.2401
any developmental	5.6	1.4	5.0	7.3	.9250
other problem	4.3	2.9	3.3	2.4	.4451
endometriosis	6.9	7.3	0.0	11.1	.8560
uterus	10.8	17.1	0.0	10.0	.5067
ovary	8.2	5.4	8.0	0.0	.3011
undescended testes	21.4	25.9	20.6	19.1	.8815
infertility	8.3	4.6	4.0	8.6	.4124
cancer	3.3	2.9	4.9	2.4	.9034
death	5.3	4.3	4.9	0.0	.2006

*Outcomes defined in Table 4

Table 6e - Associations of Possible Confounders With Selected Outcomes in Children

	X-Rays During Pregnancy			Birth Control Pills During Pregnancy		
Outcome*	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
miscarriage	**6.5%**	**16.4%**	**.0076**	19.1%	14.9%	.5993
gender (boy)	-	-	-	-	-	-
premature	6.1	3.8	.2759	**11.8**	**3.7**	**.0912**
low birthweight	9.1	9.1	.9928	17.7	8.7	.2031
abnormal head size	0.0	0.8	.3871	0.0	0.8	-
birth defect	7.1	5.4	.5045	5.9	5.7	.9722
slow thyroid	0.0	2.0	.1597	0.0	1.9	-
hypothyroidism	1.0	0.8	.7902	0.0	0.8	-
other thyroid	2.0	1.4	.6163	5.9	1.3	.1169
any thyroid	3.1	3.9	.7149	5.9	3.8	.6509
hearing	**6.1**	**2.9**	**.0995**	0.0	3.4	-
ear infections	11.1	10.1	.7551	11.8	10.5	.8679
asthma	**12.4**	**4.3**	**.0008**	5.9	5.4	.9246
other resp	**14.6**	**3.5**	**<.0001**	0.0	4.9	-
hayfever	6.3	4.6	.4766	5.9	4.6	.8054
eczema	0.0	1.2	-	0.0	1.0	-
diabetes	3.0	2.0	.4949	0.0	2.1	-
other hormone	2.1	0.9	.3085	0.0	2.2	-
retained in grade	6.3	3.9	.2934	5.9	4.2	.7293
special ed	10.1	6.0	.1422	11.8	6.3	.3624
special ed - reading	5.6	3.1	.2161	5.9	3.4	.5686
special ed - math	1.1	1.2	.9288	**5.9**	**1.1**	**.0691**
special ed - speech	**7.9**	**2.8**	**.0129**	5.9	3.4	.5686
special ed - behavioral	2.3	1.2	.4400	5.9	1.3	.1203
learning disability	3.1	2.9	.9028	5.9	2.9	.4647
mental retardation	0.0	0.8	-	0.0	0.8	-
add	1.0	1.1	.9787	0.0	1.2	-
adhd	2.1	0.8	.2102	0.0	0.9	-
dyslexia	2.1	1.2	.4950	5.9	1.3	.1128
speech	**8.3**	**3.0**	**.0108**	0.0	3.8	-
hand/eye coord	1.0	1.8	.5784	5.9	1.7	.1967
drawing	1.0	0.9	.9079	0.0	0.9	-
balance	1.0	0.9	.8969	**5.9**	**0.9**	**.0435**
reversal of letters	2.1	1.8	.8695	5.9	1.8	.2277
attention	**5.2**	**2.3**	**.0928**	5.9	2.6	.4074
impulsivity	2.1	0.8	.2094	0.0	0.9	-

	X-Rays During Pregnancy			Birth Control Pills During Pregnancy		
Outcome*	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
hyperactivity	4.1	1.7	.1037	5.9	1.8	.2260
att or impu or hyper	**9.4**	**3.2**	**.0036**	5.9	3.9	.6800
other learning	0.0	0.9	-	0.0	0.8	-
other developmental	1.0	0.8	.7747	0.0	0.8	-
any developmental	**9.4**	**4.9**	**.0673**	5.9	5.4	.9236
other problem	**11.3**	**3.0**	**.0001**	5.9	3.9	.6790
endometriosis	4.1	7.1	.4339	**30.0**	**6.1**	**.0028**
uterus	8.0	11.5	.4594	10.0	10.9	.9256
ovary	6.4	8.0	.6977	10.0	7.5	.7638
undescended testes	**34.0**	**20.7**	**.0399**	14.3	22.3	.6148
infertility	7.9	7.5	.8998	0.0	2.6	-
cancer	4.1	3.3	.7020	0.0	3.5	-
death	7.1	4.8	.3333	5.9	4.9	.8505

*Outcomes defined in Table 4

Table 6f - Associations of Possible Confounders With Selected Outcomes in Children

	Breastfeeding - # of Months				
Outcome*	**none**	**< 3 mos**	**3 to 5**	**6+ mos**	**p-value**
slow thyroid	1.6%	2.2%	0.0%	5.8%	.1225
hypothyroidism	0.8	2.2	0.0	0.0	.5860
other thyroid	1.4	4.4	0.0	0.0	.4932
any thyroid	3.7	6.7	0.0	5.9	.7256
hearing	**2.8**	**0.0**	**7.7**	**7.6**	**.0376**
ear infections	10.8	12.8	13.2	7.6	.7429
asthma	5.0	6.7	5.1	7.6	.4546
other resp	4.7	4.3	5.1	1.9	.4495
hayfever	4.8	9.3	0.0	3.8	.5447
eczema	1.1	2.1	0.0	0.0	.4355
diabetes	1.9	4.3	0.0	3.8	.5226
other hormone	1.1	0.0	2.7	0.0	.7196
retained in grade	**4.9**	**2.1**	**0.0**	**1.9**	**.0942**
special ed	6.8	6.4	2.6	5.9	.4858
special ed - reading	3.7	2.1	2.6	2.0	.4063
special ed - math	1.3	0.0	0.0	2.0	.9015
special ed - speech	3.6	4.3	0.0	3.9	.7134
special ed - behavioral	1.8	0.0	0.0	0.0	.1527
learning disability	3.0	4.0	1.6	2.9	.7928
mental retardation	0.9	0.0	0.0	0.0	.2962
add	1.1	2.1	2.6	0.0	.9135
adhd	0.9	0.0	0.0	1.9	.8494
dyslexia	1.6	2.1	0.0	0.0	.2883
speech	3.9	2.1	0.0	5.6	.8742
hand/eye coord	1.9	2.1	0.0	1.9	.7127
drawing	**0.5**	**4.3**	**0.0**	**3.7**	**.0184**
balance	1.3	0.0	0.0	0.0	.2250
reversal of letters	2.2	0.0	0.0	1.9	.4439
attention	2.7	4.3	2.6	1.9	.8430
impulsivity	0.9	0.0	0.0	1.9	.8482
hyperactivity	1.9	2.1	0.0	3.7	.6624
att or impu or hyper	3.6	6.4	2.6	7.6	.2322
other learning	0.8	0.0	2.6	0.0	.9165
other developmental	0.8	0.0	0.0	1.9	.7121
any developmental	5.5	6.4	0.0	7.4	.9136
other problem	**3.3**	**6.4**	**5.1**	**7.4**	**.0904**
endometriosis	7.3	8.3	6.7	0.0	.2183

	Breastfeeding - # of Months				
Outcome*	**none**	**< 3 mos**	**3 to 5**	**6+ mos**	**p-value**
uterus	9.9	16.7	18.8	10.3	.4982
ovary	7.2	4.6	6.7	11.1	.6059
infertility	7.5	11.6	8.3	2.0	.3637
cancer	3.5	4.3	5.1	0.0	.4055
death	4.7	4.3	5.0	1.9	.4322

*Outcomes defined in Table 4

Table 6g - Associations of Possible Confounders With Selected Outcomes in Children

	Gender		
Outcome*	**Boy**	**Girl**	**p-value**
premature	**2.5%**	**5.3%**	**.0469**
low birthweight	**6.5**	**11.3**	**.0187**
abnormal head size	1.0	0.5	.4036
birth defect	**4.3**	**7.0**	**.0982**
slow thyroid	**0.3**	**3.4**	**.0013**
hypothyroidism	0.8	0.8	.9871
other thyroid	1.0	1.8	.3646
any thyroid	**1.8**	**5.7**	**.0048**
hearing	2.8	3.8	.4444
ear infections	11.6	9.7	.3953
asthma	5.4	5.4	.9932
other resp	5.4	4.1	.3735
hayfever	4.1	5.1	.4998
eczema	1.0	1.0	.9798
diabetes	1.5	2.5	.3299
other hormone	0.0	2.1	-
retained in grade	4.2	4.3	.9061
special ed	**8.1**	**4.7**	**.0537**
special ed - reading	**5.0**	**1.8**	**.0163**
special ed - math	1.1	1.3	.7404
special ed - speech	4.2	2.6	.2286
special ed - behavioral	1.6	1.3	.7547
learning disability	3.9	2.0	.1243
mental retardation	0.5	1.0	.4268
add	1.6	0.8	.2981
adhd	0.8	1.0	.7269

dyslexia	1.8	1.0	.3446
speech	4.1	3.3	.5284
hand/eye coordination	1.5	2.0	.6164
drawing	1.3	0.5	.2422
balance	0.8	1.3	.4999
reversal of letters	**2.8**	**1.0**	**.0636**
attention	**3.9**	**1.5**	**.0404**
impulsivity	1.0	0.8	.6842
hyperactivity	1.5	2.3	.4609
att or impu or hyper	4.4	3.5	.5386
other learning	0.8	0.8	.9750
other developmental	0.5	1.0	.4286
any developmental	5.7	5.0	.6875
other problem	**5.4**	**2.5**	**.0381**
infertility	**5.2**	**9.9**	**.0180**
cancer	3.3	3.5	.8923
death	**6.6**	**3.2**	**.0290**

*Outcomes defined in Table 4

Table 7 - Confounders Remaining in the Multivariate Analysis of Pregnancy and Health Outcomes in Children of Women who are Former EUC Workers (p<0.10)

	Confounders Used in Multivariate Models indicated by ✓(significant at p-value< 0.10)								
Outcome*	**mother < 18 (y/n)**	**mother > 35 (y/n)**	**lead exposure[1]**	**cigarette smoking[2]**	**alcohol intake[3]**	**breast-feeding months[4]**	**birth control pills[5]**	**xrays[6]**	**boy (y/n)**
miscarriage		✓						✓[p]	
gender (boy)									
premature				✓					✓[p]
low birthweight				✓					✓[p]
abnormal head size									
birth defect									
slow thyroid									✓[p]
hypothyroidism									
other thyroid			✓						
any thyroid			✓						✓[p]
hearing						✓		✓	
ear infections					✓				
asthma	✓			✓				✓	
other respiratory				✓				✓	
hayfever			✓						
eczema									
diabetes									
other hormone									
retained in grade	✓								
special ed			✓					✓	✓
special ed - reading									✓
special ed - math									
special ed - speech								✓	
special ed - behavioral			✓						
learning disability									✓
mental retardation									
add									
adhd					✓			✓	
dyslexia									
speech			✓					✓	
hand/eye coordination									

Outcome*	Confounders Used in Multivariate Models indicated by ✓(significant at p-value< 0.10)								
	mother < 18 (y/n)	mother > 35 (y/n)	lead exposure[1]	cigarette smoking[2]	alcohol intake[3]	breast-feeding months[4]	birth control pills[5]	xrays[6]	boy (y/n)
drawing						✓			
balance							✓		
reversal of letters					✓				
attention									✓
impulsivity									
hyperactivity			✓						
att or impu or					✓			✓	
other learning									
other developmental									
any			✓					✓	
other problem						✓		✓	✓
endometriosis			✓	✓			✓		
uterus									
ovary									
undescended								✓	
infertility									✓[p]
cancer									
death									✓

*Outcomes defined in Table 4

p = protective association between confounder and outcome

[1]lead exposure defined as any maternal lead exposure at EUC before or during pregnancy

[2]maternal cigarette smoking during pregnancy defined in ordinal groups (0=no smoking, 1=1-5 cigarettes per day, 2=6-10 per day, 3=>10 per day)

[3]maternal alcohol intake during pregnancy defined in ordinal groups (0= no drinking, 1=<1 drink per week, 2=1-2 per week, 3=3+ per week)

[4]breast feeding defined in ordinal groups (0=no breast feeding, 1=<3 months, 2=3-5 months, 3=6+ months of breast feeding)

[5]birth control pills defined as any birth control pills taken by the mother during pregnancy (yes/no)

[6]x-rays defined as any x-ray received by the mother during pregnancy (yes/no)

Table 8 - Relationship of Maternal Exposure at EUC to Pregnancy and Health Outcomes in Their Children

	Maternal EUC exposure before or during pregnancy		Univariate		Multivariate Regression Models***	
			OR (95%CI)	n	Logistic	Mixor
Outcome*	**Yes**	**No**			**OR (95%CI)**	**OR (95%CI)**
miscarriage	15.2%	15.0%	1.0 (0.7-1.5)	139/911	1.0 (0.7-1.4)	0.9 (0.6-1.4)
gender (boy)	50.5	48.8	1.1 (0.8-1.4)	398/799	1.1 (0.8-1.4)	**
premature	4.7	2.8	1.7 (0.8-3.7)	31/781	1.7 (0.8-3.7)	1.6 (0.3-9.8)
low birthweight	8.3	9.9	0.8 (0.5-1.3)	69/759	0.8 (0.5-1.4)	0.6 (0.3-1.5)
abnormal head size	1.1	0.3	3.4 (0.4-29.3)	6/793	3.4 (0.4-29.3)	**
birth defect	6.4	4.7	1.4 (0.7-2.6)	45/792	1.4 (0.7-2.6)	1.4 (0.6-3.1)
slow thyroid	1.9	1.6	1.2 (0.4-3.6)	14/772	1.2 (0.4-3.8)	**
hypothyroidism	1.3	0.0	zero cell	6/761	zero cell	error
other thyroid	1.7	1.0	1.8 (0.5-6.8)	11/726	0.4 (0.0-4.0)	0.4 (0.0-4.6)
any thyroid	4.3	3.0	1.5 (0.7-3.3)	27/717	1.1 (0.4-2.8)	1.1 (0.3-3.7)
hearing	3.2	3.5	0.9 (0.4-2.0)	24/747	0.8 (0.3-1.8)	**
ear infections	**13.3**	**6.7**	**2.1 (1.3-3.6)[a]**	83/773	**2.0 (1.2-3.4)[a]**	**2.2 (1.1-4.2)[b]**
asthma	**6.6**	**3.5**	**1.9 (1.0-3.9)[c]**	40/744	**2.1 (1.0-4.8)[c]**	**2.3 (0.9-6.3)[c]**
other resp	4.5	5.1	0.9 (0.4-1.7)	37/741	0.8 (0.4-1.6)	0.8 (0.3-1.9)
hayfever	5.4	3.5	1.6 (0.8-3.2)	35/728	1.0 (0.4-2.5)	1.3 (0.3-4.8)
eczema	0.9	1.3	0.7 (0.2-2.7)	8/787	0.7 (0.2-2.7)	**
diabetes	1.9	2.2	0.9 (0.3-2.3)	16/785	0.9 (0.3-2.3)	0.8 (0.3-2.6)
other hormone	1.1	1.0	1.1 (0.3-4.7)	8/773	1.1 (0.3-4.7)	**
retained in grade	4.9	3.2	1.6 (0.7-3.4)	33/784	**2.5 (1.0-6.2)[c]**	**2.6 (0.9-8.1)[c]**
special ed	**7.9**	**4.2**	**2.0 (1.0-3.8)[b]**	45/691	1.6 (0.7-3.5)	1.6 (0.6-4.2)
special ed - reading	3.7	2.9	1.3 (0.6-3.0)	26/765	1.3 (0.6-2.9)	**
special ed - math	1.3	1.0	1.4 (0.3-5.5)	9/765	1.4 (0.3-5.5)	**
special ed - speech	4.2	2.3	1.9 (0.8-4.5)	25/737	2.1 (0.8-5.3)	2.1 (0.6-7.1)
special ed - behavioral	1.5	1.3	1.2 (0.3-4.1)	10/715	0.3 (0.0-2.9)	0.3 (0.0-4.7)
learning disability	3.2	2.5	1.3 (0.5-3.1)	23/787	1.3 (0.5-3.0)	1.3 (0.4-3.6)
mental retardation	0.6	1.0	0.7 (0.1-3.4)	6/786	0.7 (0.1-3.4)	0.7 (0.1-6.5)
add	**1.7**	**0.3**	**5.5 (0.7-43.9)[c]**	9/785	5.5 (0.7-43.9)	7.5 (0.6-90.1)
adhd	1.1	0.6	1.7 (0.3-8.8)	7/752	1.5 (0.3-7.7)	1.5 (0.0-1961.2)
dyslexia	1.5	1.3	1.2 (0.3-4.1)	11/784	1.2 (0.3-4.1)	1.2 (0.2-6.5)
speech	4.3	2.8	1.5 (0.7-3.4)	25/713	1.0 (0.4-2.8)	0.6 (0.1-3.6)
hand/eye coord	1.9	1.6	1.2 (0.4-3.7)	14/786	1.2 (0.4-3.7)	1.2 (0.3-4.5)
drawing	1.5	0.0	zero cell	7/772	zero cell	error
balance	0.6	1.6	0.4 (0.1-1.7)	8/785	0.4 (0.1-1.6)	0.3 (0.0-16.1)

	Maternal EUC exposure before or during pregnancy		Univariate		Multivariate Regression Models***	
			OR (95%CI)	n	Logistic	Mixor
Outcome*	**Yes**	**No**			**OR (95%CI)**	**OR (95%CI)**
reversal of letters	2.6	0.9	2.8 (0.8-9.9)	14/778	2.3 (0.6-8.4)	2.5 (0.5-13.5)
attention	**3.6**	**1.3**	**3.0 (1.0-8.9)[b]**	21/786	**2.9 (1.0-8.8)[c]**	3.6 (0.6-21.7)
impulsivity	1.1	0.6	1.7 (0.3-8.8)	7/786	1.7 (0.3-8.8)	1.3 (0.2-8.3)
hyperactivity	2.1	1.6	1.4 (0.5-4.0)	12/738	0.5 (0.1-2.6)	0.3 (0.0-4.4)
att or impu or hyper	**4.9**	**2.5**	**2.0 (0.9-4.5)[c]**	30/752	**2.1 (0.9-5.0)[c]**	2.2 (0.7-7.0)
other learning	0.9	0.6	1.4 (0.2-7.5)	6/786	1.4 (0.2-7.5)	error
other developmental	0.6	0.9	0.7 (0.1-3.4)	6/787	0.7 (0.1-3.4)	error
any developmental	6.2	4.1	1.5 (0.8-3.0)	37/710	1.1 (0.5-2.5)	1.1 (0.3-3.7)
other problem	3.9	4.1	0.9 (0.5-1.9)	30/749	0.8 (0.4-1.6)	0.7 (0.2-2.1)
endometriosis	**9.7**	**2.5**	**4.2 (1.4-12.3)[a]**	22/355	2.0 (0.6-7.1)	**
uterus	10.6	11.4	0.9 (0.5-1.8)	42/385	0.9 (0.5-1.8)	0.8 (0.3-2.0)
ovary	7.8	7.2	1.1 (0.5-2.4)	28/372	1.1 (0.5-2.4)	1.1 (0.5-2.5)
undescended testes	21.7	22.7	0.9 (0.6-1.5)	83/371	0.8 (0.5-1.4)	0.9 (0.4-2.1)
infertility	8.2	6.9	1.2 (0.7-2.1)	54/707	1.2 (0.7-2.1)	1.2 (0.6-2.2)
cancer	2.6	4.7	0.5 (0.2-1.1)	27/787	0.5 (0.2-1.1)	**
death	4.6	5.3	0.9 (0.5-1.7)	39/796	0.9 (0.4-1.6)	0.8 (0.3-1.8)

*Outcomes defined in Table 4

[a]p-value<.01, [b]p-value<.05, [c]p-value<.10

***The multivariate models only include those confounders that were selected in stepwise logistic regression
models allowing inclusion of variables having p<0.10 and retaining variables having p<0.10 in the multivariate models. The final confounders are shown in Table 7.

error = MIXOR: estimation difficulties occurred.

** = MIXOR can't estimate the family variance as being different from zero. Use logistic regression results.

Table 9 - History of Selected Diseases

Self-Reported Disease	Women (disease n* / total n*)	Men (disease n* / total n*)
Liver cancer	0/336	0/259
Gallbladder cancer	0/336	0/259
Breast cancer	22/336	0/259
Prostate cancer	NA	11/259
Colon/rectal cancer	5/336	3/259
Bladder cancer	2/336	3/259
Leukemia	1/337	0/259
Non-hodgkins lymphoma	2/337	0/259
Multiple Myeloma	0/337	0/259
Hodgkin's disease	0/337	0/259
Other blood cancer	2/337	0/259
Malignant melanoma	8/336	9/259
Thyroid cancer	1/337	1/259
Malignant brain tumor	0/337	0/259
Other cancer	24/335	16/259
Benign brain tumor	2/337	1/259
Gallbladder disease	74/324	19/257
Hepatitis	3/333	5/252
Cirrhosis of liver	1/337	3/258
Yellow jaundice	5/327	4/251
Porphyria	0/337	0/259
Other liver disease	1/336	2/258
Stroke	29/335	11/259
Myocardial infarction	31/332	37/255
Angina	21/335	19/259
High blood pressure	153/321	113/250
High cholesterol	127/331	104/257
Lupus	4/337	1/259
Raynaud's disease	4/337	0/259
Rheumatoid arthritis	46/330	20/252
Other arthritis	112/322	54/253
Scleroderma	1/337	0/259
Chronic bronchitis	34/322	13/250
Asthma	22/332	6/254
Parkinson's	3/337	0/259

Self-Reported Disease	Women (disease n* / total n*)	Men (disease n* / total n*)
Multiple sclerosis	2/337	1/259
Other nerve affecting disease	8/336	4/257
Anemia	41/311	6/256
Diabetes	44/334	32/256
Benign thyroid tumor	6/336	4/259
Hashimoto's disease	2/337	1/259
Hypothyroidism	51/331	9/258
Hyperthyroidism	15/330	3/257
Goiter/enlarged thyroid	12/331	3/258
Other thyroid disease	6/333	3/258
Endometriosis	17/332	NA
Ovarian cysts/fibroids	62/313	NA
Uteran fibroids	63/327	NA
Infertility	40/288	NA

*Excludes former workers who developed disease/condition prior to working at EUC and those whose diagnosis date is uncertain.

Table 10 - Questions Addressing Parkinson's Symptoms

Do your arms or your legs ever shake?
During the day do your muscles ever feel stiff and aching apart from after exercise?
Do you find it difficult to get up out of a chair?
Do you shuffle when you walk?
Have you difficulty turning in bed?
Has your writing become smaller?
Do you find it difficult to open jars (other than new) or use a screwdriver or fasten the small buttons on your shirt or blouse?
Do you lose your balance when turning?

Table 11a - Cox Regression Analyses Relating Years of Exposure to Time of Onset of Selected Diseases in Men

		Hazard Ratio* (95% CI)	
Self-Reported Disease	**n**	**Model 1**	**Model 2**
Prostate Cancer	11/259	0.28 (0.04-1.95)	0.26 (0.03-2.03)
Malignant Melanoma	9/259	0.71 (0.32-1.58)	0.75 (0.34-1.67)
Gallbladder Disease	19/257	0.96 (0.68-1.37)	0.75 (0.43-1.32)
Hepatitis	5/252	0.35 (0.02-6.25)	0.41 (0.02-9.48)
Stroke	11/259	0.46 (0.13-1.64)	0.50 (0.14-1.77)
Heart Attack	37/255	0.94 (0.74-1.20)	0.98 (0.77-1.24)
Angina	19/259	0.70 (0.41-1.22)	0.74 (0.42-1.29)
High Blood Pressure	113/250	**0.80[a] (0.67-0.98)**	**0.83[b] (0.68-1.00)**
High Cholesterol	104/257	**0.79[a] (0.64-0.96)**	**0.83[b] (0.68-1.04)**
Rheumatoid arthritis	20/252	0.72 (0.38-1.35)	0.72 (0.38-1.37)
Other Arthritis	54/253	0.87 (0.68-1.10)	0.90 (0.71-1.17)
Chronic Bronchitis	13/250	1.20 (0.83-1.67)	1.32 (0.90-1.88)
Asthma	6/254	1.02 (0.50-2.07)	1.06 (0.50-2.23)
Anemia	6/256	0.10 (0.00-9.65)	0.11 (0.00-
Diabetes	31/255	1.02 (0.79-1.32)	1.06 (0.82-1.37)
Hypothyroidism	9/258	0.33 (0.04-2.97)	0.34 (0.04-3.21)

*The hazard ratio presented represents the proportional increased hazard associated
with each additional 5 years (20 quarters) worked at EUC, calculated as exp(20*parameter estimate for one quarter increase).
[a]p-value<.05, [b]p-value<.10
Model 1: only disease and exposure variable.
Model 2: control for age at interview and bmi at 40 years old.

Table 11b - Cox Regression Analyses Relating Years of Exposure to Time of Onset of Selected Diseases in Women

		Hazard Ratio* (95% CI)	
Self-Reported Disease	**n**	**Model 1**	**Model 2**
Breast Cancer	22/336	**1.27[a] (1.02-1.55)**	**1.27[a] (1.02-1.58)**
Colon or Rectal Cancer	5/336	0.89 (0.40-1.99)	0.87 (0.36-2.11)
Malignant Melanoma	7/335	0.32 (0.04-2.92)	0.37 (0.04-3.09)
Gallbladder Disease	74/324	1.02 (0.94-1.27)	1.06 (0.85-1.32)
Yellow Jaundice	5/327	1.04 (0.49-2.19)	1.13 (0.53-2.37)
Stroke	29/335	1.02 (0.79-1.35)	1.02 (0.79-1.35)
Heart Attack	31/332	0.98 (0.74-1.29)	1.00 (0.75-1.29)
Angina	21/335	0.92 (0.62-1.37)	0.90 (0.59-1.37)
High Blood Pressure	153/321	0.98 (0.85-1.10)	0.98 (0.87-1.13)
High Cholesterol	127/331	0.96 (0.83-1.08)	0.98 (0.87-1.13)
Rheumatoid arthritis	46/330	1.08 (0.89-1.35)	1.10 (0.90-1.37)
Other Arthritis	112/322	1.04 (0.90-1.20)	1.06 (0.92-1.22)
Chronic Bronchitis	34/322	0.98 (0.68-1.40)	1.00 (0.70-1.40)
Asthma	22/332	0.72 (0.41-1.32)	0.60 (0.27-1.32)
Anemia	41/311	0.64 (0.35-1.17)	0.70 (0.40-1.24)
Diabetes	44/334	1.00 (0.80-1.24)	1.08 (0.87-1.35)
Benign Thyroid Tumor	6/336	1.10 (0.62-1.99)	1.13 (0.63-2.03)
Hypothyroidism	51/331	0.96 (0.75-1.22)	0.98 (0.77-1.24)
Hyperthyroidism	15/330	1.06 (0.71-1.61)	1.08 (0.74-1.61)
Goiter/Enlarged Thyroid	12/331	0.98 (0.60-1.61)	1.04 (0.64-1.67)
Endometriosis	17/332	0.98 (0.52-1.84)	1.08 (0.58-2.03)
Ovarian Cysts/Fiboids	62/313	0.70 (0.44-1.10)	0.75 (0.48-1.17)
Uteran Fibroids	63/327	0.83 (0.59-1.17)	0.87 (0.62-1.22)
Infertility	40/288	1.58 (0.74-3.39)	**1.91[b] (0.90-4.02)**

*The hazard ratio presented represents the proportional increased hazard associated
with each additional 5 years (20 quarters) worked at EUC, calculated as exp(20*parameter estimate for one quarter increase).
[a]p-value<.05, [b]p-value<.10
Model 1: only disease and exposure variable.
Model 2: control for age at interview and bmi at 40 years old.

Table 12a - Multiple Logistic Regression Analyses Relating Total Quarters Worked at EUC with Symptoms Previously Related to Parkinson's Disease

			Continuous Quarters		Ordinal Grouping*	
Self-Reported Symptom	**%****		**Model 1**	**Model 2**	**Model 1**	**Model 2**
1. Do your arms or your legs ever shake?	6.5% (16/247)	OR*	0.99	0.99	0.89	0.86
		p-value	.4098	.4419	.5410	.5566
2. During the day do your muscles ever feel stiff and aching apart	28.5% (70/246)	OR*	1.00	1.00	0.97	1.00
from after exercise?		p-value	.3924	.4827	.8209	.9905
3. Do you find it difficult to get up out of a chair?	28.3% (70/247)	OR*	1.00	0.99	1.06	1.03
		p-value	.6381	.3691	.6735	.8336
4. Do you shuffle when you walk?	10.5% (26/247)	OR*	0.99	0.99	1.05	1.07
		p-value	.2836	.2758	.8013	.7354
5. Have you difficulty turning in bed?	9.3% (23/247)	OR*	1.00	0.99	0.96	0.95
		p-value	.6154	.4694	.8476	.8411
6. Has your writing become smaller?	5.7% (14/245)	OR*	1.00	0.99	1.37	1.26
		p-value	.8521	.5982	.1817	.3390
7. Do you find it difficult to open jars (other than new) or use a	16.2% (40/247)	OR*	1.00	1.00	**1.38**	**1.35**
		p-value	.5147	.6311	**.0330**	**.0520**
8. Do you lose your balance when turning?	8.1% (20/247)	OR*	1.00	1.00	1.13	1.14
		p-value	.7962	.7080	.5502	.5491
4+ symptoms	5.3% (13/247)	OR*	1.00	1.00	1.30	1.36
		p-value	.7400	.8474	.2796	.2265

Model 1: only symptom and exposure variable. Model 2: control for age at interview and BMI at 40 years old.
*The Odds Ratios represent the effect of a one-unit increase in continuous quarters worked at EUC or ordinal groupings (1-3, 4-11, 12-23, 24+ quarters)
**Excludes those with stroke and/or multiple sclerosis.

Table 12b - Multiple Logistic Regression Analyses Relating Total Quarters Worked at EUC with Symptoms Previously Related to Parkinson's Disease

			Continuous		Ordinal Grouping*	
Self-Reported Symptom	**%****		**Model 1**	**Model 2**	**Model 1**	**Model 2**
1. Do your arms or your legs ever shake?	8.5% (26/306)	OR*	0.98	0.98	0.77	0.75
		p-value	.2255	.2296	.1816	.1728
2. During the day do your muscles ever feel stiff and aching apart	37.6% (115/306)	OR*	1.00	1.00	1.06	1.08
from after exercise?		p-value	.9564	.7439	.5680	.4837
3. Do you find it difficult to get up out of a chair?	33.3% (102/306)	OR*	1.00	1.00	0.95	0.91
		p-value	.8137	.7979	.6413	.4254
4. Do you shuffle when you walk?	8.9% (27/305)	OR*	1.00	1.00	0.95	0.96
		p-value	.6796	.7148	.7749	.8122
5. Have you difficulty turning in bed?	13.4% (41/305)	OR*	1.00	1.01	0.98	1.01
		p-value	.6217	.4504	.9145	.9628
6. Has your writing become smaller?	9.9% (30/303)	OR*	0.98	0.98	**0.65**	**0.65**
		p-value	.1353	.1393	**.0330**	**.0328**
7. Do you find it difficult to open jars (other than new) or use a	30.4% (93/306)	OR*	1.00	1.00	0.92	0.92
screwdriver or fasten the small buttons on your shirt or blouse?		p-value	.4957	.5485	.4537	.4558
8. Do you lose your balance when turning?	17.1% (52/305)	OR*	1.00	1.00	0.88	0.90
		p-value	.7044	.8918	.3558	.4453
4+ symptoms	10.8% (33/306)	OR*	1.00	1.00	0.81	0.82
		p-value	.9102	.9944	.2166	.2589

Model 1: only symptom and exposure variable. Model 2: control for age at interview and BMI at 40 years old.
*The Odds Ratios represent the effect of a one-unit increase in continuous quarters worked at EUC or ordinal groupings (1-3, 4-11, 12-23, 24+ quarters)
**Excludes those with self-reported stroke and/or multiple sclerosis

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