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Final Report

The La Salle Electrical Utilities Company Morbidity Study I La Salle, Illinois

Prepared by

The Illinois Department of Public Health and
The University of Illinois at Chicago, School of Public Health

May 2002

ATSDR
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY
Atlanta, Georgia 30333

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ATLANTA, GEORGIA

FINAL REPORT

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

SUBMITTED BY

THE ILLINOIS DEPARTMENT OF PUBLIC HEALTH AND
THE UNIVERSITY OF ILLINOIS AT CHICAGO, SCHOOL OF PUBLIC HEALTH

May 2002

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The La Salle Electrical Utilities Company Morbidity Study I

May 2002

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16α-OHE_1	16 alpha-hydroxyestrone
2-OHE_1	2-hydroxyestrone
ANA	antinuclear antibody
ATSDR	Agency for Toxic Substances and Disease Registry
BMI	body mass index
BUN	blood urea nitrogen
BZ	Ballschmiter and Zell
CBC	complete blood count
CD	"cytotoxic t cells 3,4,5/6,8,20"
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CLIA	Clinical Laboratory Improvement Act
CRP	c-reactive protein
CV	coefficient of variation
DCC	dextran-coated charcoal
DEHP	di-(2)-ethylhexyl phthalate
DES	diethylstilbestrol
DHEAS	dehydroepiandrosterone sulfate
E2	estradiol
EDTA	ethylenediamine tetraacetic acid
ELISA	enzyme-linked immunosorbent assay
ER	estrogen receptor
EUC	La Salle Electrical Utilities Company
FSH	follicle-stimulating hormone
FTI	free thyroxine index
GGT	gamma glutamyltransferase
GI	gastrointestinal
HDL	high density lipoprotein
HDLC	high density lipoprotein cholesterol
HLA-D related	human leukocyte antigen - D related
IARC	International Agency for Research on Cancer
IDPH	Illinois Department of Public Health
IEPA	Illinois Environmental Protection Agency
IFCC	International Federation of Clinical Chemistry
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IQ	intelligence quotient
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LH	luteinizing hormone

LOD	limit of detection
LPT	lymphocyte phenotype
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean cell volume
NA	not applicable
NADH	nicotinamide adenine dinucleotide hydrogenase
NIH	National Institutes of Health
NK cells	natural killer cells
NPL	National Priorities List or Superfund
NSF	non-specific fluorescence
OR	odds ratio
OSHA	Occupational Safety and Health Administration
p	p-value
PCB	polychlorinated biphenyls
PCDD	polychlorinated diphenyl dioxins
PCDF	polychlorinated diphenyl furans
PEG	polyethyleneglycol
PNPP	p-nitro-phenylphosphate
ppb	parts per billion
QA	quality assurance
QC	quality control
r	correlation coefficient
RLU	relative light units
SGOT	serum glutamic oxaloacetic transaminase and/or AST
SGPT	serum glutamic pyruvic transaminase and/or ALT
SHBG	sex-hormone binding globulin
SMR	standardized mortality ratio
std	standard deviation
T	testosterone
T_3	triiodothyronine
T_4	thyroxine
TBG	thyroxine binding globulin
TCE	trichloroethylene
TEF	toxicity equivalency factor
TEQ	toxicity equivalency quotient
TSH	thyroid-stimulating hormone
UIC	University of Illinois at Chicago
USEPA	United States Environmental Protection Agency
USW	United Steelworkers of America
VLDL	very low density lipoprotein
VOC	volatile organic compound
WBC	white blood cell

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 two-part study consisted of a retrospective cohort mortality study of the entire EUC cohort and a cross-sectional morbidity study of 191 former employees and 26 community controls. The cohort mortality study is addressed in a separate report.

The morbidity study related measures of exposure with medical history, as well as serum lipids, liver enzymes, immune function, and endogenous hormone levels. This study included 191 former employees and 26 community residents who were not former employees. Measures of exposure included polychlorinated biphenyl (PCB) levels, lipid-adjusted PCB levels, total quarters (1/4 year) employed at the plant and a job hazard score which weighted quarters of employment by job-specific exposure level. PCB levels were significantly correlated with both total quarters worked ($r=0.71$) and hazard score ($r=0.70$). History of diabetes was significantly associated with selected measures of exposure in men and women after control for age and body mass index. Measurements of biologic effects were examined after control for confounders. Overall, this study found that exposure at the plant was significantly associated with increased triglycerides, decreased HDL-cholesterol, decreased sex-hormone binding globulin (SHBG) and decreased follicle-stimulating hormone (FSH) in women; as well as increased percent natural killer (NK) cells and decreased thyroid-stimulating hormone (TSH) in men. Associations with liver enzyme abnormalities and with most parameters of lipids, endocrine and immune function were inconsistent. Pregnancy outcomes were also compared for 115 pregnancies occurring during or after employment at the plant vs 248 pregnancies occurring without prior exposure at the plant. Results are based upon self-report and small numbers and therefore should be viewed with caution. No differences were observed in birth weight, gender, or miscarriage, but those women who worked at the plant before or during pregnancy had a higher percentage of children with learning difficulties, chronic respiratory illnesses, and ear infections than women without prior exposure. The findings in children should be viewed as preliminary and awaiting more thorough exploration in future studies.

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 over 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 was comprised of 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 cat-walk 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 was comprised of 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 which 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, both labor and management.

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 the 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 there was no un-exposed population within the plant. 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 (Figure 1). These areas were then ranked 1-4 based on the likelihood of airborne or dermal contact with PCB oil (Figure 2); 1 indicating areas of low potential exposure 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 (ug/g). Below the 12 inch level, PCB concentrations dropped off below the 0.2 ug/g detection limit. Immediate off-site residential soil PCB concentrations ranged from 0.2 to 2,600 ug/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 (ug TEQ/kg) and total furan concentrations ranged from 3.80 to 31.70 ug TEQ/kg. Dioxin concentrations in off-site residential soil samples ranged from 0.0002 to 0.0033 ug TEQ/kg with furan concentrations ranging from 0.0095 to 0.1138 ug 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 (ug/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[2]. 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. The current study was undertaken in response to community concerns. It included a retrospective cohort mortality study as well as a cross-sectional morbidity study 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. The cohort mortality study has been submitted under separate cover. This report includes the findings from the morbidity study.

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[3]. Human studies have been less consistent, with acute hepatotoxic effects[4] as well as less severe changes in liver[5-11] enzymes noted. Several reports have noted positive associations of serum PCBs with serum GGT[5-10] and serum SGOT [7,8,10,11] and negative associations with serum bilirubin [5] 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[7,8].

Urinary porphyrins have also been shown to be elevated in persons exposed to PCBs and to combinations of PCBs and related compounds[5,12-15], although results have not always been consistent. Effects of PCBs on porphyrins vary by type of congener[16], 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[16]. Interactive effects have also been found in animals[17] and humans[15] with greater effects seen in rats exposed to dioxins and PCBs than in those exposed to either alone[17] 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[15].

Lipids

PCBs and related compounds are associated with increased serum lipids in experimental animal models[3]. Human studies have also found consistent associations of serum PCBs with serum triglyceride levels[6-8,18-21]. Less consistent associations have been seen with serum cholesterol[6,9] and HDL cholesterol[8]. 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[6].

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 which differ by gender and Aroclor mixture[22]. Liver cancer has been noted more frequently in female than male rats and thyroid cancer was noted more in males[22]. 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[23] 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[24], 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[25], 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[26] 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[27,28] 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[29] 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[30] 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 which 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[31]. Kuratsune et al[32] followed the Yusho cohort and noted significant increased risks for total cancer and liver cancer in males. There have been several case control studies of breast cancer and PCB exposure in normal populations. Results were mixed, with only two[33,34] of five[33-37] studies suggesting a possible association between PCB exposure and risk of breast cancer. In a nested case-control study in Maryland, Rothman et al[38] 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.

Endocrine System

Animal data also suggest that PCBs affect thyroid function. The effects, however, may be congener and dose specific. In general, animals appear to be more sensitive to effects of PCBs on thyroid function than on steroid hormones. Aroclor 1254 reduced serum T_4 at doses 250 fold lower than the dose which altered testicular function[39]. PCBs act, in part, on testosterone through changes in its metabolism[40], although effects are not consistent[41-43]. Desauliniers et al[44] noted a paradoxical increase in T_4 at lower doses and 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 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[45]. The mechanisms by which PCBs are thought to reduce T_4 levels include increased glucuronidation, decreased binding to transthryretin, and increased conversion of T_4 to T_3 by 5'diodinases[46-49]. Human studies have, in general, found associations of

PCB exposure with alterations in thyroid function. Murai et al[50] 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[51-52]. One of the studies[51], however, showed lower T_4 levels at 2 weeks, with higher TSH levels at 2 weeks and 3 months, while the other study[52] found higher, not lower, T_4 levels at 1 week and 11 weeks, with higher TSH at 11 weeks. Nagayama et al[53] also found inverse associations of T_4 and positive associations of TSH with levels of breast milk dioxins and dioxin-like PCBs in breast fed babies. The concern over in utero effects of low level PCB exposure relates to known neurotoxic effects of hypothyroidism on developing organisms[54], with potential effects being delayed neurodevelopment, decreased intelligence, and hearing deficits.

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 estrogens[45, 55-56], although there is now some evidence that coplanar PCBs may also act as estrogens through increased binding to ER receptors[57] and that metabolites of selected ortho-substituted PCBs may act as antiestrogens[58]. Increased estrogenicity may be related to shortened menstrual cycles in women eating PCB-contaminated fish[59].

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 ug/kg body weight Aroclor 1254 was associated with increases in serum hemolytic complement activity, thymosin alpha 1 levels and natural killer cell activity in rhesus monkeys[60]. 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[61]. However, exposure to 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) of Aroclor 1254 in mallards failed to have any effect on antibody titres to sheep erythrocytes, natural killer cell activity, or lymphocyte mitogenesis[62]. In vitro studies, in addition, have failed to find effects of individual PCB congeners[63] or mixtures of PCBs with dioxins and furans[64] on various parameters of immune function. Human studies of immunotoxicity of PCB exposure are sparse. Two of the most severe acute exposures were in Yu-Cheng and Yusho after accidental ingestion of PCB and furan contaminated rice oil[65,66]. 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[66]. 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[65]. Nagayama et al[67] 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 breast fed 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[68].

Overall results in 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[69]. Tryphonas, in a comprehensive review[70] 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[71] 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[72] 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[60], 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[3], again, human data are lacking. Rylander et al[73] in an ecologic study of persons exposed to varying levels of PCBs in Sweden, noted lower birthweight and proportionately more girls with higher PCB exposure. Similarly, after the Seveso explosion relatively more girls were born[74]. A wide variety of growth and developmental abnormalities have been seen in children born after high exposure to PCBs and furans in Yu-Cheng[75,76]. 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 enter puberty, decreased penile length. Lower level in utero PCB exposure, however, has not produced consistent effects on neurodevelopment. The Jacobsons found reduced birth weight and reduced visual recognition memory[77] at seven months with relatively low level of in utero PCB exposure. At four years[78], these children had poorer short term memory function and, at ll years, lower IQs[79]. A similar North Carolina cohort[80] showed developmental delays in motor function during infancy, but no difference in visual recognition.

In a recent study from the Netherlands[81] higher levels of PCBs, PCDDs and PCDFs in breast milk were related with reduced neonatal neurological optimality and higher levels of planar PCBs were associated with higher incidence of hypotonia. Another study in the Netherlands[82], however, showed no neurological differences in the first half year of life. A recent study of Lake Ontario fish eaters[83] showed 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, motor clusters, birth weight or head circumference in children of mothers who were high vs low fish eaters.

Nervous System

There is an increasing amount of data suggesting that depletion of brain dopamine may be an additional effect of PCBs which could have large ramifications, not only in young, but also aging

populations. 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[84]. Age-related loss of the dopaminergic cells which project from the substantia nigra to the caudate-putamen is especially dramatic. As many as 60-70% of these cells are lost during the normal aging process[85]. Neurological deficits are not usually observed unless there is additional cell loss as the result of a disease process or toxic exposure[86]. 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 Parkinson's disease is unknown, but there is evidence to suggest that environmental and occupational exposures may play a role[87].

Laboratory studies in both rodents and primates have shown that exposure to PCBs during adulthood produces long-term reductions in brain dopamine content[88]. 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 which could interact with PCBs on health outcomes. Since TCE is rapidly metabolized there is no biomarker which can measure it 15 years or more after exposure. There is some, but not consistent, evidence, however, that it may affect endpoints which 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[89], 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[90]. The only cancer associated with low TCE exposure in another cohort of 1,670 persons was nonmelanotic skin cancer[91]. 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[92]. 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)[93]. 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)[94]. 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[95]. There were no elevated risks for respiratory cancer, liver cancer or leukemia. A recent study[30] 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[96,97].

Other Health Effects

Additional effects which have been noted include neurobehavioral disturbances, trigeminal neuralgia, and increased blink reflex latency[98], systemic lupus erythematosus[99], and cardiac malformations in children of mother exposed in utero[100-102]. 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 was significantly associated with dehydroepiandrosterone sulfate and negatively associated with SHBG, insulin and testosterone[103,104]. 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[4]. 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)[105]. 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)[106]. 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 effects, immunologic effects and neurodevelopment of children exposed in utero. The La Salle cohort offered a unique opportunity to explore long term hormonal and immunologic effects not previously explored of exposure to PCBs and related compounds years prior to examination. This group is unusual in the high percentage of women employees, the long lag period between exposure and examination and the existence, not only of solvents such as trichloroethylene, but also of 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 relationship between PCB exposure as estimated by serum PCB levels and work history, and biochemical markers of PCB effects on lipids, liver enzymes, thyroid function, immune function and steroid hormones. Specific hypotheses are that exposure to PCBs will be:

- Positively associated with triglycerides and cholesterol and negatively associated with HDL-cholesterol

- Positively associated with GGT, alkaline phosphatase, SGOT and SGPT and inversely associated with bilirubin

- Positively associated with TSH, LH, insulin and glucose and inversely associated with T_4, T_3, testosterone, free testosterone, SHBG and FSH

- Inversely associated with IgM, IgA, total T cells, and CD4 cells.

2. To examine the relationship between estimated PCB exposure and reproductive outcomes among female employees of EUC, including miscarriage, birth weight, and gestational age. It is hypothesized that PCB exposure will be associated with lower birth weight and increasing risks of miscarriage and premature births.

3. To more accurately characterize worker exposure to PCBs and other compounds at EUC.

MORBIDITY STUDY

This study is a cross-sectional examination of a sample of the cohort of workers previously employed at EUC. It included an in-depth survey of previous exposures, life style factors, and medical history, as well as blood and urine measurements of PCBs, hormones, lipids, immune function, liver enzymes and hormonal status.

A total of 217 persons (191 former employees and 26 local residents not employed at the plant) were included in the morbidity study. The study included an extensive interview concerning work exposures, medical and reproductive outcomes, and potential confounders, such as medication use, smoking and alcohol intake. Fasting blood for PCB levels, lipids, liver enzyme tests, endogenous hormones and immune function and spot urines for porphyrins were also collected. In addition, measurements of serum glucose, BUN, creatinine, electrolytes, phosphorus, total protein, albumin, globulin, uric acid, iron and CBC counts were made.

Recruitment

Study participants were recruited from persons previously employed at the plant and still living in the area. At the beginning of the morbidity study, the overall cohort had not been identified. Several lists of employees were used to identify 1,030 persons, including a list provided by the United Steelworkers of American (USW) in the early 1980s, previous employees who had attended community meetings during the late 1980s and 1990s, a list of persons who had participated in the pilot study, and a list derived from 400 payroll cards available to IDPH. A total of 251 persons were identified, located and approached for recruitment into the study and, of these, 191 agreed to participate in both the survey and collection of blood and urine specimens. Unexposed persons were recruited through random digit dialing from the Illinois Valley area and included persons who had never worked at the plant, were age 35 years and older, and had lived in the area for more than 15 years. If both persons from the household had worked at the plant only one was eligible to participate. A total of 26 of 146 eligible of the unexposed participated in both the survey and collection of blood and urine specimens.

Exposure Assessment

In the analyses for this study, exposure was assessed through four methods. The first was total number of years worked at the plant as determined from the social security records. The second was from the more detailed exposure and work history of the individuals evaluated by an industrial hygienist. The time of employment at each job in the plant, along with location of the job at the plant was determined for each individual. A hazard score was applied to each job category based upon location (1 to 4 based upon proximity to the "cook" department, 1 farthest and 4 closest). The hazard score was then calculated for each job worked by multiplying the hazard rank for that job by the number of months worked at that job and summed for an overall exposure score. The third exposure assessment was determined from total PCB concentration in serum received from the CDC. The fourth method was with the lipid-adjusted PCB concentration in serum. Lipid-adjusted PCB in ppb was assumed to be PCB levels in parts per billion (ppb)/(2.27xtotal cholesterol+triglycerides+62.3)x100,000. This formula has been used by the

CDC in the past and shown to correct for lipid differences due to variations in collection methods[107]. Overall, there was high agreement among the scores with a Spearman correlation of 0.71 between quarters worked and PCB level and a correlation of 0.70 between total hazard score and PCB level.

Collection and Processing of Data

Data collection for the biomarker study occurred in two phases, often, but not always on the same day during the summer of 1996. Heights and weights were taken at the time of the blood and urine collections. Participants were asked to donate blood and spot urine samples after fasting for 12 hours. Urines were first morning specimens collected at home the day of the examination. Each participant was sent a packet prior to the examination with instruction sheets about fasting, the importance of bringing current medication to the examination, and the urine collection. In the packet was a urine specimen cup containing a 100 mg vitamin C tablet to preserve the specimen for measurement of urine estrogen metabolites. A total of 8 tubes of blood were collected from each person (4 10 cc red stopper tubes, one 10 cc tiger stopper, two 5 ml EDTA lavender stopper, and one heparinized green stopper). Serum was separated from the red stopper. A total of 10 cc of serum was frozen and sent to Dr. Chatterton's laboratory for the steroid hormone analyses, one 5 cc EDTA lavender stopper tube and 10 cc of whole blood was refrigerated and sent to Smithkline Beecham daily for thyroid, chemistries and complete blood count (CBC) analyses, 15 cc of urine was frozen and sent Leon Bradlow's laboratory in New York for urine estrogens, and 10 cc of serum, one 5 cc EDTA lavender stopper and one 10 cc green stopper heparinized tube were sent to CDC for PCB and immune measurements. In addition, Angelique van Birgelen at USEPA analyzed total urine porphyrins from a separate aliquot of the urine samples. Split samples were also submitted blind to each laboratory for additional quality control.

Participants also answered questions concerning their exposures to PCBs and other chemicals at EUC, exposures to other sources of PCBs such as fish, previous incidence of selected medical conditions, reproductive history, history of congenital, developmental and endocrine problems in their children, medication use, and lifestyle factors which could serve as potential confounders, such as smoking and alcohol use. Questions were constructed to focus on those areas in which outcomes were predicted in the literature. The questionnaire was divided into two separate sections, exposure and medical history, and was administered at the study site by two separate surveyors trained by the University of Illinois Survey Research Laboratory and blinded as to the answers on the other half of the survey.

Following the survey, questionnaires were checked on site and participants were queried on site concerning any missing answers. After the field work was completed, questionnaires were again checked by study staff and participants were telephoned concerning any missing or unclear answers. Data was then coded and entered into the computer for data analysis. In addition, 10% of the surveys were re-entered as an additional quality control. Particular attention was given to the medication history, which was obtained in four separate places. Current medication use was determined at the time of the survey and blood drawing separately. In addition, survey participants were queried concerning medication use in the last 12 months, as well as within the last two weeks. A Microsoft Excel spreadsheet containing the reported medications used by each

study participant was reviewed by a registered pharmacist for drug name clarification. The data was then imported into an Microsoft Access database of drug information created by MediSource Lexicon. Using this database allowed for matching of drug names to specific identification codes that then allowed the joining of data sets. The drug names were linked to drug class information as well as active ingredient. Where gaps existed, due to differences in drug names (generic versus over the counter versus prescription name), a Registered Pharmacist reviewed the data set and indicated missing drug classification information or active ingredient information. A final spreadsheet was then exported from the joined data in the database containing ID number of the participant, all drugs reported by that participant and each drug's associated active ingredient and classification. For analyses in this report, medication was assumed to be that used within the two weeks prior to the blood draw.

Dioxin and Chlorinated Naphthalene Levels

Because of the possibility of multiple chemical exposures, a sub-study was performed to examine levels of polychlorinated dibenzo-p-dioxins (dioxins), dioxin-like PCBs, and polychlorinated naphthalenes in a subgroup of 10 former workers selected by their PCB level and years of exposure. Among those participating were three women who worked > 10 quarters only before 1952, 3 men and one woman who worked both before and after 1952, and 2 men and one woman with PCB levels >20 ppb who worked only after 1952. Results are still pending from CDC.

Notification of Participants

Participants were notified by first-class mail of all standard laboratory results as soon as they became available. Reports from Smithkline Beecham of CBC, chemistries, and thyroid results were available within a week. All results were reviewed by project physicians for abnormal results. Three individuals were subsequently called by the staff for discussion of results requiring more urgent attention. All results were sent within a few weeks to the participants and physicians if requested by the participant. The immune results were available about nine months later. These results were handled in a similar fashion. They were reviewed by Dr. Persky prior to being sent to participants and their physicians and the few results requiring more urgent attention communicated by telephone calls with Dr. Persky. PCB results were not available until April, 1998 and were sent within a few weeks to participants, as well as to physicians when requested.

PCB and Biomarker Analyses

Analyses of PCBs by CDC

Two separate methods were used by CDC to analyze for PCBs. A packed column gas chromatographic method using technical Aroclors 1242 and/or 1260 as standards and reported as total PCBs (as Aroclor 1242 and/or Aroclor 1260) and total PCBs (the sum of Aroclor 1242 and Aroclor 1260). A capillary gas chromatographic method provided concentration levels for 38 individual PCB congeners, the sum of which was reported as total PCBs. We compared the two analytical approaches using a subset of samples (n=45) in an attempt to determine the comparability of the two methods and found a Spearman correlation coefficient of 0.925 ($p<0.001$). This is indicative of a highly significant correlation between the two methods.

Subsequently, all remaining samples were analyzed for specific PCB congeners using the capillary gas chromatographic method described below. All total PCB levels presented in this report are the sum of the congeners: PCB #s 028, 052, 060, 066, 074, 099, 101, 105, 110, 118, 130, 137, 138, 146, 149, 153, 156, 157, 167, 170, 171, 172, 177, 178, 180, 183, 187, 189, 191, 193, 194, 195, 201, 203, 205, 206, 208, 209. Limits of detection for individual congeners are given in Table 1 of Appendix A. Values below the limits of detection were assumed to be zero.

All samples first underwent extraction and clean up. Serum was denatured with methanol and extracted with hexane:ethyl ether (1:1). The extracts were eluted through adsorption silica gel (deactivated to 3% with water) with hexane. Surrogates used to monitor the capillary analytical process were Ballschmiter and Zell (BZ)[108] #30 (2,4,6-trichlorobiphenyl), PCB congener BZ #204 (2,2',3,4,4',5,6,6'-octachlorobiphenyl) and hexabromobiphenyl (2,2',4,4',5,5'-hexabromobiphenyl). The recovery of surrogates was not used to correct analytical results reported for unknowns.

All specimens were analyzed by the capillary method using a 60mx0.25mm i.d. x 0.25um film thickness DB-5 and 60 m x 0.25 mm i.d. x 0.25 um film thickness DB-1701 (J&W Scientific, Folsom, CA). A Hewlett/Packard 5890 GC equipped with a HP7673 autosampler was used (Hewlett-Packard, Wilmington, DE). Individual congeners (38) (Ultra Scientific , North Kingston, RI) were used as standards with response factors being generated relative to the internal standard (1,2-dichloronaphthalene; Ultra Scientific, North Kingston, RI). Data were handled by a P-E Nelson Turbochrom Chromatography Data Station (The Perkin-Elmer Corporation, San Jose, CA). Serum pools, made from bovine serum that contained in vivo PCBs as Aroclor 1242 or Aroclor 1260 derived from goats fed these technical materials, were used as quality control materials[109]. These pools were characterized through repetitive analysis (n=20) for individual congeners setting mean, 95 and 99%, control limits. Pools analyzed with unknowns had to meet quality control limits before data were reported.

Analyses of CBCs and Chemistries by Smithkline Beecham

a. Complete Blood Counts (CBC) were determined by the Coulter Principle with employs electronic counting and sizing of particles. WBC differential analysis was based on simultaneous measurements of cell volume, high frequency conductivity and Laser Light Scatter. Hemoglobin, released by hemolysis to a stable cyanide-containing pigment, was measured by photometric absorbance.

Lipids and Liver Chemistries were determined on an Olympus AU 5200 by Smithkline Beecham. Methods for specific tests are described below:

b. Cholesterol: For this analysis, cholesterol esters present in the serum are hydrolyzed to free cholesterol and fatty acids by cholesterol esterase. The cholesterol is then oxidized by cholesterol oxidase to cholest-4-en-3-one with the simultaneous production of hydrogen peroxide, which in turn reacts with 4-aminoantipyrine to produce a chromophore. The resulting absorbance of the reaction mixture is measured bichomatically at 540/600 nm and is proportional to the cholesterol concentration in the serum.

c. Triglyceride: For this analysis triglyceride is hydrolyzed to free fatty acids and glycerol by lipase. The glycerol is then enzymatically phosphorylated and then oxidized with glycerol phosphate oxidase. The resultant hydrogen peroxide produced reacts with the chromogen 4-aminoantipyrine to give a chromophore which is measured bichromatically at 520/660 nm. The increase in absorbance of the reaction mixture is directly proportional to the triglyceride concentration in the serum.

d. HDL-Cholesterol: The automated methods for direct determination of HDL-cholesterol in serum uses (PEG)-modified enzymes, sulfated alpha-cyclodextrin, and dextrin sulfate. When cholesterol esterase and cholesterol oxidase enzymes are modified by PEG, they show selective catalytic activities toward lipoprotein fractions, with the reactivity increasing in the order LDL<VLDL=chylomicrons<HDL. In the presence of magnesium ions, sulfated alpha-cyclodextrin reduces the reactivity of cholesterol, especially in chylomicrons and very low density lipoprotein (VLDL) without the need for precipitation of lipoprotein aggregates. The results of this direct homogeneous enzymatic method correlate with those obtained by precipitation-based methods and also by an ultracentrifugation method.

e. GGT: This method is based on a modification of the method developed by Szaz[110] utilizing the water soluble substrate L-gamma-glutamyl-3-carboxyl-4nitroanilide. In the reaction, GGT catalyzes the transfer of the L-glutamyl group from the substrate to glycylglycine yielding 5-amino-2-nitrobenzoate. The resulting change in absorbance of 410/480 nm is directly proportional to the GGT activity in the sample.

f. SGOT: This method is based upon the reference method of the International Federation of Clinical Chemistry (IFCC) [111]. In this method SGOT catalyzes the transamination of aspartate and 2-oxoglutarate, forming L-glutamate and oxalacetate. The oxalacetate is then reduced to L-malate by malate dehydrogenase, while NADH is simultaneously converted to NAD^+. The decrease in absorbance due to the consumption of NADH is biochromatically measured at 340/380 nm and is directly proportional to the SGOT activity in the sample.

g. SGPT: SGPT is based upon the reference method recommended by IFCC[112]. SGPT transfers the amino group from L-alanine to 2-oxoglutarate to form pyruvate and glutamate. The pyruvate enters into a lactate dehydrogenase catalyzed reaction to produce lactate and NAD^+. The decrease in absorbance due to the consumption of NADH is biochromatically measured at 340/380 nm and is directly proportional to the SGPT activity in the sample.

h. Alkaline Phosphatase: This method is based on the method developed by Bowers and McComb[113] and has been formulated as recommended by the IFCC[114] Alkaline phosphatase activity is determined by measuring the rate of conversion of p-nitro-phenylphosphate (PNPP) in the presence of 2-amino-2-methyl-1-propanol at pH 10.4. The rate of change in absorbance due to the formation of pNP is measured bichromatically at 410/480 nm and is directly proportional to the alkaline phosphatase activity in the sample.

i. Lactate Dehydrogenase: This method employs a modification of the method originally described by Wacker[115]. L-lactate is catalyze to pyruvate by lactate dehydrogenase with the simultaneous reduction of NAD^+ to NADH. The resulting increase in the absorbance is measured bichromatically at 340/520 nm and is directly proportional to the lactate dehydrogenase activity in the sample.

j. Total Bilirubin: A stabilized diazonium salt, 3,5-dichlorophenyldiazonium terafluoroborate, reacts with bilirubin to form azobilirubin which absorbs maximally at 540/600 nm. Caffeine and a surfactant are used as reaction accelerators. The absorbance at 540/600 nm is proportional to the bilirubin concentration in the sample.

Analyses of Thyroid Hormones by Smithkline-Beecham

a. Total T_4 and Free Thyroxine Index (FTI): T_4 was determined through immunoassay, in which the control is combined with an enzyme-acceptor solution containing thyroxine antibody with a releasing agent, and an enzyme-donor solution containing enzyme substrate. The reagents are mixed and incubated at 37^0 C, and the rate of hydrolysis is measured at 450nm. The concentration of total T_4 in the patient specimens and controls are determined using a linear calibration curve[116]. FTI is calculated from T_3 uptake assay, in which ^{125}I-labeled T_3 is used as the tracer in the T_3 uptake assay to fill the unbound thyroxine binding globulin (TBG) sites. The remaining tracer is bound by albumin covalently immobilized to para-magnetic particles. Separation of bound from unbound tracer is by magnetic separation and decantation of the supernatant. The amount of T_3 radioactivity bound to the immobilized albumin binder varies inversely with the level of unbound TBG in the sample.

b. Total T_3: T_3 was determined by the Chiron Diagnostics ACS Chemiluminometric assay[117-119]. The Chiron Diagnostics ACS: 180 T_3 assay is a competitive immunoassay using direct chemiluminescent technology. T_3 in the patient sample competes with a T_3 analog, which is covalently coupled to paramagnetic particles in the Solid Phase for a limited amount of acridinium ester-labeled monoclonal mouse anti-T_3 antibody in the Lite Reagent. An inverse relationship exists between the amount of T_3 present in the patient sample and the amount of relative light units (RLUs) detected by the system.

c. TSH: TSH is based upon a double antibody immunochemiluminescent procedure. The lower limit of sensitivity of this third-generation assay is 0.003 mcIU/ml. The solid phase, a polystyrene bead enclosed within an Immulite test unit, is coated with a monoclonal antibody specific for TSH. While the participant serum sample and alkaline phosphatase-conjugated polyclonal antibody are incubated for approximately 60 minutes at 37^0 C with intermittent agitation, TSH in the sample is bound to an antibody sandwich complex. Unbound conjugate is then removed by a centrifugal wash, after which substrate is added and the test is incubated for a further 10 minutes, and read by chemiluminescence.

Analyses of Serum Hormones by Dr. Chatterton's Laboratory:

a. Sex hormone binding globulin (SHBG): The Delphia system was used for the assay of SHBG in serum. Materials were obtained from Wallac, Inc (Gaithersburg, MD). This is a solid phase two-site time-resolved fluoroimmunometric assay utilizing a sandwich technique. The intraassay and interassay coefficients of variation in recent assays[120] have been 6% and 8% respectively.

b. Dehydroepiandrosterone sulfate (DHEAS): DHEAS was measured in unextracted serum by radioimmunoassay as described previously[121]. Titrated tracers were obtained from Nuclear Corp, Boston, MA. Antiserum was obtained from ICN Biochemicals, Inc., Costa Mesa, CA: cross-reactions: 36% androsterone, 12% 5α-androstane-3,17-dione, 3% androst-4-ene-3,17-dione. Antibody-bound ligand was separated from unbound ligand by the addition of dextran-coated charcoal (DCC). The intraassay and interassay coefficients of variation were 4.6% and 10.9%.

c. Cortisol: Plasma cortisol was measured by a direct assay described previously[122]. Antiserum produced in this laboratory cross-reacts 17.4% with 11-deoxycortisol, 0.2% with cortisol phosphate, and <0.1% with dexamethasone, progesterone, estradiol, and testosterone. ^{3}H-cortisol for the assay was obtained from New England Nuclear Div., Boston, MA. Serum was diluted 1/100 in 0.1 M citrate buffer, pH 4.0, before assay. Antibody-bound ligand was separated by dextran-coated charcoal. The intraassay and interassay coefficients of variation for cortisol in recent assays were 8 and 11% respectively.

d. Follicle stimulating hormone (FSH): Antiserum and standards were obtained from the National Hormone and Pituitary Program of the NIH at Georgetown University Medical center. Iodinated FSH was obtained from Incstar Corp., Stillwater, MN. This is a double antibody method for measuring FSH in serum as described previously[123,124]. The intraassay and interassay coefficients of variation in recent assays were 2.55 and 3.5% respectively.

e. LH: LH was measured by a coated tube radioimmunoassay. Materials were obtained from Diagnostics Products Corporation, Los Angeles. In this assay LH is captured between monoclonal anti-LH antibodies immobilized on the inside surface of the polystyrene tube and the ^{125}labeled polyclonal anti-LH tracer. Results are expressed in mIU/ml in terms of the World Health Organization's First International Reference preparation of LH for immunoassay, 68/40 (1st IRP 68/40). The sensitivity is approximately 0.15 mIU/ml. Intra- and interassay coefficients of variation (CVs) average 3.0 and 7.1% respectively.

f. Testosterone: Testosterone was measured in serum by a coated tube assay obtained from Diagnostic Systems Laboratories, Webster, Texas. This assay employs ^{125}I-testosterone as the tracer. The antiserum cross-reacts <0.9% with androstenedione and androstenediol, and 5.8% with dihydrotestosterone. Intra- and interassay coefficients of variation in recent assays were 4.9% and 7.5%.

g. SHBG-Bound Testosterone: SHBG-bound testosterone was determined as described by Bonfrer et al[125] A 0.2 ml volume of serum diluted 1/8 with buffer is equilibrated with ^{3}H-estradiol overnight at 4^{0}C. A 0.10 ml suspension of a concavalin-A Sepharose conjugate (Pharmacia) is added to the serum. SHBG binds to the Con-A during a 30 min incubation period at room temperature. Testosterone in the serum maintains its equilibrium concentration with SHBG in the presence of endogenous factors such as other androgens, estrogens, and free fatty acids[126,127]. Separation of unbound ^{3}H testosterone from that bound to the Sepharose Con-A is achieved by centrifugation at 0^{0}C in order to minimize dissociation of bound estradiol. A pool of human serum is used as an internal control. The intra- and interassay CVs of recent assays were 8.2 and 10.4% respectively.

h. Estrogens:

Estradiol: The Delphia procedure was used for measurement of serum estradiol. Kits were obtained from Wallac, Inc., Gaithersburg, MD. This is a sold-phase competitive immunoassay that employs an europium labeled estradiol and time-resolved fluorescence measurement for quantification. The antiserum provided is highly specific for estradiol; only estrone (0.75%), 16-ketoestradiol (0.9%), estriol (0.4%), and estradiol 3-glucuronide (0.55%) compete significantly for estradiol. Intra- and interassay CVs for premenopausal women average 5.8% and 8.2% respectively.

SHBG-bound estradiol: SHBG-bound estradiol was determined as described by Bonfrer et al[125]. A 0.2 ml volume of serum diluted 1/8 with buffer is equilibrated with ^{3}H-estradiol overnight at 4^{0}C. A 0.10 ml suspension of a Conconavalin-A Sepharose conjugate (Pharmacia) is added to the serum. SHBG binds to the Con-A during a 30 min incubation period at room temperature. Estradiol in the serum maintains its equilibrium concentration with SHBG in the presence of endogenous factors such as other androgens, estrogens and free fatty acids[125,127]. Separation of unbound ^{3}H-estradiol from that bound to the Sepharose Con-A is achieved by centrifugation at 0^{0}C in order to minimize dissociation of bound estradiol. A pool of human serum is used as an internal control. The intra- and interassay CVs of the last 11 assays were 4.53 and 8.60%, respectively

i. Insulin: Plasma insulin was measured by an immunoradiometric assay (Diagnostic Products Corporation Los Angeles, CA) utilizing (^{125}) insulin. The antiserum cross-reacts 40% with proinsulin; no cross reactivity is detected with c-peptide or glucagon. The sensitivity of the assay is 1.2 uIU/ml. All samples were measured in one assay; the intraassay CV was 5.1%.

Quality control: External quality control standards were obtained from the American College of Pathologists. For internal quality control, a single batch of each of the quality control materials, antisera, and tracers for the assay of these analyses were prepared and reserved for all assays during the study. Blood specimens were analyzed by technicians unaware of the participants' exposure group and 5% of the samples were submitted as blind duplicates to the laboratory as an additional quality control. Serum was stored at -70^{0}C in 3-4 ml aliquots for measurement of additional hormones if subsequent literature indicates that they may be affected by PCB exposure.

Urine Analysis for 2-OHE_1 and 16α-OHE_1 by Dr. Bradlow's Laboratory

The assay was carried out by first aliquoting 10 microliters of urine, standards, or controls into microtubes. The standards contained both 2-OH estrone (E_1) and 16α-OHE_1 in concentrations of 1.25, 2.5, 5.0, 10, 20 and 40 ng/ml. 190 µl of glysulase in buffer (pH 4.1) was added to both samples, standards, and controls and incubated at room temperature for 2 hours. The samples were then neutralized with 200 µl of Tris buffer (0.1 M, pH 8.3). 2-OHE_1 and 16α-OHE_1 coupled to alkaline phosphatase were appropriately diluted with buffer and set aside. Two 96 well microtiter plates (with either 2-OHE_1 or 16α-OHE_1 antibody immobilized on the plate) were washed 5 times with PBS/0.05% Tween-20 buffer in order to hydrate the antibody. With a multichannel pipettor, 75 µl of sample or standards was aliquoted to the corresponding wells of the washed microtiter plates using the same set of pipette tips for the same sample on both plates. 2-OHE_1 or 16α-OHE_1 alkaline phosphatase conjugates (75 µl) was then aliquoted to the appropriate plate and each plate was incubated for three hours at room temperature. The plates were then washed 5 times with PBS/0.05% Tween 20 buffer. The color reagent (100 µl of paranitrophenyl phosphate in 1 M diethanolamine, 1 mg/ml) was added to each well. The assay plates were then read kinetically at 405nm.

The assay has been validated independently by gas chromatography-mass spectrometry. Using 16 urine samples from healthy premenopausal women, a correlation coefficient between the two methods of r^2 =0.8 was obtained for both 2-OHE_1 and 16α-OHE_1. Over the last few years Dr. Bradlow validated the ELISA in his laboratory. The monoclonal antibodies used for this assay were developed by Immuna Care and titer plates coated with the antibody were supplied by them for the assay. These antibodies proved to be highly specific. Cross reactivity of 16α-OHE_1 monoclonal antibody was 5.0% to 16α-OH DHEA, 0.05% to 16α-OH androstenedione, 0.08% to 4-OHE_1, 0.05% to 2-OHE_1, 0.1% to E_3, 0.01% to E_4, 0.12% to E_2, 0.01% to 2-OHE_2, and 0.15% to E_1. Cross reactivity of 2-OHE_1 monoclonal antibody was 100% to 2-OHE_2, 74% to 2-OHE_3, 0.5% to E_1, 0.5% to E_2, 0.15% to E_3, 0.1% to E_4, 0.5% to 16α-OHE_1, an 0.5% to 4-OHE_1. Within assay coefficients of variation (CVs) for women were 6.5% for 2-OHE_1, 9.1% for 16-OHE_1, and 7.8% for the ratio 2/16 OHE_1. Between assay CVs for women were 7.4% for 2-OHE_1, 12.8% for 16-OHE_1, and 8.1% for the ratio of 2/16-OHE_1. A series of stripped urine samples containing known concentrations of 2 and 16 α-OHE_1 were assayed to determined assay accuracy. Coefficients of variation ranged from 4.2% for 40ng/ml to 12.7% for 2.5 ng/ml for 2-OHE_1 and from 4.4% for 40 ng/ml to 12.8% for 2.5 ng/ml. Uniformity of antibody application to 96 well microtiter plates was determined by aliquoting female control urine using an 8-tip pipettor. Coefficients of variation among columns and rows varied from 5.7% to 11.1%.

Analyses of Immune Parameters by CDC

a. Immunoglobulins and C Reactive Protein (CRP): Immunoglobulins and CRP were measured by laser turbidometry, calibrated to the U.S. National Reference Preparation maintained at the Centers for Disease Control and Prevention[128].

b. ANA: Antinuclear antibodies (ANA) were measured by indirect immunofluorescence using HEP-2 cells (ImmunoConcepts, San Diego, CA). A test was positive if it was strongly positive at a dilution of 1/80 and possibly positive if it was weakly positive at a dilution of 1/80.

c. Lymphocyte Immunophenotyping: Lymphocyte phenotypes (LPT) were determined by methods generally consistent with established guidelines for clinical analysis and in compliance with regulations of the Clinical Laboratory Improvement Act (CLIA). Whole blood samples were prepared for analysis by a stain-and-lyse method using one FITC-labeled and one PE-labeled monoclonal antibody conjugate in each tube (Table 1). All samples were analyzed with a minimum of the first six tubes. In a subset of participants, additional tubes were included to measure lymphocytes bearing CD5 or HLA-DR.

Stained samples were analyzed on either an EPICS 741 or EPICS Elite flow cytometer (Coulter Corporation, Hialeah, FL) using the 4Cyte independent 8-bit 4-parameter acquisition system and Acmecyte customized software[129]. Both cytometers were calibrated using consistent target conditions for light scatter, fluorescence intensity, and spectral compensation parameters[130]. Data were acquired and archived in listmode files containing all information recorded during analysis[131].

The LPT percentages were determined by quadstat analysis of fluorescence distributions of events defined as lymphocytes by forward and right angle light scatter. A rectangular light scatter gate determined by the analyst during data acquisition was used to delineate lymphocytes. Quadstat cursor positions, used to dichotomize events into "negative" and "positive" populations, were determined by inspection for most phenotypes, which had clear separation between negative and positive distributions. For two phenotypes (the CD5 B-cell and the HLA-DR T-cell) that lacked a clear separation between positive and negative events, a non-specific fluorescence (NSF) control for each sample was run separately and used to determine the quadstat cutoff point.

Data from the quadstat analyses were imported into a relational database, where the final percentages for the various LPT were determined. The result reported for T-cells was obtained by discarding the minimum and maximum values of the individual CD3 results then averaging the remaining values. The result reported for B-cells was determined by the percentage of lymphocytes staining for CD20 but not for CD3 (or CD2 in samples analyzed in 1991).

Analyses of Porphyrins

Urinary porphyrin concentrations were determined according to the method of Schwartz et al[132], modified by Debets et al[133] using an acid-ethanol solution and 10ul of urine. Porphyrins were measured using a cytofluor multiwell plate reader (Milipore Co., Bedford, MA) as described before[16]. Urinary porphyrins were standardized to creatinine. Urinary creatinine concentrations were analyzed using the colorimetric determination assay kit from Sigma Chemical Co. (St. Louis, MO) and a 96-wells Thermomax ELISA plate reader (Molecular Devices Co., Menlo Park, CA)

Power of the Study

The power of our study to detect significant differences varies according to the specific endpoint measured. Below we present power calculations for several of our negative findings for one of our exposure variables, total PCBs. For analysis of disease outcomes, the power to detect a given odds ratio can be computed as a function of the sample size and the proportion with the disease outcome, where the odds ratio is the effect of an increase of one standard deviation in the continuous independent variable. For disease outcomes we coded total PCBs as an ordinal variable with four categories and estimated its effect as a continuous independent variable. Observed standard deviations of the ordinal score were used to transform effects of an increase of one level on the ordinal score into effects of an increase of one standard deviation for the purpose of power estimation. We have computed power to detect an odds ratio of 1.5 or more and 2.0 or more for each increase of one level in the ordinal variable, which we would consider to be a significant effect size in the population. Note that power is equivalent for odds ratios which go in a protective direction (1/(1.5) = .67 or less, 1/(2.0) = .5 or less). Continuous outcomes were analyzed using correlations. In the case of correlations, the power to detect a given correlation can be computed as a function of the sample size. We have computed the power of our sample to detect correlations of size .2 or more, .3 or more, and .4 or more (or equivalently -.2 or less, -.3 or less, -.4 or less), again effect sizes which we would consider to be significant in the population.

Effects of Total PCBs on Disease Outcomes:

	N	Outcome proportion	Power to Detect: OR>=1.5*	OR>=2.0*
Women:				
Cardiovascular Disease	148	.068	24%	55%
High blood pressure	144	.389	62%	95%
High fat/cholesterol	147	.333	46%	85%
Gallbladder disease	142	.190	46%	85%
Diabetes	149	.148	41%	81%
Hypothyroid	146	.116	34%	73%
Breast Cancer	149	.040	16%	37%
Men:				
Cardiovascular Disease	68	.103	21%	43%
High blood pressure	65	.385	43%	70%
High fat/cholesterol	68	.265	37%	66%
Gallbladder disease	63	.095	19%	38%

*average effect of each one unit increase across four ordinal categories.

Correlations with Total PCBs:

	N	Power to Detect: Corr >= .2	Corr >= .3	Corr >= .4
Women:				
GGT in u/l	146	68%	96%	100%
ALT in u/l	146	--	--	--
Total cholesterol	79	43%	77%	96%
LDL cholesterol	78	42%	77%	96%
TSH Ultra Sens.	82	44%	79%	97%
Triiodothyronine	79	43%	77%	96%
Total T_4	82	44%	79%	97%
Free T_4	82	--	--	--
Insulin	81	44%	79%	96%
CD4-cells	144	68%	96%	100%
NK-cells	144	--	--	--

	N	Power to Detect: Corr >= .2	Corr >= .3	Corr >= .4
Men:				
Bilirubin	64	36%	68%	92%
Alkaline Phosphatase	64	--	--	--
GGT in u/l	64	--	--	--
ALT in u/l	64	--	--	--
Triglycerides	52	30%	59%	85%
Total cholesterol	52	--	--	--
HDL cholesterol	52	--	--	--
LDL cholesterol	51	29%	58%	84%
Total chol / HDLC	52	30%	59%	85%
Triiodothyronine	53	30%	60%	86%
Total T_4	54	31%	61%	86%
Free T_4	54	--	--	--
Testosterone	54	--	--	--
Conc T bound to SHBG	54	--	--	--
Insulin	54	--	--	--
CD4-cells	62	35%	67%	91%

Statistical Analysis

Multiple regression models[134] were used to test the significance of the effect of each exposure measure, treated as an independent variable, on each morbidity outcome, treated as the dependent variable, adjusting for confounders as additional independent variables. The type of outcome determined choice of either multiple linear regression[135], for continuous biomarkers, or multiple logistic regression[136] for binary outcomes including diseases, indicators of biomarkers above or below an established threshold value, and pregnancy outcomes. Relevant confounders were determined separately for each outcome based on research literature. Details for each type of outcome are described below.

History of Selected Diseases

The numbers of persons with a previous history of having selected diseases of interest are presented in Table 2. Workers with disease beginning before the first date of employment were excluded from the analyses. For diseases with at least five cases, relationships between exposure and cumulative prevalence of the disease were analyzed using logistic regression for men and women separately with control for age and body mass index, with age and body mass index treated as continuous variables. Exposure variables were each grouped into four ordered categories. Odds ratios reflect an increase in one group (eg group 2 vs group 1, group 3 vs group 2, or group 4 vs group 3) across the four exposure categories: PCB (<3, 3-4.99,5-9.99, 10+ ppb); Lipid-adjusted PCB (<444, 444-730, 731-1499, 1500+ ppb); Quarters worked at EUC (0,1-4,5-24, 25+); Job hazard score (0,1-71,72-294,295+). The grouping for PCBs were chosen so that the lowest group was comparable to a non-exposed population, and the other three groups contain approximately equal numbers per group. Groupings for lipid PCBs were chosen to allow for similar distributions among groups (40%,20%,20%, and 20%). Groupings for quarters worked included non-EUC workers, those who worked less than one year and then the remaining participants in two group with approximately equal numbers in the groups. Groupings for job hazard score were defined as non-EUC workers, and then other participants in groups with approximately equal numbers. Tests of trend performed across groups tested for linear effects with significance levels set at $p<0.05$.

Biomarkers

A total of 220 persons participated in the study, of whom 217 (149 women and 68 men; 191 workers and 26 controls) completed both the blood drawing and questionnaire. Two different models are presented. The first model (Model 1) does not control for any confounders; the second controls for confounders previously associated with each selected endpoint. Correlations of age with PCBs and other exposure variables were high (0.22-0.49). Correlations of age with biomarkers were not high, and, in general, insignificant. Exceptions were SGOT in men ($r=-0.27$, $p=0.0331$), SHBG-bound estradiol in women ($r=0.21$, $p=0.0537$) and alkaline phosphatase in women ($r=0.23$, $p=0.006$).

For analyses of liver enzymes, persons taking glucocorticoid hormones, or oral contraceptives (women only), or who were missing information on confounding variables were excluded (Table 3). Confounders controlled in Model 2 included age, BMI, presence of diabetes, alcoholic

drinks/month, estrogen related medication (women only), and menopausal status (women only). For analyses of lipids and hormones, premenopausal women, women on estrogens, persons with diabetes, persons taking thyroid medication (men only) and persons on glucocorticoids, or anti-lipidemics (lipid analyses only), as well as those with missing data, were excluded. Confounders controlled in Model 2 for lipids and hormones included age, BMI, current smoking status, alcoholic drinks/month, and thyroid medication (women only). Analyses were also performed excluding women on thyroid medication. These results are not presented, however, since no appreciable difference was detected. For analyses of immune function, persons taking glucocorticoids or oral contraceptives (women only), as well as those with missing data, were excluded. Confounders controlled in Model 2 included age, BMI, diabetes, current smoking status, alcoholic drinks/month, estrogens (women only), and menopausal status (women only). For these analyses smoking was coded as a dichotomous variable for current smoking (yes/no) and alcohol was coded as none, $\leq$ 8/month, > 8/month for women and none, 1-16/month, and > 16/month for men.

Demographics of the total cohort included in the mortality study and for persons included in the morbidity study are given in Table 4. Participants in the morbidity study worked longer at EUC than those in the overall surviving cohort (28.4 vs 13.1 quarters) and were somewhat younger than those in the overall cohort (average age 60.7 vs 64.2 years).

Among those examined in the morbidity study, there were few differences between those included in the final analyses and the overall sample (Table 5). There were somewhat lower PCB and lipid PCB levels in those included in the lipid and hormone analyses. Women included in the lipid and hormone analyses were also somewhat older than the overall sample. Men included in the lipid and hormone analyses had somewhat higher ingestion of alcohol and cigarettes than the overall sample. There were no differences in BMI. PCB levels were strongly related to quarters worked in all groups.

Continuous biomarkers were tested for associations with four different continuous measures of exposure (current serum PCB level, lipid-adjusted PCB level, total number of quarters worked and total job score) using Spearman rank correlations. This non-parametric statistic was used because many of the observed distributions did not follow a normal or Gaussian distribution. Unadjusted and adjusted correlations were calculated. For biomarkers with established cutoff points defining normal ranges, and for whom there were sufficient numbers of defined as abnormal (eg at least two greater than the number of independent variables in each model), logistic regression was used to test for associations between exposure and abnormal biomarkers as the outcome. Resulting odds ratios reflect an increase of one group across the four experimental categories (ie group 2 vs group 1, group 3 vs group 2, or group 4 vs group 3). Crude and adjusted odds ratios were calculated. The association between quarters worked and continuous biomarkers was also examined by categorizing quarters worked into the non-EUC workers (zero quarters worked) and three tertiles of exposure where each quarter was assumed to be 3 months (1-4, 5-24, 25+). Hazard score was divided into four categories (0, 1-71, 72-294, 295+). Means of continuous biomarkers were computed within each of the four categories of

quarters worked to provide a further description of trends. Spearman correlations were computed using ranks of 1 through 4 corresponding to membership by category of quarters worked.

Reproductive Outcomes

A total of 149 women were surveyed, of whom 135 had been pregnant with a total of 440 pregnancies. The outcomes of the pregnancies, as well as the inclusion criteria for specific analyses are given in Table 6. Differences in outcomes between pregnancies with exposure prior to or during pregnancy vs pregnancies without exposure prior to or during the pregnancy were analyzed using logistic regression after control for age of the mother, smoking during pregnancy (yes/no), drinking during pregnancy (yes/no) and x-rays during pregnancy (yes/no). For outcomes in children, the above confounders were controlled, as well as gender of the child and whether the child was breast fed (yes/no).

RESULTS

Exposure

The relationships of PCB and lipid PCB with quarters worked and with job hazard score are given in Table 7. There were very high correlations among the respective variables ($r= 0.97$ between total PCB and lipid-adjusted PCB, $r= 0.95$ between quarters worked and job hazard score, $r=0.71$ between quarters worked and PCB level and $r=0.70$ between job hazard score and PCB level).

History of Selected Diseases

Relationships of exposure with history of selected diseases are presented in Tables 8-9. Each association tested is presented as an odds ratio (OR), for the increase in odds of disease associated with an increase in one group of exposure and corresponding p-value. The most consistent association was with diabetes, which was significantly associated with lipid PCB (OR=1.69, CI: 1.06-2.68), quarters worked (OR=3.03, CI: 1.37-6.67), and job hazard score (OR=3.26, CI: 1.53-6.96) in women and with PCB (OR=2.72, CI: 1.02-7.25) in men after control for confounders. The only other significant associations in women after control for age and BMI were for job hazard score with ovariectomy and abnormal vaginal bleeding, and with quarters worked and job hazard score for hypothyroidism. There were no other significant associations in men. One man gave a history of diagnosis of porphyria in 1990, several years after the plant closed. Levels of porphyrins in his urine from this study, however, were not elevated compared with those of other participants.

Biomarker Results

The results of the biomarker analyses are given in Tables 10-20. Men and women are presented separately. Biomarkers are treated as continuous variables and tested for associations with four measures of exposure: current total PCB level, current lipid-adjusted PCB levels, total number of quarters worked, total job hazard score as defined above. Each association tested is summarized

by the Spearman rank correlation and corresponding p-value. In addition, Tables 2-17 in Appendix A present mean values for each of the biomarkers by quarters worked at the plant and by total job score categorized into four levels. In general, the results for the categorized exposure are similar to those for continuous exposure measurements. Where slight differences existed they are noted in footnotes at the end of the section. Tables 18-20 present associations for exposure with clinically abnormal values. In these analyses, variables with the number of abnormal < 2 more than independent variables in the model are not presented because the small numbers did not allow for adequate statistical testing.

Liver Enzyme Tests

Associations of total PCB levels with liver enzyme tests were examined after control for confounders and are presented in Tables 10-11. In women, alkaline phosphatase was associated with all exposure variables (Table 10), but only the association with PCB (r=0.18) remained significant after control for confounders. Bilirubin was significantly and inversely associated with quarters worked after control for confounders (r=-0.17). In men SGOT was associated with PCB (r=0.28) and lipid PCB (r=0.26) levels (Table 11), but only after control for confounders. There were no significant associations of any of the indices of exposure with GGT, LDH, SGPT or urinary porphyrins in men or women.

Lipids

Associations of total PCB level with serum lipids are presented in Tables 12-13. PCB and lipid PCB levels were significantly and positively associated with triglycerides after control for confounders in women (r=0.45 for PCB and r=0.31 for lipid PCB) (Table 12), but not in men. HDL cholesterol was inversely associated with PCB (r=-0.29) and lipid PCB level (r=-0.25) in women, but not in men, after adjustment for confounders. When lipids were dichotomized into normal and abnormal according to Smithkline Beecham normal values (Table 19), high triglyceride was significantly associated in women with PCB (adjusted OR=3.11, CI:1.41-6.83), but not with lipid PCB, years worked or job hazard score, after control for confounders. There were no significant associations with total cholesterol or LDL cholesterol when analyzed continuously[a].

Endogenous Hormones

Associations of total PCB levels with endogenous hormones were examined with partial Spearman correlation analysis and are presented in Tables 14-15. Among women, SHBG was significantly and inversely associated with all measures of exposure and after adjustment for confounders (Table 14). Adjusted correlations varied from -0.34-0.46. Similarly, percent SHBG-bound estradiol was inversely related to quarters worked and job hazard score after control for confounders[b] (r=-0.32 and -0.29 respectively). FSH was inversely associated with PCB, lipid PCB, and quarters worked after control for confounders, with adjusted correlations varying from -0.25 to -0.29. Dehydroepiandrosterone (DHEA) sulfate was inversely associated with PCB, lipid-adjusted PCB, and job hazard score but the association was not significant after adjustment for age. T_3 uptake was inversely associated with PCB (r=-0.23) after control for confounders. Urine 2-OH estrone was significantly and inversely related to PCB, lipid PCB, and hazard score after control for confounders[c], with adjusted correlations varying from -0.23 to -0.30. Since 16-

OH was also inversely related to measures of exposure, although not significantly, there were no associations of the ratio of 2-OH/16-OH with any of the exposure variables. There were no significant associations of PCB with T_4, FTI, T_3, cortisol, insulin[d], LH, or testosterone.

Among men, TSH was inversely and significantly associated with all measures of exposure (Table 15). It remained significant after control for confounders for all measures of exposure. Adjusted correlations varied from -0.35 to -0.37. The percent of testosterone bound to SHBG but not the concentration of testosterone bound to SHBG, was positively associated with job hazard score, but not with the other exposure variables. The relationship was not significant after control for confounders. T_3 uptake was inversely associated with all exposure variables after control for confounders (r=-0.29 to -0.43) There were no other associations of any exposure with any endogenous hormone analyzed continuously in men[e].

The only hormonally related variable for which there were clinically normal values was glucose, which, in non-diabetics, was elevated in too few people to allow for adequate analysis. In addition to the above variables the relationships of exposure with serum glucose were examined both including and excluding diabetics and after control for potential confounders (not shown in the Tables). Excluding diabetics there was no significant relationship of any of the exposure variables with serum glucose after control for confounders. Including diabetics, there was no relationship of any exposure with serum glucose in men. In women, there were significant and borderline significant associations of glucose with PCB and lipid PCB levels, respectively, but not with quarters worked or job hazard score, after control for confounders[f].

Immune Function

Associations of total PCB levels with parameters of immune function are given in Tables 16-17. In women, IgA was significantly associated with PCBs and with lipid-adjusted PCBs, but only the association with PCBs was significant after control for confounders (r=0.18) (Table 16). C reactive protein (CRP) was significantly associated with all measures of exposure, but only the association with PCBs remained significant after control for confounders (r=0.17). There were no significant associations with WBC, IgM, NK cells, IgG, total T or B cells, or T cell subtypes. In men, percent NK cells was significantly associated with all measures of exposure and after control for confounders (Table 17). Adjusted correlations varied from 0.38 to 0.41. Percent T-cells was significantly and inversely associated with PCBs and lipid-adjusted PCB levels before and after control for confounders (adjusted r=-0.38 and -0.41, respectively), but not with quarters worked or job hazard score. Percent monocytes was significantly associated with lipid PCB after adjustment for confounders (r=0.29). Percent B cells and CD5 B cells were inversely associated with quarters worked, but these were not significant after control for confounders. When analyses were done dichotomizing biomarkers with defined normal values as > normal vs normal, high CRP was significantly associated in women with PCBs (OR=2.16, CI:1.34-3.49) and with lipid-adjusted PCBs (OR=1.94, CI: 1.22-3.07), but not with years worked or job hazard score after control for confounders (Table 19).

Other Measured Variables

In addition to the above biomarkers which were primary hypotheses of the study, several other parameters were measured, including BUN, creatinine, sodium, potassium, chloride, magnesium, inorganic phosphate, total protein, albumin, globulin, uric acid, total iron, iron binding capacity, hemoglobin, hematocrit, and platelet count. These comprised a large number of analyses for which several might be expected to yield associations by chance alone. Findings should therefore be viewed as preliminary and hypothesis generating, rather than hypothesis testing. They are not presented in tables in the text, but are included in Tables 18-19 in Appendix A and discussed briefly below.

In women, there were significant inverse association for serum iron with quarters worked and job hazard score after control for confounders. There were also positive associations of platelet count with job hazard score after control for other variables. Serum albumin was significantly associated with all measures of exposure in women, but the associations were no longer significant after control for confounders. Chloride in women was also significantly and inversely associated with PCBs and lipid PCBs after control for confounders. Sodium was significantly and inversely associated and total protein and globulin were positively associated with PCB after control for confounders. There were no significant associations between any of these biomarkers with any measure of exposure in men after control for potential confounders.

[a]. LDL cholesterol in men was significantly associated with quarters worked after control for confounders when the quarters worked was categorized, but not when it was analyzed continuously.

[b]. SHBG bound estradiol in women was significantly related to job hazard score when the hazard score was analyzed continuously, but not when it was categorized.

[c]. 2-OH estrone was significantly associated with quarters worked, when quarters worked was treated as a categorized variable, but not when it was treated as a continuous variable.

[d]. Insulin in women was significantly associated with quarters worked when quarters worked was categorized, but not when it was analyzed continuously.

[e]. Cortisol in men was significantly associated with quarters worked after control for confounders when quarters worked was categorized, but not when it was analyzed continuously.

[f]. Glucose was significantly associated with quarters worked analyzed as a categorized, but not when it was analyzed as a continuous variable, when diabetics were included.

Quality Control - Split Samples

Results of the analyses for split samples are given in Tables 21-23. Coefficients of Variation (CVs), defined as 100 times the ratio of the standard deviation divided by the mean, were performed on duplicate samples. The coefficients of variation for immune, lipid, and liver enzymes were generally less $\leq$ 10% (Tables 21,23). The only exceptions were percent and

absolute number of basophils, for which the CV were 33.4% and 33.3%, CD5 B-cells for which the CV was 11.5%, IgM for which the CV was 10.7% and CRP for which the CV was 10.5%. CVs for endogenous hormones were more variable. CVs for thyroid function, % estradiol bound to SHBG, and % testosterone bound to SHBG were $\leq$ 10.4%. CVs for SHBG, DHEAS, cortisol, estradiol, insulin, FSH, concentration of estradiol bound to SHBG, concentration of LH and testosterone varied from 13.8 to 32.5%.

Reproductive Outcomes

Results of the analyses of reproductive outcomes are presented in Tables 24-25. There was a significantly higher percent of children born after or before their due dates (not on time delivery) in women exposed before or during pregnancy, but no significant differences between the groups in percent with low birth weight, spontaneous abortions, miscarriage, premature delivery or having a male vs female child (Table 24). Women exposed prior to or during the pregnancy were also significantly more likely to have children with chronic respiratory illnesses, frequent ear infections, developmental problems, hyperactivity, reversal of letters, and learning problems (Table 25). Timing of exposure was unrelated to the children having birth defects, hearing problems, hormonal problems, cancer, thyroid problems, abnormal uterus, abnormal ovaries, female infertility, endometriosis or undescended testes (Table 25). There were too few children (<5) with the following problems to allow for analysis of diabetes, immune problems, abnormal head size at birth, hyperthyroidism, hypothyroidism, abnormality of the vagina, abnormality of the cervix, or two undescended testes.

DISCUSSION

Results from the morbidity study are consistent with previous work suggesting that PCBs may be estrogenic. These effects have been seen with a variety of congeners[55,57,58,137], although, in general they have been more frequent with ortho-substituted congeners[45,55]. It has been hypothesized that PCBs act either through increased numbers or sensitization of estrogen receptors at the tissue level[45,137]. PCBs have also been shown to increase in vitro hydroxylation to the more estrogenic 16-OH vs 2-OH estrone[138]. In this study we found inverse associations of measures of exposure with both 2-OH and 16-OH estrone metabolites, although only the association with 2-OH estrone was significant. We did not find an altered ratio of 16/2 OH estrone in this group of postmenopausal women, unlike the previous report[138]. This study does lend support to an additional mechanism by which PCBs may be acting: through decreased SHBG and, therefore, greater availability of estrogens for action at the tissue level. The hypothesis is supported by the decreases in SHBG and percent bound estradiol in postmenopausal women, as well as the decreases in FSH consistent with peripheral estrogenization. It is also consistent with the elevations in triglycerides and biliary cancer[139], both of which are thought to be estrogen related.

Several of the findings in this study suggest an effect of PCB exposure in women on diabetes and its associated hormonal alterations, including increased history of diabetes, as well as increased triglycerides, decreased SHBG and decreased HDL. These associations are consistent and strong. However, there were no consistent associations with serum glucose and insulin levels and the

associations with HDL were not as striking as those with triglycerides and SHBG. In our cohort mortality study (submitted under separate cover) we found decreased, not increased, mortality from diabetes in men, and no association in women. Previous literature on the effects of PCBs on diabetes is limited. An occupational study did not find significant associations of serum PCBs with glucose[6], although it did not examine specific hormone levels. Dioxin exposure has been associated with increased prevalence of diabetes in the Ranch Hand Study[140], as well as suggestions of increased diabetes mortality after the Seveso accident[141] and in the IARC International Cohort Study[142].

The multiple exposures at the plant preclude delineation of specific effects. There is no previous data on endocrine effects of chlorinated naphthalenes. There is one study of TCE exposure[103,104] in which exposure was associated with decreased SHBG as in this study. In that study insulin levels were altered in those with increased TCE exposure, although there was no significant difference in diagnosed diabetes. In that report workers were exposed at the time of data collection. TCE is metabolized quickly, unlike PCBs, and it is difficult to postulate TCE induced hormonal effects in this cohort >15 years after exposure. Previous studies have suggested that the estrogenic effects of PCBs are specific to non-dioxin like congeners. Unfortunately, the number of women from whom we will have dioxin and dioxin like PCB measurements will be too few to examine this hypothesis.

A wide variety of animal and human studies have shown effects of PCBs on the thyroid gland. Animal studies, in general, have shown decreased T_4 and FTI secondary to decreased binding to transthyretin and increased glucuronidation, with less consistent alterations in T_3 or TSH[46-49,143]. These changes have been most striking with dioxin-like congeners, in rodent models, and in female animals[44]. Studies in humans have not been consistent, with increased T_4 seen after a mixed furan and PCB exposure[50] and decreased T_4 in pregnant women[51,52] and their infants[51] associated with ingestion of fish containing dioxins and PCBs. The failure of most animal studies to find an increase in TSH in association with consistently decreased T_4 levels suggests that there may be decreased sensitivity of the pituitary to changes in peripheral thyroid levels. Data from this cohort, with strong inverse associations of TSH seen with all measures of exposure and no difference in T_4 or FTI in men suggests that TSH may be appropriately compensating for a tendency to increased peripheral hormone levels. The history of hypothyroidism in women, however, suggests an opposite effect, although without changes in levels of T_4, FTI or T_3, the clinical significance of the finding is unclear.

This study does not provide support for an effect of PCBs on testosterone levels. Data on effects of PCBs on serum androgens in animals has been inconclusive[39-43] and studies of testosterone levels in human studies are notably lacking. Studies of effects of dioxins in animals[144,145] are more consistent and suggest that the decreases seen in serum testosterone may be due to increased metabolism through enzyme induction and/or increased synthesis of androgens. Support for the animal dioxin data is found in at least one[146] of two[146,147] studies in humans.

This study does show a strong association between PCB exposure and serum triglyceride levels. This is consistent with previous literature[6-8,18-21], which has found stronger associations with

triglycerides than cholesterol or HDL-cholesterol. The fact that the relationship persisted after lipid adjustment suggests that it is not completely secondary to partitioning of the PCBs in blood fat particles.

Especially in light of the consistent effects on SHBG and triglycerides in this study, the lack of consistent associations with most measures of liver enzymes is notable. Most of the previous cohorts which have found a greater number of persons exposed to PCBs with abnormal tests for liver enzymes have examined participants at the time of, or shortly after, exposure[5-11]. Our failure to see consistent associations in this cohort >15 years after exposure, therefore, may not be inconsistent with previous findings. The inverse association between bilirubin and quarters worked in women has been noted previously[6] and is thought to be secondary to induction of glucuronyl transferases.

In general, this study fails to find associations of exposures with most measures of immune function examined. In men there was a consistent association of percent natural killer cells with all measures of exposure and in women there were associations of IgA and CRP levels with PCB, but not with other exposure variables, after control for confounders. The significance of these findings is not clear. Previous studies have shown increases[60], decreases[68] and no change[63] in natural killer cells with PCB exposure. Similarly, exposure to PCBs and furans have shown transient decreases, not increases in IgA[65,66]. To the best of our knowledge CRP has not been examined in relation to PCB exposure. It is considered a general measure of inflammation and has been associated with acute illness, as well as coronary heart disease[148] and selected cancers[149]. It has been suggested that measures of cell subtypes and antibodies may not be an adequate measure of immune response and that more functional measures, such as primary immune response, are more appropriate for investigations of immunotoxic effects[70]. In addition, it is possible that complex mixtures of different PCB congeners and other exposures, such as chlorinated naphthalenes, may have effects on the immune system which cannot be predicted given the lack of previous immune data.

The significant inverse associations of serum iron and positive associations of platelet count, as well as the inverse association of sodium and chloride in women should be viewed with caution. These findings were not replicated in men, were inconsistent among different exposure categories, and, in general, not supported by previous literature. Studies relating iron to PCBs, TCE or chlorinated naphthalenes, however, are lacking. The results, while intriguing, must await future investigations.

This study does not lend support to an effect of in utero exposure to PCBs on birth weight, miscarriage or sex ratio. The data, unfortunately, were not sufficient to examine detailed effects on gestational age. Previous literature has not been consistent, with some[73,75-76,77] but not all[150] studies seeing decreases in birth weight after inutero PCB exposure. This study does suggest that exposure may be associated with infections and learning deficits. These findings are consistent with previous literature[76-79], but the results presented in this report are based on small numbers and need to be replicated in other studies.

Strengths and Limitations

The major strength of this study is the in-depth examination of the relationships of PCB exposure with endocrine and immune biomarkers, many of which have not been previously explored in human studies. Several of the findings, such as the consistent decrease in SHBG levels in highly exposed postmenopausal women, are new and suggest intriguing explanations of the previously noted estrogenic effects of PCBs.

An important limitation to the study, however, is the difficulty in measuring exposure and potential confounders in a plant which has not only been closed, but destroyed many years prior to the study. Exposure at the plant appears to have been widespread. Some jobs, such as cook, were probably associated with greater exposure, but this is difficult to quantify. Serum PCB levels allow for a very rough approximation of PCB exposure, but the lack of measurement of dioxin-like PCBs and the variability in biologic half life renders characterization of individual congener exposures a formidable undertaking. To date, we have no measure of chlorinated naphthalene or TCE exposure, although our pilot study may suggest that measurements of serum chlorinated naphthalenes might be feasible in the future.

This study also suffers from the limitation of any retrospective cohort morbidity study in which only a relatively small sample of former employees are examined. Thus, the numbers of quarters worked by participants in the biomarker study was higher than worked by the overall cohort. By examining only the survivors, the study could miss those persons most affected by the exposure and the results, therefore, could be biased towards the null hypothesis. Conversely, those volunteering for the study might be former employees with medical problems which they relate to their exposure, with resulting participant and recall biases towards positive associations. This is more of a potential problem for self-reported medical and reproductive endpoints than for objective measures of biomarkers.

Self-reported data without verification from medical records could also potentially bias the results towards the null hypothesis through poor precision of endpoint measurements. Examination of associations of PCB levels with objective measurements of biomarkers, again, should minimize these difficulties. PCBs have fairly long half lives, averaging 2-6 years[151,152], with substantial variation among individual congeners. Thus, precise estimation of original exposure may be difficult, although serum measurements should give an approximation of current exposure and should therefore be useful for a cross-sectional analysis of current exposure with biomarkers.

The large number of analyses in this study could yield positive findings by chance alone. The strength and consistency of several of the findings, such as associations of exposure with triglycerides, SHBG, and FSH in women and association of exposure with NK cells and TSH in men, as well as cohorence with animal data and biologic plausibility, suggest that they may reflect real biologic differences.

Despite the above limitations, this study is a unique opportunity to examine a wide variety of health effects in a cohort which was exposed to an unusual mixture of contaminants. Our data suggests that these exposures, either alone or in combination, may have been associated with previously unreported effects on the endocrine system. Further studies should help in the delineation of the specific exposure effects, as well as the influence of these exposures on the long term development of the children of parents exposed at the plant.

CONCLUSIONS

1. There was a significant positive association of serum triglycerides with PCB and lipid-adjusted PCB levels and an inverse association of HDL with PCB and lipid PCB levels in women, but not men, after control for confounders. This finding is consistent with previous literature. There were no other associations of exposure with serum lipids in women and no consistent associations in men.

2. Alkaline phosphatase was significantly associated with PCB level and bilirubin was inversely associated with quarters worked in women. SGOT was significantly associated with PCB and lipid PCB levels in men. These associations, while not consistent, are similar to those seen in previous studies.

3. Analyses of endogenous hormones revealed significant inverse associations of TSH with all measures of exposure after control for confounders in men, but not in women. SHBG was inversely associated with all measures of exposure, and percent estradiol bound to SHBG was inversely associated with quarters worked and hazard score, after adjustment for confounders among women, but not men. FSH was inversely associated with PCB, lipid PCB and quarters worked in women after control for confounders. There were significant associations of history of diabetes with selected measures of exposure in men and in women. With diabetics included in the analysis there was a significant association of serum glucose with PCBs after control for confounders in women, but not in men. This is one of the first studies to examine the effects of occupational PCB exposure on endogenous hormones. Previous studies have noted associations of PCB exposure with decreased levels of thyroxine and variable effects on TSH. The inverse associations with SHBG, FSH and percent SHBG-bound estradiol are new and consistent with other studies suggesting that non-coplanar PCBs may be estrogenic.

4. Analyses of immune function revealed a variety of findings which were not necessarily supported by previous literature. In women IgA and CRP were significantly associated with PCB after control for confounders. In men, percent NK cells were significantly associated with all measures of exposure, and percent T cells was inversely associated with PCB and lipid PCB, after control for confounders.

5. There were no significant associations between exposure and birth weight, gender of the child, miscarriage or premature delivery. Women exposed before or during pregnancy, however, were significantly more likely to have children with chronic respiratory infections, frequent ear infections, developmental problems, hyperactivity, reversal of letters or learning problems. These findings,

while consistent with previous literature, were based on self report and small numbers and must therefore be viewed with caution.

RECOMMENDATIONS

1. Examine the association of specific PCB congeners and groups of congeners with measures of lipids, liver enzymes, immune function, and endogenous hormones

2. Survey the entire surviving cohort with a more in-depth telephone interview targeting specific health parameters in former workers as well as more detailed histories of their children

3. Obtain more precise measures of exposure through measurement of serum PCBs and, if possible, chlorinated naphthalenes in a larger number of former EUC workers.

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TABLES

Table 1 - Summary of Reagents Used to Determine Lymphocyte Phenotypes

Tube number	Conjugate Specificity		Conjugate Source		Lymphocyte Phenotypes Identified
	FITC	PE	FITC	PE	
1	CD45	CD14	BDIS	BDIS	Gating Control for All Lymphocytes
2	CD4	CD8	Coulter	Coulter	CD4 and CD8 Lymphocytes
3	CD8	CD3	Coulter	BDIS	All T-cells; Cytotoxic T-cells
4	CD3	CD4	BDIS	Coulter	All T-cells; Helper T-cells
5	CD3	CD20	BDIS	Coulter	All T-cells; All B-cells
6	CD3	CD56/ CD16	BDIS	BDIS	All T-cells; Natural Killer (NK) Cells
7	CD19	-	Sigma	-	All B-cells; NSB for CD5
8	CD19	CD5	Sigma	BDIS	All B-cells; CD5 B-cells
9	-	CD3	-	BDIS	All T-cells; NSB for HLA-Dr
10	HLA-Dr	CD3	Sigma	BDIS	All T-cells; HLA-DR T-cells

Reagent Sources: Becton-Dickinson Immunocytometry Systems (BDIS), San Jose, CA; Coulter Corporation, Hialeah, FL; Sigma Immunochemicals, St. Louis, MO.

Table 2 - Number of Participants by Self-Reported Disease

Self-Reported Disease	Women (disease n* / total n*)	Men (disease n* / total n*)
Anemia	28/136	2/67
Angina	5/149	5/68
Benign Thyroid Tumor	4/148	3/68
Blood in Urine	7/147	6/68
Breast Cancer	6/149	na
Breast Fibroids	26/145	na
Cardiovascular Disease	10/148	7/68
Chronic Bronchitis	14/141	5/67
Chronic Sinusitis	23/140	2/66
Cirrhosis	1/149	0/67
Collagen Disease	1/149	0/68
Diabetes	22/149	7/68
Eczema	12/145	2/68
Endometriosis	11/147	na
Gallbladder Disease	27/142	6/63
Goiter	3/147	0/68
Gout	6/148	11/68
Hashimotos	0/149	0/68
High Blood Pressure	56/144	25/65
High Fat/Cholesterol	49/147	18/68
Hyperthyroidism	3/147	0/68
Hypothyroidism	17/146	2/68
Hysterectomy	58/137	na
Immune System Problem	6/149	2/68
Liver Cancer	0/149	0/68
Liver Disease/Hepatitis	3/149	1/65
Low White Blood Cell	4/148	1/68
Multiple Sclerosis	1/149	0/68
Neuritis	10/149	3/67
Osteoporosis	16/149	na
Ovarian Cysts/Fibroids	38/132	na
Ovary Removed	56/137	na
Parkinsons	3/149	0/68
Poor Leg Circulation	17/145	7/67
Porphyria	0/149	1/68
Protein in Urine	3/149	2/68
Psoriasis	6/147	4/67
Pulmonary/Respiratory	12/147	4/65
Raynaud's Disease	0/149	0/68
Rheumatoid Arthritis	14/147	4/67
Scleroderma	1/149	0/68
Shingles	17/149	4/68
Thyroid Cancer	2/148	0/68

Self-Reported Disease	Women (disease n* / total n*)	Men (disease n* / total n*)
Uterine Fibroids	35/144	na
Vaginal Bleeding	34/143	na
Vaginal Pain	12/143	na
Yellow Jaundice	5/142	2/65

*Excludes former workers who got disease/condition prior to working at EUC.

Table 3 - Number of Participants and Exclusions in Each Biomarker-Specific Analysis

Liver & Immune Analysis

Women (n=146)

- 146 out of the 149 women interviewed were included in the final liver & immune analyses. Women on steroid and oral contraceptive medications were excluded. The 3 exclusions were as follows:
  - 1 on steroids
  - 2 on oral contraceptives

Men (n=64)

- 64 out of the 68 men who participated in both the blood draw and questionnaire were included in the final liver & immune analyses. Men on steroid medications were excluded. The 4 exclusions were as follows:
  - 3 on steroids
  - 1 with missing alcohol information

Lipid Analysis

Post-Menopausal Women (n=79)

- Of the 149 women who participated in both the blood draw and questionnaire, 125 were post-menopausal (only post-menopausal women included in this analysis).
- 79 out of the 125 post-menopausal women were included in the final lipid analysis. Post-menopausal women who were diabetic or on estrogen-related, steroid, or anti-lipidemic medications were excluded. The 46 exclusions were as follows:
  - 23 on estrogens
  - 1 on steroids
  - 3 on anti-lipidemics
  - 1 on estrogen & anti-lipidemics
  - 9 medicated diabetics
  - 4 non-medicated diabetics
  - 3 medicated diabetic on anti-lipidemics
  - 1 medicated diabetic on estrogen & anti-lipidemics
  - 1 non-medicated diabetic on anti-lipidemics

Men (n=52)

- 52 out of the 68 men who participated in both the blood draw and questionnaire were included in the final lipid analysis. Men who were diabetic or who were on steroid, thyroid, or anti-lipidemic medications were excluded. The 16 exclusions were as follows:
  - 3 on steroids
  - 2 on anti-lipidemics
  - 2 on thyroid medication
  - 1 on thyroid & anti-lipidemic medications
  - 1 on anti-lipidemics with missing alcoholic drink info.
  - 4 medicated diabetics
  - 3 non-medicated diabetics

Hormone Analysis

Post-Menopausal Women (n=82)

- Of the 149 women who participated in both the blood draw and questionnaire, 125 were post-menopausal. (only post-menopausal women included in this analysis).
- 82 out of the 125 post-menopausal women were included in the final hormone analysis. Post-menopausal women who were diabetic or who were on steroid or estrogen-related medications were excluded. The 43 exclusions were as follows:

24 on estrogens
1 on steroids
12 medicated diabetics
5 non-medicated diabetics
3 medicated diabetic on anti-lipidemics
1 medicated diabetic on estrogen

Men (n=54)

- 54 out of the 68 men who participated in both the blood draw and questionnaire were included in the final hormone analysis. Men who were diabetic or who were on steroid or thyroid medications were excluded. The 14 exclusions were as follows:

3 on steroids
3 on thyroid medication
4 medicated diabetics
3 non-medicated diabetics
1 with missing alcohol information

Table 4 - Comparison of Mean Quarters Worked and Age in Total Cohort and Interviewed Cohort

Category	Total Cohort*		Interviewed Cohort**	
	n	Mean (std)	n	Mean (std)
Quarters Worked				
total	3305	13.1 (24.4)	188	28.4 (30.5)
women	1652	14.6 (25.6)	125	26.9 (27.5)
men	1216	14.5 (26.0)	63	31.2 (35.7)
Age in 1996				
total	1788	64.2 (12.3)	188	60.7 (12.3)
women	1038	68.0 (12.3)	125	62.3 (12.3)
men	750	59.0 (10.1)	63	57.5 (11.7)

*mean age includes only total cohort known to be alive in 1996.
**excludes controls and workers first employed at EUC in 1978 or later.

Table 5 - Exposure and Demographic Variables by Gender and Biomarker-Specific Analyses

Category	Women			
	All Women n=149	Lipid Analysis n=79	Hormone Analysis n=82	Liver & Immune n=146
	Mean (range)	Mean (range)	Mean (range)	Mean (range)
Total PCB in ppb	6.2 (0.4-33.0)	6.0 (1.0-22.6)	6.0 (1.0-22.6)	6.3 (0.4-33.0)
Lipid Adjusted PCB in ppb	833.1 (86.6-4446.0)	800.2 (132.7-3225.3)	798.5 (132.7-3225.3)	842.8 (86.6-4446.0)
Quarters Worked	26 (0-145)	29 (0-145)	29 (0-145)	27 (0-145)
Job Exposure Score	228 (0-1296)	241 (0-1296)	240 (0-1296)	229 (0-1296)
Age	61 (35-83)	65 (35-83)	66 (35-83)	61 (35-83)
BMI	29 (17-58)	29 (19-58)	28 (17-58)	29 (17-58)
Mean PCB by Quarters worked				
Controls (0 quarters)	2.6 (0.4-8.0)	2.5 (1.0-8.0)	2.7 (1.0-8.0)	2.7 (0.4-8.0)
1-4 quarters	2.9 (0.4-17.6)	3.8 (1.3-17.6)	3.8 (1.3-17.6)	2.9 (0.4-17.6)
5-24 quarters	3.8 (0.6-10.9)	4.1 (1.5-10.9)	4.1 (1.5-10.9)	3.8 (0.6-10.9)
25+ quarters	10.8 (1.5-33.0)	10.0 (1.7-22.6)	10.0 (1.7-22.6)	11.0 (1.5-33.0)
	%	%	%	%
% Smoking	19%	20%	21%	19%
% Drinking by Group:				
0 drinks/month	53%	49%	50%	53%
1-8 drinks/month	31%	37%	37%	31%
9+ drinks/month	16%	14%	13%	16%

Category	Men			
	All Men n=68	Lipid Analysis n=52	Hormone Analysis n=54	Liver & Immune n=64
	Mean (range)	Mean (range)	Mean (range)	Mean (range)
Total PCB in ppb	12.2 (0.3-109.8)	8.9 (0.3-64.8)	8.7 (0.3-64.8)	11.5 (0.3-109.8)
Lipid Adjusted PCB in ppb	1797.5 (42.9-15486.6)	1291.0 (42.9-9606.8)	1261.3 (42.9-9606.8)	1680.1 (42.9-15486.6)
Quarters Worked	32 (0-135)	27 (0-135)	26 (0-135)	30 (0-135)
Job Exposure Score	272 (0-1266)	221 (0-1266)	217 (0-1266)	254 (0-1266)
Age	57 (37-86)	55 (37-82)	55 (37-82)	57 (37-86)
BMI	29 (20-54)	29 (20-54)	29 (20-54)	30 (20-54)
Mean PCB by Quarters worked				
Controls (0 quarters)	1.9 (1.4-2.3)	1.9 (1.4-2.2)	1.9 (1.4-2.2)	1.9 (1.4-2.2)
1-4 quarters	2.4 (0.3-5.3)	2.5 (0.3-5.3)	2.5 (0.3-5.3)	2.4 (0.3-5.3)
5-24 quarters	6.8 (0.5-36.5)	5.2 (0.5-11.6)	5.0 (0.5-11.6)	6.8 (0.5-36.5)
25+ quarters	23.9 (3.2-109.8)	18.0 (3.2-64.8)	18.0 (3.2-64.8)	22.8 (3.2-109.8)
	%	%	%	%
% Smoking	18%	23%	22%	19%
% Drinking by Group:				
0 drinks/month	33%	27%	26%	31%
1-16 drinks/month	36%	39%	41%	38%
17+ drinks/month	31%	35%	33%	31%

Table 6 - Female Reproductive - Number of Participants

Number of Participants

149 women were surveyed
- 135 reported having ever been pregnant
- 14 reported having never been pregnant

135 women had **440 pregnancies**, with outcomes as follows:
- 398 live births
- 7 still births
- 1 induced abortion
- 16 spontaneous abortions
- 15 miscarriages
- 2 tubal or ectopic pregnancies
- 1 molar pregnancy

Outcomes of Pregnancy Analysis

363 (115 exposed/248 unexposed) out of the 398 live births were included in the "Outcomes of Pregnancy" Analysis (except for miscarriage). The 35 exclusions were as follows:
- 8 exposed to DES
- 2 exposed to German Measles or Rubella
- 16 with unknown DES exposure
- 2 with missing alcoholic exposure
- 3 with missing x-ray exposure
- 3 with unknown DES and unknown alcohol exposure
- 1 with unknown DES and unknown x-ray exposure

Adverse Outcomes in Children Analysis

361 (115 exposed/246 unexposed) out of the 398 live births were included in the Adverse Outcomes in Children Analysis. The 37 exclusions were as follows:
- 35 exclusions listed above
- 2 with missing breast feeding exposure

Spontaneous Abortion and Miscarriage Analysis

- spontaneous abortion analysis, n=379 (outcome: 16 spontaneous abortions/ 363 live births. exposure: 117 exposed/262 unexposed). The 61 exclusions were as follows:
  - 35 live birth exclusions listed above
  - 24 pregnancies not resulting in either spontaneous abortion or live birth
- miscarriage analysis , n=376 (outcome: 13 miscarriages/363 live births; exposure: 118 exposed/258 unexposed). The 64 exclusions were as follows:
  - 35 live birth exclusions listed above
  - 27 pregnancies not resulting in either miscarriage or live birth
  - 2 miscarriages with all confounding information missing
- spontaneous abortion/miscarriage analysis, n=392 (outcome: 29 outcome/ 363 live births; exposure: 120 exposed/272 unexposed) The 48 exclusions were as follows:
  - 35 live birth exclusions listed above
  - 11 pregnancies not resulting in spontaneous abortion, miscarriage, or live birth
  - 2 miscarriages with all confounding information missing

Table 7 - Spearman Correlations Between Exposure Variables

Category	Total n=217	Women n=149	Men n=68
	r (p-value)	r (p-value)	r (p-value)
Total PCB and Lipid-Adjusted PCB	.97 (.0001)	.97 (.0001)	.98 (.0001)
Total PCB and Quarters Worked	.71 (.0001)	.68 (.0001)	.77 (.0001)
Total PCB and Job Score	.70 (.0001)	.67 (.0001)	.75 (.0001)
Lipid-Adjusted PCB and Quarters Worked	.70 (.0001)	.69 (.0001)	.77 (.0001)
Lipid-Adjusted PCB and Job Score	.70 (.0001)	.68 (.0001)	.77 (0001)
Quarters Worked and Job Score	.95 (.0001)	.95 (.0001)	.95 (.0001)

Table 8 - Relationship of EUC Exposure with Self-Reported Disease-Women

Self-Reported Disease	n		PCB		Lipid PCB		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Yellow Jaundice	5/142	OR*	1.2	1.1	0.9	0.8	1.3	1.2	1.3	1.2
		p-value	.6941	.8888	.8548	.6286	.5942	.7058	.6150	.7504
Cardiovascular Disease	10/148	OR*	1.3	1.0	1.2	0.9	1.3	1.0	1.3	1.0
		p-value	.3778	.8808	.5278	.6818	.4546	.9539	.4817	.8851
Angina	5/149	OR*	2.4	1.9	2.1	1.5	2.4	1.7	1.6	1.0
		p-value	.0642	.2278	.0867	.3539	.1932	.4333	.3548	.9390
High Blood Pressure	56/144	OR*	1.4	1.1	1.3	0.9	1.5	1.2	1.4	1.1
		p-value	.0192	.5531	.1275	.7442	.0252	.3583	.0521	.7537
High Fat/Cholesterol	49/147	OR*	1.3	1.2	1.1	1.0	1.1	1.0	1.2	1.1
		p-value	.0859	.4202	.3781	.9249	.6545	.9136	.3082	.6772
Poor Leg Circulation	17/145	OR*	1.2	1.1	1.2	1.1	1.4	1.3	1.2	1.1
		p-value	.4922	.7756	.5174	.8077	.2425	.3769	.4424	.6964
Rheumatoid Arthritis	14/147	OR*	1.6	1.3	1.5	1.2	1.8	1.5	1.5	1.3
		p-value	.0734	.3571	.0918	.4327	.0840	.2064	.1697	.4172
Pulminary/Respiratory	12/147	OR*	1.3	1.0	1.2	1.0	1.6	1.3	1.6	1.3
		p-value	.3314	.9858	.4228	.8722	.1972	.4189	.1708	.4002
Chronic Bronchitis	14/141	OR*	1.0	0.9	1.1	0.9	1.1	1.1	1.3	1.2
		p-value	.9554	.6705	.8381	.8047	.6333	.8418	.3498	.5200
Neuritis	10/149	OR*	1.3	1.0	1.4	1.2	1.7	1.5	1.8	1.6
		p-value	.3743	.8888	.2306	.6190	.1791	.3430	.1052	.2399
Gallbladder Disease	27/142	OR*	1.2	1.0	1.2	1.0	1.2	1.0	1.2	1.0
		p-value	.2785	.9904	.3531	.8797	.4479	.8922	.3415	.9708
Psoriasis	6/147	OR*	1.0	0.9	0.9	0.8	0.9	0.8	0.8	0.7
		p-value	.9333	.7096	.8450	.6326	.7631	.6179	.5173	.3704
Eczema	12/145	OR*	0.7	0.7	0.7	0.6	0.7	0.7	0.6	0.6
		p-value	.2508	.2641	.1993	.2026	.1262	.1367	.0803	.0814
Shingles	17/149	OR*	1.5	1.6	1.5	1.6	1.1	1.1	1.1	1.0
		p-value	.0816	.0870	.0542	.0569	.6774	.7492	.8260	.9255

Self-Reported Disease	n		PCB		Lipid PCB		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Blood in Urine	7/147	OR*	0.8	0.9	0.8	0.8	0.6	0.6	0.7	0.7
		p-value	.6426	.7256	.6001	.6725	.1796	.2106	.3693	.4314
Gout	6/148	OR*	1.7	1.6	1.8	1.8	1.0	0.9	1.1	1.0
		p-value	.1703	.2529	.1144	.1708	.9228	.8777	.8653	.9189
Anemia	28/136	OR*	0.8	0.9	0.9	0.9	0.7	0.8	0.7	0.7
		p-value	.3662	.6802	.4068	.7256	.0881	.2842	.0403	.1592
Immune System Problem	6/149	OR*	1.1	0.9	1.1	0.9	0.7	0.7	0.7	0.6
		p-value	.7563	.8331	.8485	.7016	.2800	.2465	.2964	.2754
Diabetes	22/149	OR*	1.4	1.5	1.6	1.7	2.6	3.0	2.6	3.3
		p-value	.0756	.0720	.0249	.0270	.0044	.0060	.0017	.0023
Hypothyroidism	17/146	OR*	1.0	0.7	1.0	0.7	0.7	0.6	0.8	0.6
		p-value	.9309	.1806	.9278	.2003	.1959	.0280	.3162	.0455
Chronic Sinusitis	23/140	OR*	0.9	0.9	0.9	0.8	0.9	0.8	0.9	0.9
		p-value	.7727	.6247	.4858	.3518	.4457	.3353	.6735	.5388
Osteroporosis	16/149	OR*	1.4	1.1	1.2	1.0	1.4	1.2	1.1	0.9
		p-value	.1682	.6547	.3859	.9093	.2439	.5621	.6720	.7454
Endometriosis	11/147	OR*	0.6	0.9	0.7	0.9	0.9	1.1	0.8	1.0
		p-value	.1653	.6721	.1966	.6787	.6739	.8760	.4718	.9707
Abnormal Vaginal Bleeding	34/143	OR*	0.7	0.8	0.7	0.8	0.7	0.7	0.6	0.6
		p-value	.0519	.2318	.0585	.2297	.0261	.0677	.0075	.0237
Vaginal Pain	12/143	OR*	0.9	1.0	0.9	1.1	0.8	0.8	0.7	0.7
		p-value	.6997	.8942	.8042	.7998	.3428	.4477	.2238	.3152
Ovarian Cysts/Fibroids	38/132	OR*	0.7	0.9	0.7	1.0	0.8	1.0	0.8	1.0
		p-value	.0346	.6807	.0885	.9414	.2926	.9025	.2833	.8278
One or Both Ovaries Removed	56/137	OR*	1.0	1.1	1.0	1.1	1.3	1.4	1.5	1.8
		p-value	.8494	.7417	.9603	.5695	.1330	.0497	.0191	.0035

Self-Reported Disease	n		PCB		Lipid PCB		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Hysterectomy	58/137	OR*	1.1	1.2	1.1	1.2	1.1	1.2	1.3	1.4
		p-value	.6429	.3313	.6184	.3322	.4629	.2934	.1370	.0559
Uteran Fibroids	35/144	OR*	1.1	1.2	1.0	1.1	0.8	0.8	0.9	1.0
		p-value	.6698	.4607	.9585	.7540	.1954	.2990	.6737	.9216
Breast Fibroids	26/145	OR*	0.8	0.8	0.8	0.8	0.7	0.7	0.7	0.8
		p-value	.2008	.3731	.2520	.4531	.0522	.1315	.1007	.2430
Breast Cancer	6/149	OR*	1.0	0.7	1.2	0.9	1.0	0.8	1.1	0.8
		p-value	.9500	.3494	.5771	.8117	.9230	.6714	.8814	.6740

Model 1: only disease and exposure variable.

Model 2: control for age and BMI.

*The Odds Ratios represent the effect of a one-unit increase in the following ordinal exposure variables: 1) PCB (<3, 3-4.99, 5-9.99, 10+ ppb), 2) Lipid adjusted PCB (<444, 444-730, 731-1499, 1500+ppb), 3) Quarters worked at EUC (0, 1-4, 5-24, 25+), and 4) Job score (0, 1-71, 72-294, 295+).

Table 9 - Relationship of EUC Exposure with Self-Reported Disease-Men

Self-Reported Disease	n		PCB		Lipid PCB		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Cardiovascular Disease	7/68	OR*	1.0	1.0	1.1	1.0	1.4	1.3	1.9	1.6
		p-value	.9004	.9171	.7892	.9664	.4438	.5901	.1778	.3501
Angina	5/68	OR*	0.6	0.5	0.6	0.5	0.6	0.6	0.8	0.6
		p-value	.2123	.1261	.2268	.1171	.3338	.2109	.6146	.2854
High Blood Pressure	25/65	OR*	1.1	1.1	1.1	1.1	1.1	1.2	1.2	1.2
		p-value	.5362	.6791	.6711	.8059	.6079	.5867	.5311	.5779
High Fat/Cholesterol	18/68	OR*	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
		p-value	.7837	.6876	.7835	.7105	.7224	.7025	.6554	.6057
Poor Leg Circulation	7/67	OR*	1.1	1.0	1.1	1.0	1.0	0.9	1.1	1.0
		p-value	.8614	.9071	.7471	.9604	1.0000	.8689	.8466	.9186
Chronic Bronchitis	5/67	OR*	2.8	3.0	3.3	4.8	2.5	2.8	2.3	3.7
		p-value	.0855	.0743	.0611	.0517	.1818	.1579	.1589	.0924
Gallbladder Disease	6/63	OR*	0.7	0.7	0.6	0.6	0.4	0.4	0.5	0.5
		p-value	.4047	.3752	.2678	.2335	.0550	.0532	.1397	.1153
Blood in Urine	6/68	OR*	0.9	0.7	0.8	0.7	0.7	0.6	0.7	0.6
		p-value	.7140	.3406	.5415	.3068	.3679	.2660	.4137	.2880
Gout	11/68	OR*	1.1	1.1	1.0	1.1	1.6	1.9	1.1	1.5
		p-value	.7281	.7256	.9968	.8560	.2055	.1325	.7052	.3565
Diabetes	7/68	OR*	2.6	2.7	2.1	2.2	1.8	1.8	1.9	2.2
		p-value	.0452	.0454	.0747	.0737	.2503	.2553	.1778	.1630

Model 1: only disease and exposure variable. Model 2: control for age and BMI.,

*The Odds Ratios represent the effect of a one-unit increase in the following ordinal exposure variables: 1) PCB (<3, 3-4.99, 5-9.99, 10+ ppb), 2) Lipid adjusted PCB (<444, 444-730, 731-1499, 1500+ppb), 3) Quarters worked at EUC (0, 1-4, 5-24, 25+), and 4) Job score (0, 1-71, 72-294, 295+).

Table 10 - Relationship of EUC Exposure with Liver Biomarkers-Women*

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Bilirubin in mg/dl	146	r	.06	.02	.08	.04	-.12	-.17	-.11	-.16
		p-value	.4369	.8095	.3313	.6517	.1517	.0450	.2032	.0583
Alkaline Phosphatase in u/l	146	r	.27	.18	.21	.12	.21	.12	.24	.14
		p-value	.0012	.0304	.0119	.1669	.0112	.1531	.0038	.1051
GGT in u/l	146	r	.13	.07	.07	.00	.08	-.00	.11	.01
		p-value	.1257	.4228	.3831	.9638	.3464	.9882	.2007	.9235
AST (SGOT) in u/l	146	r	.02	-.00	.01	-.01	-.09	-.12	-.06	-.09
		p-value	.7967	.9848	.8817	.9385	.2596	.1617	.4552	.2686
ALT (SGPT) in u/l	146	r	-.02	.03	-.05	-.00	-.06	-.05	-.01	-.02
		p-value	.8141	.6818	.5337	.9693	.4448	.5213	.9272	.8461
Total LDH in u/l	140	r	.05	-.06	.05	-.04	.05	-.05	.05	-.06
		p-value	.5670	.5148	.5504	.6391	.5924	.6044	.5639	.5271
Porphyrin/Creatinine in ug/mg	144	r	.01	-.10	.01	-.09	-.03	-.09	-.05	-.11
		p-value	.9205	.2655	.9401	.2709	.7492	.2752	.5716	.1977

*This sample of women excludes those on steroid and oral contraceptive medications.

Model 1: Spearman rank correlation between continuous biomarker and continuous exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and continuous exposure variables when the effect of the following confounders are removed: age, BMI, diabetes, alcoholic drinks/month, estrogen related meds, and menopausal status.

Table 11 - Relationship of EUC Exposure with Liver Biomarkers-Men*

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Bilirubin in mg/dl	64	r	.08	.16	.08	.15	.09	.16	.07	.14
		p-value	.5442	.2240	.5543	.2460	.4787	.2270	.5659	.2878
Alkaline Phosphatase in u/l	64	r	-.07	-.06	-.09	-.08	-.11	-.11	-.07	-.08
		p-value	.5705	.6298	.4987	.5308	.3775	.4108	.5562	.5281
GGT in u/l	64	r	.12	.18	.10	.16	.01	.09	.01	.10
		p-value	.3301	.1664	.4196	.2091	.9265	.4837	.9609	.4386
AST (SGOT) in u/l	**64**	**r**	.12	**.28**	.10	**.26**	-.16	-.03	-.12	.02
		p-value	.3379	**.0283**	.4205	**.0452**	.2187	.8283	.3426	.8559
ALT (SGPT) in u/l	64	r	-.01	.22	-.02	.21	-.18	.04	-.16	.11
		p-value	.9488	.0914	.8712	.1069	.1442	.7744	.2150	.4076
Total LDH in u/l	60	r	-.03	-.03	-.07	-.08	-.08	-.12	-.08	-.14
		p-value	.8177	.8207	.6077	.5463	.5321	.3843	.5585	.3203
Porphyrin/Creatinine in ug/mg	64	r	.01	-.07	.05	-.03	.03	-.10	.10	-.04
		p-value	.9517	.6213	.7068	.8309	.8167	.4689	.4188	.7668

*This sample of men excludes those on steroid medications.

Model 1: Spearman rank correlation between continuous biomarker and continuous exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and continuous exposure variables when the effect of the following confounders are removed: age, BMI, diabetes, and alcoholic drinks/month.

Table 12 - Relationship of EUC Exposure with Lipid Biomarkers-Women*

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Triglycerides in mg/dl	79	r	.39	.45	.25	.31	.20	.21	.20	.20
		p-value	.0004	.0001	.0240	.0078	.0770	.0747	.0770	.0833
Total Cholesterol in mg/dl	79	r	-.01	.06	-.18	-.12	-.05	-.04	-.06	-.05
		p-value	.9227	.6345	.1159	.2910	.6744	.7557	.6190	.6497
HDL Cholesterol in mg/dl	79	r	-.23	-.29	-.18	-.25	-.14	-.12	-.09	-.07
		p-value	.0431	.0124	.1067	.0288	.2323	.2900	.4284	.5383
LDL Cholesterol in mg/dl	78	r	-.08	-.01	-.22	-.15	-.04	-.04	-.05	-.06
		p-value	.4735	.9546	.0549	.2024	.7639	.7600	.6510	.5997
Total Chol/HDLC	79	r	.19	.31	.06	.17	.05	.05	.01	-.00
		p-value	.0951	.0080	.6241	.1500	.6677	.6950	.9120	.9768

*This sample of women excludes pre-menopausal women, diabetics and those on estrogen-related, steroid, and anti-lipidemic medications.
Model 1: Spearman rank correlation between continuous biomarker and continuous exposure variable.
Model 2: Partial Spearman rank correlation between continuous biomarker and continuous exposure variables when the effect of the following confounders are removed: age, BMI, current smoking status, alcoholic drinks/month, and thyroid meds.

Table 13 - Relationship of EUC Exposure with Lipid Biomarkers-Men*

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Triglycerides in mg/dl	52	r	.19	.24	.02	.08	-.04	.01	-.09	-.01
		p-value	.1781	.1006	.8652	.5851	.7637	.9407	.5301	.9453
Total Cholesterol in mg/dl	52	r	.15	.19	-.00	.04	.14	.19	.04	.11
		p-value	.2991	.2030	.9724	.7657	.3076	.1930	.7669	.4406
HDL Cholesterol in mg/dl	52	r	-.12	-.19	-.00	-.08	.04	-.03	.03	-.06
		p-value	.3905	.1914	.9856	.6064	.7913	.8198	.8366	.6627
LDL Cholesterol in mg/dl	51	r	.20	.24	.07	.13	.20	.24	.11	.18
		p-value	.1681	.1071	.6225	.4010	.1667	.1101	.4408	.2339
Total Chol/HDLC	52	r	.17	.23	.01	.08	.03	.09	-.02	.06
		p-value	.2359	.1214	.9298	.6026	.8439	.5526	.8759	.6653

*This sample of men excludes diabetics and those on steroid, thyroid, and anti-lipidemic medications.
Model 1: Spearman rank correlation between continuous biomarker and continuous exposure variable.
Model 2: Partial Spearman rank correlation between continuous biomarker and continuous exposure variables when the effect of the following confounders are removed: age, BMI, current smoking status, and alcoholic drinks/month.

Table 14 - Relationship of EUC Exposure with Hormone Levels-Women*

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
TSH Ultra Sens. in mciu/ml	82	r	-.06	-.14	-.05	-.14	-.03	-.07	-.02	-.04
		p-value	.5939	.2403	.6472	.2402	.7713	.5467	.8740	.7399
Triiodothyronine in ng/dl	79	r	-.06	.03	-.08	.04	.01	.01	-.01	-.03
		p-value	.5766	.7861	.5048	.7630	.9337	.9144	.9314	.8084
T_3 Uptake in %	82	r	-.15	-.23	-.08	-.17	-.17	-.17	-.16	-.16
		p-value	.1874	.0407	.4745	.1312	.1312	.1298	.1460	.1697
Total T_4 in mcg/dl	82	r	.10	.17	.10	.18	.03	.07	.01	.03
		p-value	.3938	.1445	.3639	.1233	.7779	.5429	.9606	.8284
Free T_4 Index	82	r	.05	.09	.10	.14	-.03	.02	-.05	-.01
		p-value	.6787	.4446	.3718	.2110	.7641	.8513	.6593	.9475
SHBG in nmol/L	82	r	-.29	-.37	-.27	-.34	-.42	-.46	-.40	-.43
		p-value	.0076	.0010	.0160	.0027	.0001	.0001	.0002	.0001
DHEA Sulfate in umol/L	82	r	-.31	-.12	-.30	-.09	-.21	-.08	-.24	-.13
		p-value	.0050	.3101	.0055	.4558	.0599	.4703	.0321	.2537
Cortisol in nmol/L	82	r	.06	.06	.06	.06	.13	.14	.11	.13
		p-value	.6123	.6346	.5657	.5811	.2554	.2233	.3059	.2597
Estradiol (E2) in pmol/L	82	r	.05	.07	.07	.10	.07	.05	.06	.02
		p-value	.6777	.5684	.5263	.3692	.5299	.6752	.5898	.8392
FSH in mIU/ml	82	r	-.23	-.28	-.23	-.29	-.26	-.25	-.23	-.21
		p-value	.0366	.0129	.0412	.0104	.0182	.0262	.0353	.0683
% of E2 bound to SHBG	82	r	-.11	-.22	-.04	-.15	-.26	-.32	-.25	-.29
		p-value	.3314	.0560	.7256	.1837	.0166	.0041	.0258	.0103
Conc. E2 bound to SHBG in pmol/L	82	r	.05	.02	.11	.08	-.01	-.04	-.01	-.04
		p-value	.6361	.8487	.3225	.4650	.9354	.7280	.9495	.7127
Insulin in uIU/mL	81	r	.09	.09	.03	.03	.21	.16	.20	.14
		p-value	.4365	.4291	.7840	.7696	.0622	.1552	.0699	.2200
2-OHE$_1$/Creatinine	79	r	-.18	-.30	-.15	-.27	-.18	-.22	-.18	-.23
		p-value	.1163	.0102	.1853	.0217	.1228	.0554	.1068	.0495

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
16α-OHE_1/Creatinine	79	r	-.16	-.22	-.11	-.17	-.13	-.15	-.13	-.14
		p-value	.1557	.0554	.3405	.1465	.2433	.2147	.2596	.2191
2-OHE_1/16α-OHE_1	79	r	.02	-.02	-.01	-.06	-.02	-.05	-.05	-.07
		p-value	.8637	.8384	.9418	.6279	.8618	.6906	.6536	.5330

*This sample of women excludes pre-menopausal women, diabetics, and those on steroid and estrogen-related medications.

Model 1: Spearman rank correlation between continuous biomarker and continuous exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and continuous exposure variables when the effect of the following confounders are removed: age, BMI, current smoking status, alcoholic drinks/month, and thyroid meds.

Table 15 - Relationship of EUC Exposure with Hormone Levels-Men*

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
TSH Ultra Sens. in mciu/ml	54	r	-.38	-.37	-.36	-.35	-.38	-.37	-.37	-.36
		p-value	.0047	.0087	.0075	.0140	.0051	.0089	.0056	.0098
Triiodothyronine in ng/dl	53	r	-.02	.07	-.06	.03	-.11	-.06	-.07	.02
		p-value	.9046	.6564	.6765	.8177	.4267	.6978	.6295	.9095
T_3-Uptake in %	54	r	-.37	-.43	-.34	-.41	-.23	-.29	-.26	-.33
		p-value	.0064	.0019	.0125	.0032	.0903	.0433	.0541	.0178
Total T_4 in mcg/dl	54	r	.18	.21	.16	.19	.22	.21	.25	.26
		p-value	.1818	.1383	.2506	.1807	.1170	.1362	.0678	.0658
Free T_4 Index	54	r	-.06	-.05	-.07	-.07	.08	.05	.10	.07
		p-value	.6649	.7338	.5942	.6423	.5638	.7354	.4791	.6349
SHBG in nmol/L	54	r	.07	-.00	.09	-.00	.10	.02	.16	.07
		p-value	.6030	.9988	.5402	.9898	.4774	.8781	.2483	.6507
DHEA Sulfate in umol/L	54	r	-.06	.06	-.03	.07	-.08	.01	-.05	.03
		p-value	.6635	.6880	.8057	.6334	.5889	.9703	.7196	.8511
Cortisol in nmol/L	54	r	.11	.13	.11	.12	.24	.24	.22	.20
		p-value	.4455	.3747	.4305	.4188	.0795	.0974	.1107	.1627
Estradiol (E2) in pmol/L	54	r	.00	-.02	.03	.01	-.03	-.00	-.07	-.05
		p-value	.9871	.9149	.8419	.9328	.8032	.9808	.6135	.7544
LH in mIU/ml	54	r	-.16	-.22	-.15	-.22	.16	.09	.13	.04
		p-value	.2605	.1288	.2729	.1179	.2395	.5355	.3631	.8060
Testosterone (T) in nmol/L	54	r	-.00	.03	.06	.06	.01	.02	.07	.05
		p-value	.9814	.8602	.6767	.6617	.9319	.8899	.6287	.7130
% of T bound to SHBG	54	r	.10	.01	.14	.05	.19	.09	.27	.16
		p-value	.4910	.9626	.2978	.7272	.1610	.5369	.0456	.2644
Conc. T bound to SHBG in nmol/L	54	r	.01	.01	.08	.06	.04	.01	.11	.06
		p-value	.9376	.9320	.5849	.6779	.8009	.9476	.4448	.6616

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Insulin in uIU/mL	54	r	-.09	-.09	-.10	-.07	-.09	.01	-.11	.01
		p-value	.5234	.5296	.4513	.6136	.5302	.9293	.4110	.9495
2-OHE_1/Creatinine	53	r	.04	.01	.11	.08	.09	.04	.16	.09
		p-value	.7860	.9384	.4237	.6109	.5341	.7737	.2599	.5262
16α-OHE_1/Creatinine	53	r	.09	.05	.13	.08	.01	-.05	.08	.00
		p-value	.5341	.7330	.3665	.5795	.9366	.7449	.5823	.9888
2-OHE_1/16α-OHE_1	53	r	-.17	-.13	-.10	-.06	-.09	-.06	-.12	-.10
		p-value	.2300	.3761	.4764	.6638	.5257	.6847	.3828	.5130

*This sample of men excludes diabetics and those on steroid and thyroid medications.

Model 1: Spearman rank correlation between continuous biomarker and continuous exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and continuous exposure variables when the effect of the following confounders are removed: age, BMI, current smoking status, and alcoholic drinks/month.

Table 16 - Relationship of EUC Exposure with Immune Biomarkers-Women*

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
IgG in mg/dl	143	r	-.04	-.01	-.03	-.01	.03	.03	.03	.04
		p-value	.6539	.8650	.7459	.8922	.7398	.6904	.7583	.6397
IgA in mg/dl	143	r	.20	.18	.19	.17	.12	.07	.11	.06
		p-value	.0158	.0356	.0224	.0520	.1652	.4353	.2000	.5223
IgM in mg/dl	143	r	-.05	.06	-.07	.03	-.06	.02	-.00	.08
		p-value	.5375	.5029	.4041	.7363	.4975	.8407	.9995	.3465
C-reactive protein in mg/dl	143	r	.22	.17	.19	.14	.19	.11	.24	.14
		p-value	.0075	.0417	.0268	.1136	.0264	.2018	.0047	.0967
T-cells as % of Lymphocytes	144	r	-.05	-.04	-.06	-.06	.02	.02	.07	.08
		p-value	.5813	.6616	.4981	.5121	.8321	.8185	.4269	.3605
CD4-cells as % of Lymphocytes	144	r	.05	.05	.02	.01	.13	.10	.18	.14
		p-value	.5201	.5833	.8100	.9481	.1189	.2456	.0295	.0967
CD8-cells as % of Lymphocytes	144	r	-.13	-.12	-.11	-.09	-.13	-.09	-.15	-.09
		p-value	.1164	.1736	.1997	.2760	.1214	.3051	.0754	.2934
CD4-cells/CD8-cells	144	r	.12	.12	.09	.08	.14	.10	.18	.13
		p-value	.1425	.1803	.2693	.3386	.0897	.2223	.0318	.1378
B-cells as % of Lymphocytes	144	r	-.03	.03	-.02	.05	.02	.05	-.01	.00
		p-value	.7602	.6914	.8484	.5558	.8362	.5427	.8810	.9580
NK-cells as % of Lymphocytes	144	r	.00	-.06	-.02	-.08	-.11	-.14	-.14	-.16
		p-value	.9860	.4763	.8540	.3496	.2027	.1150	.1040	.0654
CD5B-cells	144	r	.03	.07	.04	.08	.01	.04	-.00	.00
		p-value	.7219	.4043	.6562	.3259	.8723	.6730	.9722	.9604
White Blood Cell count in thous/μl	146	r	.13	.17	.10	.12	.04	.01	.10	.07
		p-value	.1210	.0675	.2295	.1443	.6040	.9078	.2529	.4064
Absolute Neutrophils in cells/μl	146	r	.12	.15	.09	.11	.07	.04	.11	.09
		p-value	.1434	.0857	.2756	.2034	.4015	.6148	.1753	.2705
Neutrophils in %	146	r	.05	.05	.05	.03	.08	.05	.07	.05
		p-value	.5226	.5936	.5794	.6987	.3637	.5309	.3982	.5719

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Absolute Lymphocytes in cells/μl	146	r	.04	.07	.02	.05	-.01	-.02	.04	.03
		p-value	.6135	.3987	.8505	.5844	.8648	.8095	.6430	.7405
Lymphocytes in %	146	r	-.06	-.03	-.05	-.02	-.05	-.02	.-.05	-.03
		p-value	.4958	.7452	.5201	.8139	.5640	.7865	.5478	.7032
Absolute Monocytes in cells/μl	146	r	.11	.11	.09	.09	-.01	-.02	.06	.07
		p-value	.1834	.1846	.2726	.2881	.9096	.8346	.4895	.4449
Monocytes in %	146	r	-.01	-.04	-.01	-.05	-.07	-.06	-.05	-.02
		p-value	.8784	.6252	.8598	.5803	.4279	.5147	.5422	.7826
Absolute Eosinophils in cells/μl	146	r	.13	.08	.11	.07	-.00	-.04	.05	.02
		p-value	.1220	.3547	.1788	.4209	.9664	.6815	.5833	.7746
Eosinophils in %	146	r	.06	.00	.06	.01	-.04	-.05	-.01	-.01
		p-value	.4526	.9665	.4668	.9056	.6524	.5585	.8705	.8765
Absolute Basophils in cells/μl	146	r	.05	.07	.03	.05	-.01	-.03	.01	-.02
		p-value	.5380	.4366	.6770	.5945	.9085	.6842	.9021	.8028
Basophils in %	146	r	.01	.01	.00	-.00	-.03	-.04	-.05	-.07
		p-value	.9075	.9113	.9784	.9826	.7152	.6033	.5779	.4168

*This sample of women excludes those on steroid and oral contraceptive medications.

Model 1: Spearman rank correlation between continuous biomarker and continuous exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and continuous exposure variables when the effect of the following confounders are removed: age, BMI, diabetes, current smoking status, alcoholic drinks/month, estrogen related medications, and menopausal status.

Table 17 - Relationship of EUC Exposure with Immune Biomarkers-Men*

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
IgG in mg/dl	64	r	.08	-.03	.07	-.03	-.05	-.13	-.04	-.11
		p-value	.5426	.8379	.6037	.8326	.6778	.3205	.7566	.4260
IgA in mg/dl	64	r	.18	.11	.18	.12	.16	.16	.16	.18
		p-value	.1499	.4170	.1510	.3615	.1926	.2231	.2071	.1756
IgM in mg/dl	64	r	.04	.02	.02	-.00	-.00	.02	.00	.02
		p-value	.7595	.8519	.8679	.9959	.9954	.9046	.9857	.8646
C-reactive protein in mg/dl	64	r	.02	-.04	-.00	-.05	.04	.00	-.02	-.06
		p-value	.8898	.7759	.9976	.7207	.7552	.9723	.8664	.6757
T-cells as % of Lymphocytes	62	r	-.27	-.38	-.30	-.41	-.09	-.17	-.13	-.22
		p-value	.0359	.0036	.0168	.0015	.4952	.2015	.3044	.1024
CD4-cells as % of Lymphocytes	62	r	-.10	-.05	-.14	-.11	-.04	-.04	-.07	-.07
		p-value	.4457	.6944	.2677	.4125	.7362	.7926	.5801	.5897
CD8-cells as % of Lymphocytes	62	r	-.02	-.09	-.01	-.06	.03	.04	.01	.04
		p-value	.8874	.5218	.9490	.6738	.8385	.7748	.9600	.7543
CD4-cells/CD8-cells	62	r	-.01	.07	-.05	.01	.00	.03	.01	.02
		p-value	.9481	.6111	.7262	.9269	.9798	.8421	.9514	.8748
B-cells as % of Lymphocytes	62	r	-.16	-.01	-.13	.00	-.25	-.16	-.21	-.12
		p-value	.2268	.9670	.3091	.9940	.0469	.2296	.1024	.3864
NK-cells as % of Lymphocytes	62	r	.38	.41	.36	.38	.33	.38	.33	.40
		p-value	.0023	.0017	.0046	.0033	.0087	.0035	.0080	.0023
CD5B-cells	62	r	-.17	-.03	-.15	-.02	-.30	-.19	-.24	-.11
		p-value	.1753	.8159	.2316	.8654	.0191	.1657	.0622	.4108
White Blood Cell count in thous/μl	64	r	-.07	-.10	-.05	-.09	-.01	-.08	-.04	-.13
		p-value	.6063	.4481	.6856	.4788	.9196	.5349	.7259	.3242
Absolute Neutrophils in cells/μl	64	r	-.06	-.06	-.05	-.07	.04	.03	.01	-.01
		p-value	.6414	.6251	.6837	.6247	.7463	.8266	.9313	.9685
Neutrophils in %	64	r	-.01	.04	-.01	.03	.15	.21	.13	.21
		p-value	.9569	.7622	.9322	.8236	.2527	.1058	.2977	.1097

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Absolute Lymphocytes in cells/μl	64	r	-.02	-.07	-.04	-.09	-.08	-.14	-.12	-.20
		p-value	.8786	.6225	.7806	.5164	.5493	.2871	.3640	.1345
Lymphocytes in %	64	r	-.10	-.13	-.12	-.15	-.18	-.21	-.20	-.24
		p-value	.4476	.3384	.3312	.2459	.1521	.1114	.1113	.0621
Absolute Monocytes in cells/μl	64	r	.20	.19	.24	.24	.18	.13	.20	.15
		p-value	.1133	.1458	.0527	.0697	.1642	.3324	.1215	.2539
Monocytes in %	64	r	.22	.21	.28	.29	.15	.13	.18	.17
		p-value	.0861	.1069	.0256	.0264	.2495	.3440	.1497	.1900
Absolute Eosinophils in cells/μl	64	r	.10	.03	.09	.03	.06	.00	.08	.03
		p-value	.4430	.8124	.4787	.8364	.6182	.9968	.5189	.8375
Eosinophils in %	64	r	.12	.05	.10	.04	.01	-.04	.06	.01
		p-value	.3639	.7050	.4325	.7574	.9243	.7383	.6627	.9330
Absolute Basophils in cells/μl	64	r	.06	.08	.04	.05	.17	.19	.18	.21
		p-value	.6126	.5553	.7661	.7281	.1752	.1454	.1511	.1167
Basophils in %	64	r	.01	.00	-.03	-.04	.10	.13	.14	.18
		p-value	.9513	.9798	.8157	.7836	.4297	.3380	.2555	.1779

*This sample of men excludes those on steroid medications.

Model 1: Spearman rank correlation between continuous biomarker and continuous exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and continuous exposure variables when the effect of the following confounders are removed: age, BMI, diabetes, current smoking status, and alcoholic drinks/month.

Table 18 - Number of Participants with Low or High Biomarker Values

Biomarker	Women			Men		
	n	Low	High	n	Low	High
Hormone[1]:						
TSH Ultra Sensitive	82	7	12	54	1	2
T_3	79	0	1	53	0	1
T_3-Uptake	82	0	1	54	0	5
T_4	82	0	2	54	1	1
Free T_4 Index	82	0	2	54	0	0
Lipid[2]:						
Triglycerides	79	NA[5]	13	52	NA[5]	17
Total Cholesterol	79	NA[5]	68	52	NA[5]	31
HDL Cholesterol	79	7	NA[5]	52	15	NA[5]
LDL Cholesterol	78	NA[5]	59	51	NA[5]	28
Chol/HDLC	79	NA[5]	45	52	NA[5]	33
Liver[3]:						
Bilirubin	146	NA[5]	5	64	NA[5]	4
Alk. Phosphatase	146	0	6	64	0	0
GGT	146	NA[5]	18	64	NA[5]	1
AST (SGOT)	146	NA[5]	6	64	NA[5]	0
ALT (SGPT)	146	NA[5]	7	64	NA[5]	3
LDH	146	NA[5]	3	64	NA[5]	0
Immune[4]:						
IgA	143	2	10	64	5	0
IgG	143	5	9	64	1	3
IgM	143	14	14	64	5	1
CRP	143	NA[5]	28	64	NA[5]	6
WBC	146	4	6	64	0	2
Abs. Neutrophils	146	1	3	64	0	1
Abs. Lymphocytes	146	0	3	64	1	1
Abs. Monocytes	146	0	0	64	0	0
Abs. Eosinophils	146	5	3	64	2	3
Abs. Basophils	146	NA[5]	1	64	NA[5]	0
CD4-cells	144	4	18	60	2	8
CD4/CD8	144	7	6	62	7	1
Anti-Nuclear Antibody1[a]	141	NA[5]	24	64	NA[5]	5

Biomarker	Women			Men		
	n	Low	High	n	Low	High
Anti-Nuclear Antibody2[a]	141	NA[5]	18	64	NA[5]	3

[1] Exclusions for hormone analysis by gender are: 1)Women-excludes pre-menopausal women, diabetics, and those on steroid and estrogen-related medications. 2)Men-excludes diabetics and those on steroid and thyroid medications.
[2] Exclusions for lipid analysis by gender are: 1)Women-excludes pre-menopausal women, diabetics, and those on estrogen-related, steroid, and anti-lipidemic medications. 2)Men-excludes diabetics and those on steroid, thyroid and anti-lipidemic medications.
[3] Exclusions for liver analysis by gender are: 1)Women-excludes those on steroid and oral contraceptive medications. 2)Men-excludes those on steroid medications.
[4] Exclusions for immune analysis by gender are: 1)Women-excludes those on steroid and oral contraceptive medications. 2)Men-excludes those on steroids.
[5]No low or high range defined.
[a]Anti-Nuclear Antibody was analyzed two different ways: 1) Weakly Positive classified as Positive and 2) Weakly Positive classified as Negative.

Table 19 - Relationship of EUC Exposure and High and Low Biomarker Values-Women

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
HIGH										
Hormones[1]:										
TSH Ultra-Sensitive (4.8+ mciu/ml)	12/82	OR*	1.1	0.9	1.0	0.8	0.9	0.8	0.8	0.8
		p-value	.8200	.8534	.9255	.5262	.5929	.5813	.3710	.4147
Lipids[2]:										
Triglycerides (200+ mg/dl)	13/79	OR*	2.4	3.1	1.7	1.8	1.2	1.4	1.2	1.3
		p-value	.0063	.0048	.0668	.0838	.5386	.3147	.5432	.4001
Total Cholesterol (200+ mg/dl)	68/79	OR*	0.9	0.9	0.7	0.6	1.3	1.2	1.2	1.1
		p-value	.7480	.6639	.2462	.2127	.3567	.5320	.4718	.7041
LDL Cholesterol (131+ mg/dl)	59/79	OR*	1.0	1.1	0.8	0.9	1.5	1.6	1.3	1.2
		p-value	.9753	.6589	.4581	.6292	.0842	.1289	.2819	.4877
Chol/HDLC ratio (4.45+)	45/79	OR*	1.4	1.8	1.2	1.5	1.1	1.1	1.0	1.0
		p-value	.1449	.0335	.4675	.1140	.5218	.7922	.8598	.8761
Liver[3]:										
GGT (46+ u/l)	18/146	OR*	1.0	1.1	1.0	1.1	1.0	1.0	1.0	1.0
		p-value	.8755	.6589	.8496	.7874	.8810	.9304	.9892	.9265
Immune[4]:										
IgG[5]	10/143	OR*	0.9	1.2	1.0	1.3	1.7	1.3	1.4	2.7
		p-value	.8097	.6178	.9622	.4190	.6395	.5002	.2979	.0520
IgM[6]	14/143	OR*	1.0	0.9	1.1	1.0	1.2	1.3	1.2	1.4
		p-value	.8904	.7850	.8347	.9559	.4697	.4161	.5430	.3513
C-reactive protein (.85+ mg/dL)	28/143	OR*	1.8	2.2	1.7	1.9	1.5	1.4	1.8	1.7
		p-value	.0021	.0017	.0042	.0052	.0624	.1992	.0131	.0541
CD4-cells (61+ %)	18/144	OR*	1.0	0.8	1.0	0.8	1.2	0.9	1.3	1.1
		p-value	.8877	.3964	.8660	.3837	.5248	.8027	.3277	.7920
Anti-Nuclear Antibody 1[7]	24/141	OR*	0.9	0.7	1.0	0.8	1.2	1.1	1.4	1.3
		p-value	.5779	.1657	.9385	.4144	.3901	.6244	.1662	.3213

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Anti-Nuclear Antibody 2[7]	18/141	OR*	1.1	0.9	1.2	1.1	1.4	1.3	1.6	1.5
		p-value	.5828	.8103	.3421	.7869	.2542	.3132	.0899	.1480
LOW										
Immune[4]:										
IgM[8]	14/143	OR*	1.1	1.0	1.1	0.9	1.3	1.3	1.2	1.1
		p-value	.7135	.8712	.8347	.7987	.3233	.4227	.5430	.7332

*The Odds Ratios represent the effect of a one-group increase in the ordinal exposure variable (4 groups) in logistic regression.
Model 1: only biomarker and exposure variable in logistic regression.
Model 2: logistic regression between ordinal exposure variable and dichotomous biomarker controlling for the following confounders: 1)Hormones-age, BMI, current smoking status, alcoholic drinks/month, and thyroid meds. 2)Lipids-age, BMI, current smoking status, alcoholic drinks/month, and thyroid medications. 3)Liver-age, BMI, diabetes, alcoholic drinks/month, estrogen related medications, and menopausal. 4)Immune-age, BMI, diabetes, current smoking status, alcoholic drinks/month, estrogen related.
[1]Exclusions for hormone analysis are pre-menopausal women, diabetics, and those on steroid and estrogen-related medications.
[2]Exclusions for lipid analysis are pre-menopausal women, diabetics, and those on estrogen-related, steroid, and anti-lipidemic medications.
[3]Exclusions for liver analysis are those on steroid and oral contraceptive medications.
[4]Exclusions for immune analysis are those on steroid and oral contraceptive medications.
[5]High IgG for women based on age: 1) 1588+ mg/dl is high for women 30-44 years old, 2) 1492+ mg/dl is high for women 45-59 years old, and 3) 1814+ mg/dl is high for women 60+ years old.
[6]High IgM for women based on age 1) 317+ mg/dl is high for women 30-44 years old, 2) 255+ mg/dl is high for women 45-59 years old, and 3) 310+ mg/dl is high for women 60+ years old.
[7]Anti-Nuclear Antibody was analyzed two different ways: 1) Weakly Positive classified as Positive and 2) Weakly Positive classified as Negative.
[8]Low IgM for women based on age 1) <77 mg/dl is low for women 30-44 years old, 2) <66 mg/dl is low for women 45-59 years old, and 3) <64 mg/dl is low for women 60+ years old.

Table 20 - Relationship of EUC Exposure an High and Low Biomarker Values-Men

Biomarker	n		PCB in ppb		Lipid PCB in ppb		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
HIGH										
Lipids[1]:										
Triglycerides (200+ mg/dl)	17/52	OR*	1.0	1.1	0.9	0.9	0.8	0.9	0.6	0.7
		p-value	.8491	.7167	.5680	.8550	.4269	.6377	.0930	.2574
Total Cholesterol (200+ mg/dl)	31/52	OR*	1.3	1.6	1.2	1.4	1.2	1.5	0.9	1.1
		p-value	.2839	.1589	.5469	.2818	.5004	.3230	.7937	.7766
LDL Cholesterol (131+ mg/dl)	28/51	OR*	1.4	1.5	1.3	1.5	1.6	1.7	1.1	1.3
		p-value	.1697	.1587	.2564	.1729	.1449	.1092	.7039	.5193
Chol/HDLC ratio (4.45+)	33/52	OR*	1.3	1.5	1.1	1.3	1.2	1.4	1.0	1.2
		p-value	.2490	.1647	.6450	.3400	.4651	.2836	.9480	.5744
Immune[2]:										
CD4-cells (61+ %)	8/60	OR*	0.7	0.7	0.6	0.6	1.2	1.1	0.8	0.7
		p-value	.2484	.3970	.1619	.2426	.7266	.7738	.5603	.4680
LOW										
Lipids[1]:										
HDL Cholesterol (<35 mg/dl)	15/52	OR*	1.0	1.1	0.9	1.0	1.1	1.2	0.7	0.8
		p-value	.8968	.7819	.6683	.9173	.7234	.6298	.3148	.6163

*The Odds Ratios represent the effect of a one-group increase in the ordinal exposure variable.

Model 1: only biomarker and exposure variable.

Model 2: Lipid analysis controls for : age, BMI, current smoking status, and alcoholic drinks/month. Immune analysis also controls for diabetes.

[1]Exclusions for Lipid analysis include: diabetics and those on steriod, thyroid and anti-lipidemic medications.

[2]Exclusions for Immune analysis include: those on steroid medications.

Table 21 - Technical Errors of Liver and Lipid Measurements with Coefficients of Variation Calculated from Split Samples

Laboratory Measurement	No. Split Samples	Mean	Technical Error[a]	Coefficient of Variation[b]
Bilirubin in mg/dl	21	0.7	0.1	10.1%
Alkaline Phosphatase in u/l	21	72.8	1.7	2.4%
Total LDH in u/l	21	157.3	9.8	6.2%
GGT in u/l	21	32.9	1.4	4.2%
AST (SGOT) in u/l	21	20.8	1.0	4.9%
ALT (SGPT) in u/l	21	25.0	1.0	4.1%
Triglycerides in mg/dl	21	172.4	3.4	1.9%
Total Cholesterol in mg/dl	21	230.2	3.7	1.6%
HDL Cholesterol in mg/dl	21	51.5	1.7	3.4%
LDL Cholesterol in mg/dl	21	141.6	3.0	2.1%
Chol/HDL ratio	21	4.9	0.1	2.7%

[a]Technical errors of measurements were computed as the square root of: $Sd_i^2/2n$ where d_i is the difference in value between the two identical samples and n is the number of pairs of split samples.
[b]The coefficient of variation was computed as the technical error/mean.

Table 22 - Technical Errors of Hormone Measurements with Coefficients of Variation Calculated from Split Samples

Laboratory Measurement	No. Split Samples	Mean	Technical Error[a]	Coefficient of Variation[b]
TSH, ultra-sens	21	2.9	0.2	5.5%
T_3 in ng/dl	20	124.6	2.8	2.2%
T_3-Uptake in %	21	28.9	1.0	3.4%
T_4 in mcg/dl	21	8.2	0.3	3.3%
Free T_4 Index	21	2.3	0.1	5.7%
SHBG in nmol/L	22	91.2	22.1	24.3%
DHEA Sulfate in umol/L	22	4.2	1.1	26.6%
Cortisol in nmol/L	22	524.8	140.3	26.7%
Estradiol (E2) in pmol/L	19	107.9	22.3	20.7%
Insulin in uIU/mL	14	9.8	1.8	18.5%
FSH in mIU/ml	11	47.5	15.4	32.5%
%E2 bound to SHBG	11	37.0	2.8	7.5%
Conc. E2 bound to SHBG in pmol/L	11	37.0	7.7	20.9%
LH in mIU/ml	8	11.3	1.6	13.8%
Testosterone (T) in nmol/L	8	23.3	5.2	22.3%
% T bound to SHBG	8	33.4	3.5	10.4%
Conc. T bound to SHBG in nmol/L	8	7.7	1.7	21.6%

[a] Technical errors of measurements were computed as the square root of: $Sd_i^2/2n$ where d_i is the difference in value between the two identical samples and n was the number of pairs of split samples.

[b]The coefficient of variation was computed as the technical error/mean.

Table 23 - Technical Errors of Immune Measurements with Coefficients of Variation Calculated from Split Samples

Laboratory Measurement	No. Split Samples	Mean	Technical Error[a]	Coefficient of Variation[b]
T-cells as % of Lymphocytes	22	71.2	0.9	1.2%
CD4-cells as % of Lymphocytes	22	50.4	0.8	1.5%
CD8-cells in % of Lymphocytes	22	28.9	0.7	2.4%
B-cells as % of Lymphocytes	22	13.1	0.7	5.9%
NK-cells as % of Lymphocytes	22	11.7	0.5	4.6%
CD5b-cells	22	4.8	0.5	11.5%
IgG in mg/dl	22	1060.5	34.7	3.3%
IgA in mg/dl	22	233.0	7.9	3.4%
IgM in mg/dl	22	129.6	13.9	10.7%
C-reactive protein in mg/dl	22	0.56	0.06	10.5%
White Blood Cell count in thous/μl	15	5.9	0.2	4.2%
Abs. Neutrophils in cells/μl	15	3666.9	132.2	3.6%
Neutrophils in %	15	61.2	0.9	1.5%
Abs. Lymphocytes in cells/μl	15	1615.6	102.8	6.4%
Lymphocytes in %	15	27.9	0.8	2.8%
Abs. Monocytes in cells/μl	15	409.2	31.9	7.8%
Monocytes in %	15	7.1	0.6	8.0%
Abs. Eosinophils in cells/μl	15	192.3	18.3	9.5%
Eosinophils in %	15	3.3	0.3	7.7%
Abs. Basophils in cells/μl	15	33.1	11.0	33.3%
Basophils in %	15	0.6	0.2	33.4%

[a]Technical errors of measurements were computed as the square root of: $Sd_i^2/2n$ where d_i is the difference in value between the two identical samples and n was the number of pairs of split samples.
[b]The coefficient of variation was computed as the technical error/mean.

Table 24 - Relationship of EUC Exposure[a] with Pregnancy Outcomes

Outcome of Pregnancy	Exposed Rate	Unexposed Rate	Odds Ratio	p-value[b]
spontaneous abortion (up to 12 weeks)	1.7% (2/117)	5.3% (14/262)	0.2	.0624
miscarriage (after 12 weeks)	2.5% (3/118)	3.9% (10/258)	0.7	.6088
spon. abortion/miscarriage	4.2% (5/120)	8.8% (24/272)	0.4	.0672
low birth weight (< 2500 grams)	8.1% (9/110)	8.1% (19/235)	1.2	.6559
not on-time delivery	40.9% (47/115)	25.8% (64/248)	2.3	.0011
premie delivery	6.1% (7/115)	4.4% (11/248)	1.5	.4379
premie or early delivery	16.5% (19/115)	12.9% (32/248)	1.5	.2137
late delivery	24.4% (28/115)	12.9% (32/248)	2.4	.0039
male sex	60.9% (70/115)	51.2% (127/248)	1.5	.0721

[a]Pregnancy exposure defined as: Mother ever worked at EUC prior to or during pregnancy

[b]Confounders controlled for in Logistic Regression: age of mother, smoking during pregnancy (yes/no), drinking during pregnancy (yes/no), and x-rays during pregnancy (yes/no)

Table 25 - Relationship of EUC Exposure[a] with Adverse Outcomes in Children

Adverse Outcome in Child[b]	Exposed Rate	Unexposed Rate	Odds Ratio	p-value[c]
birth defects	7.8% (9/115)	4.5% (11/246)	1.7	.3036
hearing problems	8.7%(10/115)	4.5% (11/244)	1.9	.1608
chronic respiratory problems	**10.7% (12/112)**	**5.4% (13/242)**	**2.7**	**.0280**
frequent ear infections	**13.0% (15/115)**	**5.8% (14/242)**	**2.7**	**.0147**
developmental problems	**6.1% (7/115)**	**0.4% (1/244)**	**30.3**	**.0112**
hyperactivity	**7.8% (9/115)**	**1.2% (3/244)**	**7.3**	**.0051**
reversal of letters	**6.1% (7/115)**	**1.6% (4/244)**	**4.0**	**.0350**
learning problems	**12.2% (14/115)**	**1.6% (4/244)**	**7.9**	**.0007**
hormonal problems	0.9% (1/114)	2.1% (5/238)	0.6	.6744
any cancer	0.9% (1/115)	4.1% (10/244)	0.3	.2132
slow thyroid	1.7% (2/115)	1.2% (3/241)	1.5	.7046
any thyroid condition	3.5% (4/115)	3.7% (9/243)	1.2	.8002
abnormal uterus	0.0% (0/41)	6.1% (7/115)	0.0	.9472
abnormal ovaries	7.5% (3/40)	3.5% (4/113)	2.5	.2629
female infertility	8.1% (3/37)	10.6% (12/113)	0.6	.4851
endometriosis	4.9% (2/41)	4.5% (5/111)	2.0	.4755
one undescended testicle	5.9% (4/68)	5.7% (7/122)	1.0	.9913

[a]Exposure to child defined as: Mother ever worked at EUC prior to birth.
[b]Other adverse outcomes with too few numbers (<5 total) could not be analyzed: diabetes, immune problems, abnormal head size at birth, hypothyroidism, hyperthyroidism, abnormality of vagina, abnormality of cervix, and two undescended testicles.
[c]Confounders controlled for in Logistic Regression: age of mother, smoking during pregnancy (yes/no), drinking during pregnancy (yes/no), x-rays during pregnancy (yes/no), sex of child, and breast feeding (yes/no).

FIGURES

Figure 1 - EUC Work Areas

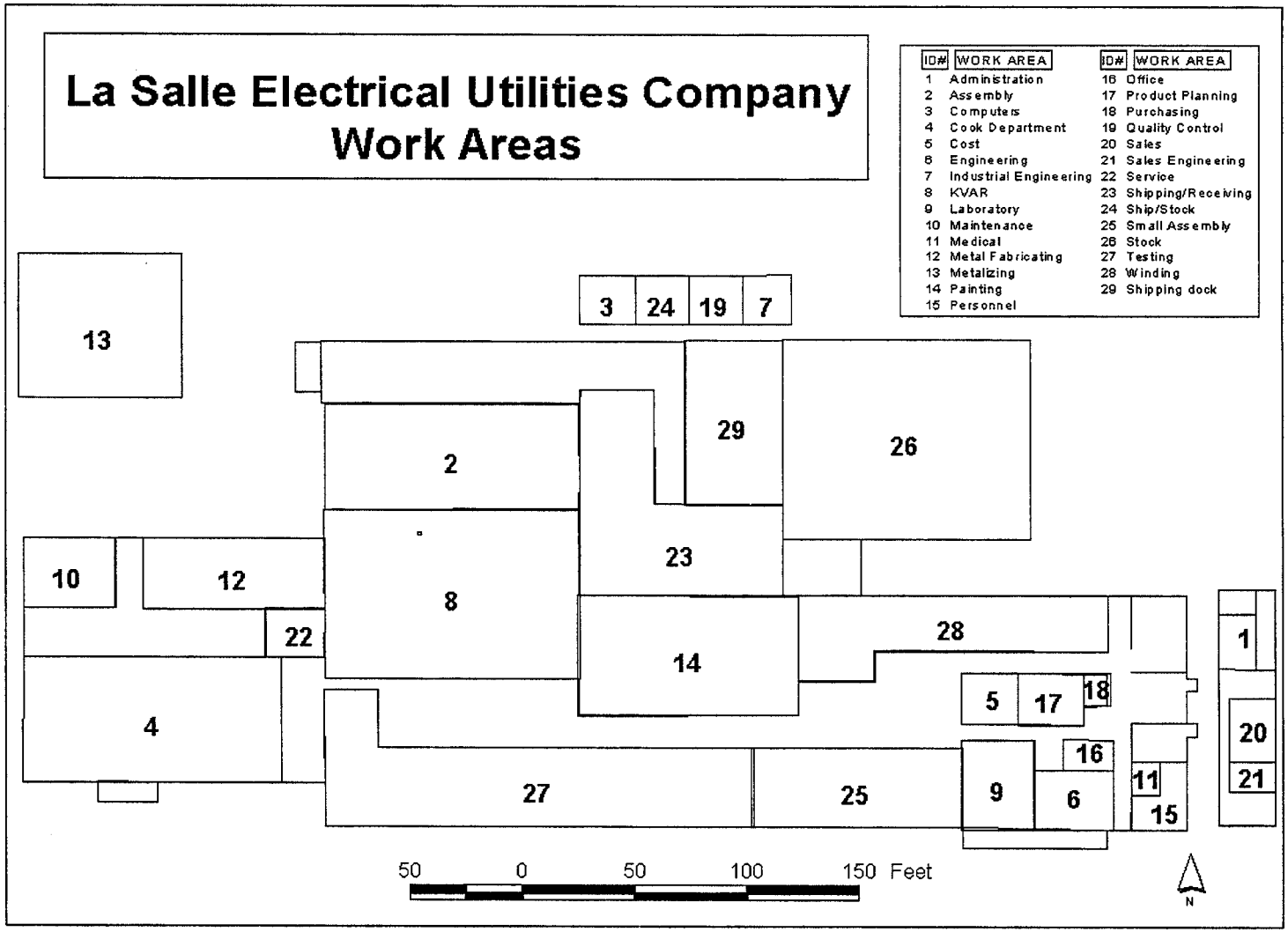
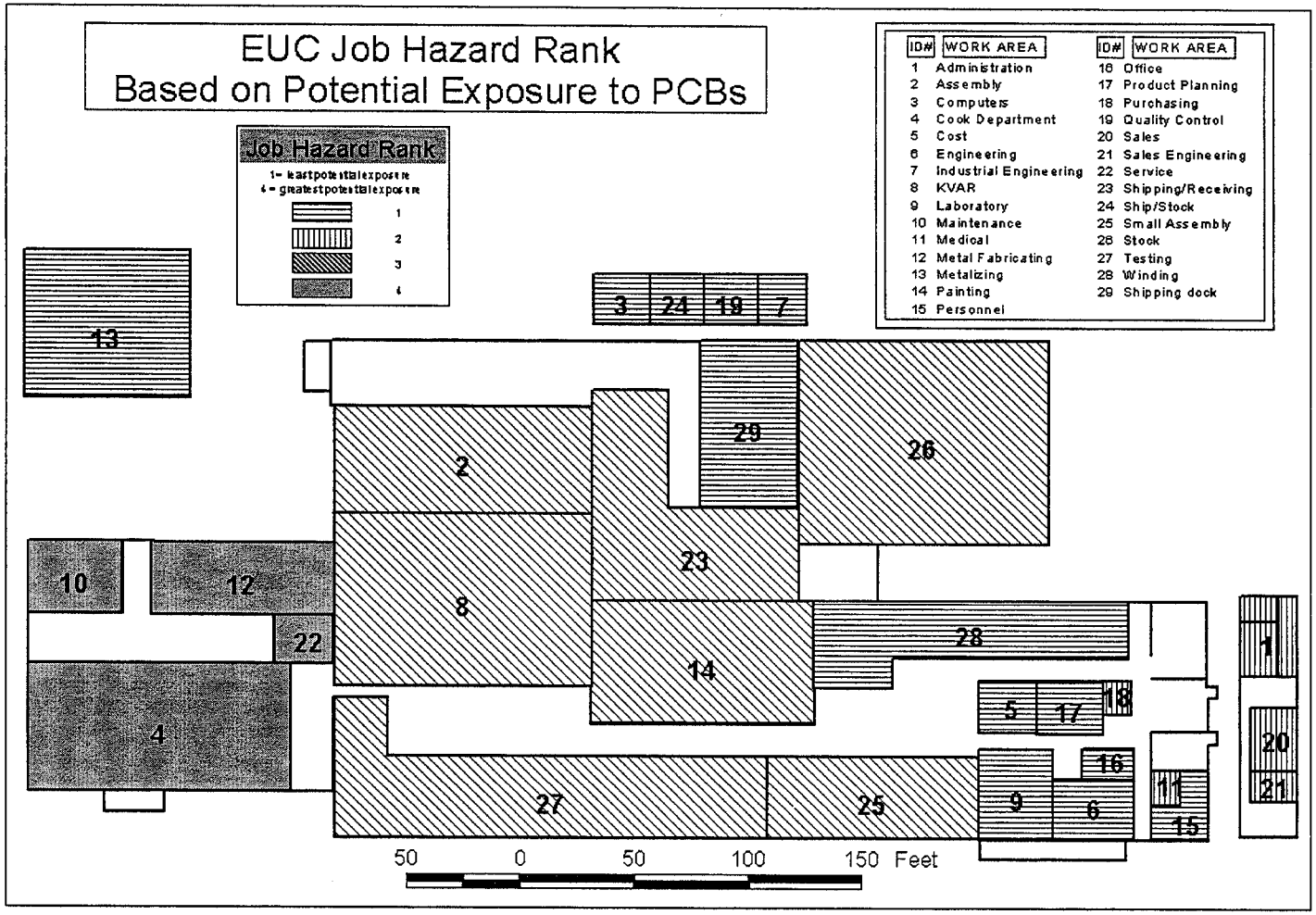


Figure 2 - Hazard Scores



REFERENCES

1. IDPH (1993). Public Health Assessment, La Salle Electric Utilities. Illinois Department of Public Health (CERCLIS No. ILD9,807943333)

2. IDPH (1991). Incidence of Cancer in the Zip Code Area 61301 of La Salle, La Salle County, Illinois, Illinois Department of Public Health.

3. EPA: Estimating exposure to dioxin-like compounds, Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related compounds and Risk Characterization of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds,
1994.

4. Drinker CK, Warren MF, Bennett GA: The problem of possible systemic effects from certain chlorinated hydrocarbons. This J 19: 283-299, 1937

5. Emmett EA, Maroni M, Jeffreys J, Schmith J, Levin BK, Alvares A: Studies of transformer repair workers exposed to PCBs: II Results of clinical laboratory investigations. Am J Indust Med 14: 47-62, 1988

6. Lawton RW, Ross MR, Feingold J, Brown JF: Effects of PCB exposure on biochemical and hematological findings in capacitor workers. Environ Health Perspect 60: 165-184, 1985

7. Fitzgerald EF, Standfast SJ, Youngblood LG, Melius JM, Janerich DT: Assessing the health effects of potential exposure to PCBs, dioxins and furans from electrical transformer fires: The Binghamton State Building Medical Surveillance Program. Arch Environ Health 41: 368-376, 1986

8. Smith AB, Schloemer J, Lowry LK, Smallwood AW, Ligo RN, Tanaka S, Stringer W, Jones M, Hervin R, Glueck CK: Metabolic and health consequences of occupational exposure to polychlorinated biphenyls. Brit J Ind Med 39: 361-369, 1982

9. Kreiss K, Zack MM, Kimbrough RD, Needham LL, Smerek AL, Jones BT: Association of blood pressure and polychlorinated biphenyl levels. JAMA 245: 2505-2509, 1981

10. Maroni M, Columbi A, Arbosti G, Cantoni S, Foa V: Occupational exposure to polychlorinated biphenyls in electrical workers. II Health effects. Brit J Indust Med 38: 55-60, 1981

11. Fishbein A, Wolff MS, Lilis R, Thornton J, Selikoff IJ: Clinical findings among PCB-exposed capacitor manufacturing workers. Ann NY Acad Sci 703-715, 1979

12. Gladen BC, Rogan WJ, Ragan NB, Spierto FW: Urinary porphyrins in children exposed transplacentally to polyhalogenated aromatics in Taiwan. Arch Environ Health 43: 54-57, 1988

13.Chang KJ, Lu FJ, Tung TC, Lee TP: Studies on patients with polychlorinated biphenyl poisoning. Res Commun Chem Pathol Pharmacol 30: 547-54, 1980

14. Colombi A, Marroni A, Ferioloi M, Catoldi M, Jun LK, Valla C, Foa V: Increase in urinary porphyrin excretion in workers exposed to polychlorinated biphenyls. J Appl Toxicol 2: 117-121, 1982

15. Hryhorzcuk DO, Wallace WH, Persky V, Furner S, Webster JD, Oleske D, Haselhorst B, Elefson R, Zugerman C: A morbidity study of former pentachlorophenol production workers. Environ Health Perspect 106: 401-408, 1998

16. van Birgelen APJM, DeVito MJ, Akins JM, Ross DG, Diliberto JJ, Birnbaum LS: Relative potencies of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls derived from hepatic porphyrin accumulation in mice. Toxicol Appl Pharmacol 138: 98-109, 1996

17. van Birgelen AP, Fase KM, van der Kolk J, Poiger H, Brouwer A, Seinen W, van der Berg M: Synergistic effect of 2,2',4,4',5,5'-hexachlorobiphenyl and 2,3,7,8-tetrachlorodibenzodioxin on hepatic porphyrin levels in the rat. Environ Health Perspect 104: 550-557, 1996

18. Hara I: Health status and PCBs in blood of workers exposed to PCBs and of their children. Environ Health Perspect 59: 85-90, 1985

19. Stark AD, Costas K, Chang HG, Vallet HL: Health Effects of low-Level exposure to polychlorinated biphenyls. Environ Res 41: 174-183, 1986

20. Baker EL, Landrigan PJ, Glueck CJ, Zack MM, Liddle JA, Burse VW, Housworth WJ, Needham LL: Metabolic consequences of exposure to polychlorinated biphenyls (PCB) in sewage sludge. Am J Epidemiol 112: 553-563, 1980

21. Chase KH, Wong O, Thomas D, Stat D, Berney BW, Simon RK: Clinical and metabolic abnormalities associated with occupational exposure to polychlorinated biphenyls (PCBs). J Occup Med 24: 109-114, 1982

22. Mayes BA, McConnell EE, Neal BH, Brunner MJ, Hamilton SB, Sullivan TM, Peters AC, Ryan MJ, Toft JD, Singer AW, Brown JP, Menton RG, Moore JA: Comparative carcinogenicity in Sprague-Dawley rats of the polychlorinated biphenyl mixtures Aroclors 1016, 1242, 1254, and 1260. Toxicol Sci 41: 62-76, 1998

23. Brown DP: Mortality of workers exposed to polychlorinated biphenyls-an update. Arch Environ Health 42: 333-339, 1987

24. Kimbrough RD, Doemland ML, LeVois ME: Mortality in male and female capacitor workers exposed to polychlorinated biphenyls. JOEM 41: 161-171, 1999

25. Sinks T, Steele G, Smith AB, Watkins K, Shults RA: Mortality among workers exposed to polychlorinated biphenyls. Am J Epidemiol 136: 389-398, 1992

26. Gustavsson P, Hogstedt C: A cohort study of Swedish capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Indust Med 32: 234-239, 1997

27. Bertazzi PA, Riboldi L, Pesatori A, Radice L, Zocchetti C: Cancer mortality of capacitor manufacturing workers. Am J Indust Med 11: 165-176, 1987

28. Tironi A, Pesatori AC, Consonni D, Zocchetti C, Bertazzi PA: Mortality of capacitor manufacturing workers exposed to PCBs. Epidemiology 6 (Supp) S112, 1995

29. Yassi A, Tate R, Fish D: Cancer mortality in workers employed at a transformer manufacturing plant. Am J Indust Med 25: 425-437, 1994

30. Loomis D, Browning SR, Schenck AP, Gregory E, Savitz DA: Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. Occup Environ Med 54: 720-728, 1997

31. Hsieh SF, Yen YY, Lan SJ, Hsieh CC, Lee CH, Ko YC: A cohort study on mortality and exposure to polychlorinated biphenyls. Arch Environ Health 51: 417-424, 1996

32. Kuratsune M, Ikeda M, Nakamura Y, Hirohata T: A cohort study on mortality of "Yusho" patients. in Unusual Occurrences as Clues to Cancer Etiology, R.W. Miller et al (eds) Japan Sci Soc Press Tokyo/Taylor & Francis, LTD, pp 61-66, 1988

33. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N: Blood levels of organochlorine residues and risk of breast cancer. JNCI 85: 648-652, 1993

34. Moyish KB, Ambrosone CB, Vena JE, Shields PG, Mendola P, Kostyniak P, Greizerstein H, Graham S, Marshall JR, Schisterman EF, Freudenheim JL: Environmental organochlorine exposure and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 7: 181-188, 1998

35. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N: Breast cancer and serum organochlorines: a prospective study among white, black and Asian women. JNCI 86: 589-599, 1994

36. Hunter: DJ, Hankinson SE, Laden F, Colditz GA, Manson JAE, Willett WC, Speizer FE, Wolff MS: Plasma organochlorine levels and the risk of breast cancer. New Eng J Med 337, 1253-1258, 1997

37. Helhouser KJ, Alberg AJ, Huang HY, Hoffman SC, Strickland PT, Brock JW, Burse VW, Needham LL, Bell DA, Lavigne JA, Yager JD, Comstock GW: Serum concentrations of

organochlorine compounds and the subsequent development of breast cancer. Cancer Epidemiol Biomarkers Prev 8: 525-532, 1999

38. Rothman N, Cantor KP, Blair A, Bush D, Brock JW, Helzhouser K, Zahm SH, Needham LL, Pearson GR, Hoover RN, Comstock GW, Strickland PT: A nested case-control study of non-Hodgkins lymphoma and serum organochlorine residue. Lancet 350: 240-244, 1997

39. Gray LE, Ostby J, Marshall R, Andrews J: Reproductive and thyroid effects of low-level polychlorinated biphenyl (Aroclor 1254) exposure. Fund Appl Toxicol 20: 288-294, 1993

40. Nagata K, Matsunaga T, Buppodom P, Ishimatsu M, Yamato H, Yoshihara S, Yoshimura H: Unique induction of cytochrome p-450 isoenzymes in rat liver microsomes by treatment with 3,4,5,3',4'- pentachlorobiphenyl and its effects on testosterone metabolism. J Pharmacobio-Dyn 8: 948-957, 1985

41. Abiola F, Lorgue G, Benoit E, Soyez D, Riviere JL: Effects of PCBs on plasma enzymes, testosterone level, and hepatic xenobiotic metabolism in the grey partridge, Perdix perdix. Bull Envir Contam Toxicol 43: 473-480, 1989

42. Yeowell HN, Waxman DJ, Wadhera A, Goldstein JA: Suppression of the constitutive, male-specific rat hepatic cytochrome p-450 2c and its mRNA by 3,4,5,3',4',5'-hexachlorobiphenyl and 3-methylcholanthrene. Mol Pharmacol 32: 340-347, 1987

43. Yeowell HN, Waxman DJ, LeBlanc GA, Linko P, Goldstein JA: Suppression of male-specific cytochrome p450 2c and its mRNA by 3,4,3',4',5'-hexachlorobiphenyl in rat liver is not causally related to changes in serum testosterone. Arch Biochem Biophysics 271: 508-514, 1989

44.Desauliniers D, Poon R, Phan W, Leingartner K, Foster WG, Chu I: Reproductive and thyroid hormone levels in rats following 90-day exposure to PCB 28 (2,4,4'-trichlorobiphenyl) or PCB 77 (3,3',4,4'-tetrachlorobiphenyl. Toxicol Ind Health 13: 627-638, 1997

45. McKinney JD, Waller CL: Polychlorinated biphenyls as hormonally active structural analogues. Environ Health Perspect 102: 290-297, 1994

46. Corey DA, Juarez de Ku LM, Bingman VP, Meserve LA: Effects of exposure to polychlorinated biphenyl (PCB) from conception on growth, and development of endocrine, neurochemical, and cognitive measures in 60 day old rats. Growth, Development and Aging 60: 131-143, 1996

47. Kato Y, Haraguchi K, Shibahara T, Masuda Y, Kimura R: Reduction of thyroid hormone levels by methylsulfonyl metabolites of polychlorinated biphenyl congeners in rats. Arch Toxicol 72: 541-544, 1998

48. Visser TJ, Kaptein E, van Toor H, van Raaij JAGM, van den Berg KJ, Joe CTT, van Engelen JGM, Brouwer A: Glucuronidation of thyroid hormone in rat liver: effects of in vivo treatment with microsomal enzyme inducers and in vitro assay conditions. Endocrinology 133: 2177-2186, 1993

49. Brouwer A, Ahlborg VG, Van den Berg M, Birnbaum LS, Boersma ER, Bosveld B, Denison MS, Gray LE, Hagmar L, Holene E, Huisman M, Jacobson SW, Jacobson JL, Koopman-Esseboom C, Koppe JG, Kulig BM, Morse DC, Muckle G, Peterson RE, Sauer PJJ, Seegal RF, Smits-Van Prooije AE, Touwen BCL, Weisglas-Kuperus N, Winneke G: Functional aspect of developmental toxicology of polyhalogenated aromatic hydrocarbons in experimental animals and human infants. Eur J Pharmacol Environ Toxicol Pharmacol Section 293: 1-40, 1995

50. Murai K, Okamura K, Tsuji H, Kajiwara E, Watanabe D, Akagi K, Fujishima M: Thyroid function in "Yusho" patients exposed to polychlorinated biphenyls (PCB). Environ Res 44: 179-187, 1987

51. Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, Lutkeschipholt IJ, Van der Paauw CG, Tuinstra LGMT, Brouwer A, Sauer PJJ: Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. Pediatric Res 36: 468-473, 1994

52. Pluim HJ, de Vijlder JJM, Olie K, Kok JH, Vulsma T, van Tijn DA, van der Slikke JW, Koppe JG: Effects of pre- and postnatal exposure to chlorinated dioxins and furans on human neonatal thyroid hormone concentrations. Environ Health Perspect 101: 504-508, 1993

53. Nagayama J, Iida T, Hirakawa H, Matsueda T, Okamura K, Hasegawa M, Sato K, Ma HY, Yanagawa T, Igarashi H, Fukushige J, Watanabe T: Effects of lactational exposure to chlorinated dioxins and related chemicals on thyroid functions in Japanese babies. Organohalogen Compounds 33: 446-450, 1997

54. Porterfield SP: Vulnerability of the developing brain to thyroid abnormalities: Environmental insult to the thyroid system. Environ Health Perspect 102 (Suppl 2): 125-130, 1994

55. Jansen HT, Cooke PS, Porcelli J, Liu TC, Hansen LG: Estrogenic and antiestrogenic actions of PCBs in the female rat: in vitro and in vivo studies. Reproduc Toxicol 7: 237-248, 1993

56. Korach KS, Sarver P, Chae K, McLachlan JA, McKinney JD: Estrogen receptor-binding activity of polychlorinated hydroxybiphenyls: conformationally restricted structural probes. Mol Pharmacol 33: 120-126, 1988

57. Nesaretnam K, Corcoran D, Dils RR, Darbe P: 3,4,3',4'-tetrachlorobiphenyl acts as an estrogen in vitro and in vivo. Mol Endocrinol 10: 923-936, 1996

58. Moore M, Mustain M, Daniel K, Chen I, Safe S, Zacharewski T, Gillesby B, Joyeux A, Balaguer P: Antiestrogenic activity of hydroxylated polychlorinated biphenyl congeners identified in human serum. Toxicol Appl Pharmacol 142: 160-168, 1997

59. Mendola P, Buck GM, Sever LE, Zielezny M, Vena JE: Consumption of PCB-contaminated freshwater fish and shortened menstrual cycle length. Am J Epidemiol 146: 955-960, 1997

60. Tryphonas H, Luster MI, White KL, Naylor PH, Erdos MR, Burleson GR, Germolec D, Hodgen M, Hayward S, Arnold DL: Effects of PCB (Aroclor 1254) on non-specific immune parameters in rhesus (Macaca mulatta) monkeys. Int J Immunopharmac 13: 639-647, 1991

61. Arnold DL, Bryce F, McGuire PF, Stapley R, Tanner JR, Wrenshall E, Mes J, Fernie S, Tryphonas H, Hayward S, Malcolm S: Toxicological consequences of Aroclor 1254 ingestion by female rhesus (Macaca mulatta) monkeys. Part 2. Reproduction and infant findings. Fd Chem Toxic 33: 457-474, 1995

62. Fowles JR, Fairbrother A, Trust KA, Kerkvliet NI: Effects of Aroclor 1254 on the thyroid gland, immune function, and hepatic cytochrome p450 activity in mallards. Environ Res 75: 119-129, 1997

63. Fernlof G, Gadhasson I, Podra K, Darnerud PO, Thuvander A: Lack of effects of some individual polybrominated diphenyl ether (PBDE) and polychlorinated biphenyl (PCB) congeners on human lymphocyte functions in vitro. Toxicology Letters 90: 189-197, 1997

64. Omara FO, Flipo D, Brochu C, Denizeau F, Brousseau P, Potworowski EF, Fournier M: Lack of suppressive effects of mixtures containing low levels of methylmercury (meHg), polychlorinated dibenzo-p-dioxins (PCDDS), polychlorinated dibenzofurans (PCDFS), and Aroclor biphenyls (PCBs) on mixed lymphocyte reaction, phagocytic, and natural killer cell activities of rat leukocytes in vitro. J Toxicol Environ Health Part A, 54: 561-577, 1998

65. Lu YC, Wu YC: Clinical findings and immunological abnormalities in Yu-Cheng patients. Environ Health Perspect 59: 17-29, 1985

66. Nakanishi Y, Shigematsu N, Kurita Y, Matsuba K, Kanegae H, Ishimaru S, Kawazoe Y: Respiratory involvement and immune status in Yusho patients. Environ Health Perspect 59: 31-36, 1985

67. Nagayama J, Iida T, Hirakawa H, Matsueda T, Tsuji H,, Hasegawa M, Sato K, Ma HY, Yanagawa T, Igarashi H, Fukushige J, Watanabe T: Effects of lactational exposure to chlorinated dioxins and related chemicals on lymphocyte subpopulations in Japanese babies. Organohalogen Compounds 33: 440-445, 1997

68. Svensson BG, Hallberg T, Nilsson A, Schutz A, Hagmar L: Parameters of immunological competence in subjects with high consumption of fish contaminated with persistent organochlorine compounds. Int Arch Occup Environ Health 65: 351-358, 1994

69. National Institute of Public Health and the Environment: Report of the Bilthoven Symposium: Advancement of epidemiological studies in assessing the human health effects of immunotoxic agents in the environment and the workplace. November 12-14, 1997. Bilhoven, The Netherlands.

70. Tryphonas H: Immunotoxicity of PCBs (Aroclors) in relation to Great Lakes. Environ Health Perspect 103 (Supp 9): 35-46, 1995

71. Harper N, Connor K, Steinberg M, Safe S: Immunosuppressive activity of polychlorinated biphenyl mixtures and congeners: nonadditive (antagonistic) interactions. Fund Appl Toxicol 27: 131-139, 1995

72. Smialowicz RJ, DeVito MJ, Riddle MM, Williams WC, Birnbaum LS: Opposite effects of 2,2',4,4',5,5'-Hexachlorobiphenyl and 2,3,7,8-tetrachlorodibenzo-p-dioxin on the antibody response to sheep erythrocytes in mice. Fundam Appl Toxicol 37: 141-149, 1997

73. Rylander L, Stromberg U, Hagmar L: Decreased birthweight among infants born to women with a high dietary intake of fish contaminated with persistent organochlorine compounds. Scand J Work Environ Health 21: 368-375, 1995

74. Mocarelli P, Brambilla P, Gerthoux PM, Patterson DG Jr, Needham LL: Change in sex ratio with exposure to dioxin. Lancet 348: 409, 1996

75. Guo YL, Lambert GH, Hsu CC: Growth abnormalities in the population exposed in utero and early postnatally to polychlorinated biphenyls and dibenzofurans. Environ Health Perspect 103 (Suppl 6): 117-122, 1995

76. Chao WY, Hsu CC, Guo YL: Middle-ear disease in children exposed prenatally to polychlorinated biphenyls and polychlorinated dibenzofurans. Arch Environ Health 52: 257-262, 1997

77. Jacobson SW, Fein GG, Jacobson JL, Schwartz PM, Dowler JK: The effect of intrauterine PCB exposure on visual recognition memory. Child Development 56: 853-860, 1985

78. Jacobson JL, Jacobson SW, Humphrey HEB: Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J Pediatr 116: 38-45, 1990

79. Jacobson JL, Jacobson SW: Intellectual impairment in children exposed to polychlorinated biphenyls in utero. New Eng J Med 335: 783-189, 1996

80. Gladen BC, Rogan WJ, Hardy P, Thullen J, Tingelstad J, Tully M: Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichlorethene transplacentally and through human milk. J Pediatr 113: 991-995, 1988

81. Huisman M, Koopman-Esseboom C, Fidler V, Hadders-Algra M, van der Paauw CG, Tuinstra LGMTh, Weisglas-Kuperus N, Sauer PJJ, Touwen BCL, Boersma ER: Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. Early Human Development 41: 111-127, 1995

82. Pluim HP, van der Goot M, van der Slikke JW, Koppe JG: Missing effects of background dioxin exposure on development of breast-fed infants during the first half year of life. Chemosphere 33: 1307-1315, 1996

83. Lonky E, Reihman J, Darvill T, Mather J, Daly H: Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. J Great Lakes Res 22: 198-212, 1995

84. Amenta, F., Zaccheo, D. And Collier, W.L. (1991). Neurotransmitters, neuroreceptors and aging. Mechanisms of Aging and Development **61**, 249-273.

85. McGeer, PL, Itagaki S, Akiyama H, and McGeer EG (1989). Comparison of neuronal loss in Parkinson's disease and aging. In, "Parkinsonism and Aging" (D.B. Calne, D. Guippa, M. Trabucchi, G. Comi and R. Horowski, Eds.), pp. 25-34, Raven Press, New York, NY.

86. Weiss, B: Risk assessment: The insidious nature of neurotoxicity and the aging brain. Neurotoxicology 11, 305-314, 1990.

87. Tanner CM: The role of environmental toxins in the etiology of Parkinson's Disease. Trends Neurosci. 12, 49-54, 1989.

88. Seegal RF, Bush B, and Brosch KO: Decreases in dopamine concentrations in adult, non-human primate brain persist following removal from polychlorinated biphenyls. Toxicology 86 71-87, 1994.

89. Bogen KT, Gold LS: Trichloroethylene cancer risk: simplified calculation of PBPK-based MCLs for cytotoxic end points. Reg Toxicol Pharmacol 25: 26-42, 1997

90. Tola S, Vilhunen R, Jarvinen E, Korkala ML. A Cohort Study on Workers Exposed to TCE. JOM 22: 737-740, 1980.

91. Axelson O, Selden A, Andersson K, Hogstedt C: Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. JOM 36: 256-262, 1994

92. Anttila A, Pukkala E, Sallmen M, Hernberg S, Hemminki K: Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. JOEM 37: 797-806, 1995

93. Morgan RW, Kelsh MA, Zhao K, Heringer S: Mortality of aerospace workers exposed to tricloroethylene. Epidemiology 9: 424-431, 1998

94. Spirtas R, Stewart PA, Lee JS, Marano DE, Forbes CD, Grauman DJ, Pettigrew HM, Blair A, Hoover RN, Cohen JL: Retrospective cohort mortality study of workers at an aircraft maintenance facility I Epidemiological results. Brit j Ind Med 48: 515-530, 1991

95. Blair A, Hartge P, Stewart PA, McAdams M, Lubin J: Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow-up. Occup Environ Med 55: 161-171, 1998

96. Lagakos SW, Wessen BJ, Zelen M. An Analysis of Contaminated Well Water and Health Effects in Woburn, Massachusetts. J Am Stat Soc 81:583-596, 1986;

97 Fagliano J, Berry M, Bove F, Burke T. Drinking Water Contamination and the Incidence of Leukemia: an Ecologic Study. AJPH 80:1209-1212, 1990.

98. Feldman RG, Chirico-Post J, Proctor SP. Blink Reflex Latency after Exposure to Trichloroethylene in Well Water Arch Environ Health 43:143-148, 1988.

99. Kilburn KH, Warshaw RH. Prevalence of Symptoms of SLE and of Fluorescent Antinuclear Antibodies Associated with Chronic Exposure to TCE ant other Chemicals in Well Water. Environ Res 57:1-9, 1992.

100. Goldberg SJ, Lebowizt MD, Graver EJ, Hicks S. An Association of Human Congenital Cardiac Malformations and Drinking Water Contaminants. JACC 16:155-164, 1990.

101. Dawson BV, Johnson PD, Goldberg SJ, Ulreich JB. Cardiac Teratogenesis of TCE and DCE in a Mammalian Model. JACC 16:1304-9, 1990;

102. Dawson BV, Johnson PD, Goldberg SJ, Ulreich JV. Cardiac Teratogenesis of Halogenated Hydrocarbon-Contaminated Drinking Water. JACC. 21:1466-72, 1993.

103. Chia SE, Goh VHH, Ong CN: Endocrine profiles of male workers with exposure to trichloroethylene. Am J Ind Med 32: 217-222, 1997

104. Goh VH, Chia SE, Ong CN: Effects of chronic exposure to low doses of trichloroethylene on steroid hormone and insulin levels in normal men. Environ Health Perspect 106: 41-44, 1998

105. Ward EM, Ruder AM, Suruda A, Smith AB, Fessler-Flesch CA, Zahm SH: Acute and chronic liver toxicity resulting from exposure to chlorinated naphthalenes at a cable manufacturing plant during World War II. Am J Indust Med 30: 225-233, 1996

106. Ward EM, Ruder AM, Suruda A, Smith AB, Halperin W, Fessler CA, Zahm SH: Cancer mortality patterns among female and male workers employed in a cable manufacturing plant during World War II. JOM 36: 850-868, 1994

107. Phillips DL, Pirkle JL, Burse VW, Bernert JT, Henderson LO, Needham LL: Chlorinated hydrocarbon levels in human serum: Effects of fasting and feeding. Arch Environ Contam Toxicol 18: 495-500, 1989

108. Ballschmiter K, Zell M: Fresenius Z. Anal Chem., 302:20-31, 1980

109. Burse VW et al: Use of reference pools to compare the qualitative and quantitative determination of polychlorinated biphenyls by packed and capillary gas chromatography with electron capture detection. Part 1 Serum. Analyst 115: 243-251, 1990

110. Szaz GZ: A kinetic photometric method for serum gamma-glutamyl transpeptidase. Clin Chem 15: 124-136, 1969

111. International Federation of Clinical Chemistry, Clin Chem 23: 887. 1977

112. IFCC Methods for the measurement of catalytic concentrations of enzymes. part 3, IFCC. Method for alanine aminotransferase (l-alanine2-oxoglutarate aminotransferase, ec 2.6.1.2). Clin Chim Acta 105:145F-72F, 1980

113. Bowers GN, McComb RB: Measurement of total alkaline phosphatase activity in human serum. Clin Chem 21: 1988-1995, 1975

114. Tietz NW, ed Textbook of Clinical Chemistry, WB Saunders, 1986

115. Wacker WEC, Ulmer DD, Vallee BL: N Eng J Med 255: 499, 1956

116. Henderson DR, Friedman SB, Harris JD et al: Cedia TM, a new homogenous immunoassay system. Clin Chem 32: 1637-1641, 1986

117. Chodra IJ: A radioimmunoassay for measurement of thyroxine in unextracted serum.. J Clin Endocrinol Metab 34: 938-947, 1972

118. Hollander CS, Shenkman L, Mitsuma T, Asper SP: Triodothyronine toxicosis developing during antithyroid drug therapy for hyperthyroidism. Johns Hopkins Med J 131: 184-188,1972

119. Eastman CJ et al: The radioimmunoassay of triiodothyronine and its clinical application. J Clin Path 28: 225-230, 1975

120. Kowalski W, Chatterton Rt, Jr: Peripheral and not central suppression of ovarian function during osmotic pump infusion of ACTH (1-24) for one menstrual cycle in the cynomology monkey, and its partial compensation by a transitory elevation of sex hormone-binding globulin levels. Endocrinology 130: 3582-3592, 1992

121. Persky VW, Chatterton RT, Van Horn LV, Grant MD, Langenberg P, Marvin J: Hormone levels in vegetarian and nonvegetarian teenage girls: potential implications for breast cancer risk. Cancer Res 52: 578-583, 1992

122. Chatterton RT, Jr, Kazer RR, Rebar RW: Depletion of luteal phase progesterone during constant infusion of cortisol phosphate in the cynomologus monkey. Fertil Steril 56: 547-554, 1991

123. Hudgkins GA, Chatterton RT, Jr, Torre J, Jr, Slager SE, Fatkin LT, Keith LG, Rebar RW, DeLeon-Jones FA, King JM: Hormonal and psychological profiles in response to a written examination. In Molecular Biology of Stress. UCLA Symposia on Molecular and Cellular Biology. New Series Vol 97, edited by Zinder O and Bresnitz S, New York, NY: Alan R Liss, Inc, 1988

124. Kustin J, Kazer RR, Hohffman DI, Chatterton RT, Jr, Haan JN, Green OC, Rebar RW: Insulin resistance and abnormal ovarian responses to human chorionic gonadotropin in chronically anovulatory women. Am J Obstet Gynecol 157: 1468-1473, 1987

125. Bonfrer JMG, Bruning PF, Nooijen WJ: A simple method for the measurement of the steroid fraction bound to sex hormone binding globulin in serum. J Steroid Biochem 33: 227-231, 1989

126. Street C, Howell RJS, Perry L, Al-Othman S, Chard T: Inhibition of binding of gonadal steroids to serum binding proteins by non-esterified fatty acids: the influence of chain length and degree of unsaturation. Acta Endocrinol 120: 175-179, 1989

127. Street C, Howell RJS, Perry L, Al-Othman S, Chard T: Inhibition of binding of gonadal steroids to serum binding proteins by non-esterified fatty acids: the influence of chain length and degree of unsaturation. Acta Endocrinol 120: 175-179, 1989

128. Reimer CB, Smith SJ, Wells TW, Nakamura RM, Keitges PW, Ritchie RF et al: Collaborative calibration of the U.S. National and the College of American Pathologists Reference Preparations for Specific Serum Proteins. Am J Clin Path 77: 12-19, 1982

129. Margolick JB, Scott ER, Chadwick K, Shapiro HM, Hetzel AD, Smith SJ, Vogt RF: Comparison of lymphocyte immunophenotypes obtained from two different data acquisition and analysis systems simultaneously on the same flow cytometer. Cytometry 13: 198-203, 1992

130. Vogt RF, Cross GD, Phillips DL, Henderson LO:. A model system evaluating fluorescein-labeled microbeads as internal standards to calibrate fluorescence intensity on flow cytometers. Cytomtetry 10: 294-302, 1989

131. Vogt RF, Henderson LO, Ethridge SF, Huang EY, White JT, Meredith NK: Lymphocyte immunophenotyping with extended quantitative analysis of list mode files for epidemiologic health studies. Ann New York Acad Sci 677: 462-464, 1993

132. Schwartz S, Edmondson P, Stephenson B, Sarker D, Freyholtz H: Direct spectrofluorimetric determination of porphyrin in diluted urine. Ann Clin Res 8: 156-167, 1976

133. Debets FMH, Reeinders JH, Debets AJM, Lossbroek TG, Strik JJTWA, Koss G: Biotransformation and porphyinogenic action of hexachlorobenzene and its metabolites in a primary liver cell culture. Toxicology 19: 185-196, 1981

134. McCullagh P and Nelder JA: Generalized Linear Models. London: Chapman and Hall, 1989

135. Neter J, Kutner M, Nachtsheim C, and Wasserman W: Applied Linear Statistical Models. McGraw-Hill, 1996

136. Hosmer D and Lemeshow S: Applied Logistic Regression. John Wiley and Sons, 1989

137. Patnode LA, Curtis LR: 2,2',4,4',5,5'- and 3,3',4,4',5,5'-hexachlorobiphenyl alteration of uterine progesterone and estrogen receptors coincides with embryo toxicity in mink (Mustela vison). Toxicol Appl Phamacol 127: 9-18, 1994

138. Bradlow HL, Davis DL, Lin G, Sepkovic D, Tiwari R: Effects of pesticides on the ratio of 16alpha/2-hydroxyestrone: a biologic marker of breast cancer risk. Environ Health Perspect 103 (Supp): 147-150, 1995

139. Fraumeni JF, Devesa SS, McLaughlin JK, Stanford JL: Biliary Tract Cancer. in Schottenfeld D and Fraumeni JF, ed. Cancer Epidemiology and prevention. Oxford University Press, New York, Oxford, pp794-805, 1996

140. Henriksen GL, Ketchum NS, Michalek JE, Swaby JA: Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. Epidemiology 8: 252-258, 1997

141.Bertazzi PA, Bernucci I, Brambilla G, Consonni D, Pesatori AC: The Seveso studies on early and long-term effects of dioxin exposure: A review. Environ Health Perspect 106 (Suppl 2): 625-633, 1998

142. Vena J, Boffetta P, Becher H, Benn T, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N, Pesatori AC, Saracci R, Steenland K, Kogevinas M: Exposure to dioxin and nonneoplastic

mortality in the expanded IARC International Cohort Study of Phenoxy Herbicide and Chlorophenol Production Workers and Sprayers. Environ Health Perspect 106 (Suppl 2) 645-653, 1998

143. Brouwer A, Klasson-Webler E, Bokdam, Morse DE, Traag WA: Competitive inhibition of thyroxin binding to transthyretin by monohydroxy metabolites of 3,4,3',4'-tetrachlorobiphenyl. Chemosphere 20: 1257-1262, 1990

144. Mebus CA, Reddy VR, Piper WN: Depression of rat testicular 17-hydroxylase and 17,20-lyase after administration of 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) Biochem Phamacol 36: 727-731, 1987

145. Moore RW, Jefcoate CR, Peterson RE: 2,3,7,8-Tetrachlorodibenzo-p-dioxin inhibits steroidogenesis in the rat testis by inhibiting the mobilization of cholesterol to cytochrome $p450_{scc}$ Toxicol Appl Pharmacol 109: 85-97, 1991

146. Egeland GM, Sweeney MH, Fingerhut MA, Wille KK, Schnorr TM, Halpern WE: Total serum testosterone and gonadotropins in workers exposed to dioxins. Am J Epidemiol 139: 272-281, 1994

147. Henriksen GL, Michalek JE, Swaby JA, Rahe AJ: Serum dioxin, testosterone, and gonadotropins in veterans of Operation Ranch Hand. Epidemiology 7: 352-357, 1996

148. Danesh J, Collins R, Appleby P, Peto R: Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease. JAMA 279: 1477-1482, 1998

149. Maccio A, Lai P, Santona MC, Pagliara L, Melis GB, Mantovani G: High serum levels of soluble IL-2 receptor, cytokines and C reactive protein correlate with impairment of T cell response in patients with advance epithelial ovarian cancer. Gynecologic Oncology 69: 248-252, 1998

150. Pluim HJ, van der Goot M, Oliek, van der Slikke JW, Koope JG: Missing effects of background dioxin during the first half year of life. Chemosphere 33: 1307-1315, 1996

151. Phillips DL, Smith AB, Burse VW, Steele GK, Needham LL, Hannon WH: Half-life of polychlorinated biphenyls in occupationally exposed workers. Arch Environ Health 44: 351-354, 1989

152. Shirai JH, Kissel JC: Uncertainty in estimated half-lives of PCBs in humans: impact on exposure assessment. Sci Total Environ 187: 199-210, 1996

APPENDIX A - TABLES OF OTHER BIOMARKER RESULTS

Appendix Table 1 - PCB Congener Limits of Detection (all values in ng/ml or ppb)

Analyte	Limit of Detection
PCB028	0.03
PCB052	0.02
PCB056+060	0.08
PCB066	0.05
PCB074	0.05
PCB099	0.05
PCB101	0.05
PCB105	0.05
PCB110	0.06
PCB118	0.05
PCB130	0.12
PCB137	0.10
PCB138	0.03
PCB146	0.04
PCB149	0.08
PCB153	0.04
PCB156	0.03
PCB157	0.07
PCB167	0.10
PCB170	0.03
PCB171	0.08
PCB172	0.06
PCB177	0.05
PCB178	0.05
PCB180	0.02
PCB183	0.05
PCB187	0.03
PCB189	0.04
PCB191	0.08
PCB193	0.06
PCB194	0.04
PCB195	0.04
PCB201	0.06
PCB203	0.04
PCB205	0.09
PCB206	0.02
PCB208	0.08
PCB209	0.06

Appendix Table 2 - Relationship of EUC Quarters Worked with Liver Biomarkers-Women*

Biomarker	n		non-workers n=19	1-4 qrts n=24	5-24 qrts n=46	25+ qrts n=57	Spearman Correlation		
								Model 1	Model 2
Bilirubin in mg/dl	146	mean	0.8	0.7	0.7	0.7	r	-.11	-.16
		std.dev.	0.3	0.2	0.3	0.2	p-value	.1697	.0540
Alkaline Phosphatase in u/l	**146**	**mean**	**66.7**	**64.3**	**79.3**	**86.6**	**r**	**.19**	.12
		std.dev.	**20.8**	**17.9**	**58.6**	**80.5**	**p-value**	**.0222**	.1547
GGT in u/l	146	mean	34.6	22.5	36.5	60.7	r	.09	.01
		std.dev.	43.4	18.2	57.1	170.2	p-value	.2946	.9383
AST (SGOT) in u/l	146	mean	21.7	17.5	20.6	19.9	r	-.09	-.12
		std.dev.	10.4	6.3	11.1	20.8	p-value	.2578	.1726
ALT (SGPT) in u/l	146	mean	21.4	14.3	22.1	21.0	r	-.07	-.07
		std.dev.	17.1	4.9	23.5	42.7	p-value	.3772	.4070
Total LDH in u/l	140	mean	155.5	147.9	159.1	156.2	r	.02	-.06
		std.dev.	25.4	28.0	42.1	32.7	p-value	.7959	.4895
Porphyrin/Creatinine in ug/ml	144	mean	.07	.08	.08	.09	r	-.01	-.07
		std.dev.	.02	.04	.04	.07	p-value	.8942	.4266

*This sample of women excludes those on steroid and oral contraceptive medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinals exposure variable when the effect of the following confounders are removed: age, BMI, diabetes, alcoholic drinks/month, estrogen related meds, and menopausal status.

Appendix Table 3 - Relationship of EUC Job Exposure Score with Liver Biomarkers-Women*

Biomarker	n		non-workers n=19	score 1-71 n=39	score 72-294 n=43	score 295+ n=45	Spearman Correlation		
								Model 1	Model 2
Bilirubin in mg/dl	**146**	**mean**	**0.8**	**0.7**	**0.7**	**0.7**	**r**	**-.13**	**-.19**
		std.dev.	**0.3**	**0.2**	**0.2**	**0.2**	**p-value**	**.1166**	**.0263**
Alkaline Phosphatase in u/l	**146**	**mean**	**66.7**	**74.8**	**77.7**	**85.9**	**r**	**.21**	.09
		std.dev.	**20.8**	**62.9**	**46.8**	**80.9**	**p-value**	**.0106**	.2871
GGT in u/l	146	mean	34.6	31.9	30.3	69.5	r	.09	-.02
		std.dev.	43.4	57.8	28.3	190.8	p-value	.2902	.7914
AST (SGOT) in u/l	146	mean	21.7	18.3	19.0	21.6	r	-.05	-.08
		std.dev.	10.4	8.3	8.7	23.7	p-value	.5861	.3676
ALT (SGPT) in u/l	146	mean	21.4	15.3	19.1	25.4	r	-.02	-.04
		std.dev.	17.1	7.9	17.7	50.1	p-value	.8107	.6711
Total LDH in u/l	140	mean	155.5	147.0	162.8	156.5	r	.06	-.06
		std.dev.	25.4	28.7	43.5	31.1	p-value	.5127	.4979
Porphyrin/Creatinine in ug/mg	144	mean	.07	.08	.09	.07	r	-.05	-.11
		std.dev.	.02	.05	.08	.03	p-value	.5751	.2167

*This sample of women excludes those on steroid and oral contraceptive medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, diabetes, alcoholic drinks/month, estrogen related meds, and menopausal status.

Appendix Table 4 - Relationship of EUC Quarters Worked Exposure with Liver Biomarkers-Men*

Biomarker	n		non-workers n=5	1-4 qrts n=14	5-24 qrts n=21	25+ qrts n=24	Spearman Correlation		
								Model 1	Model 2
Bilirubin in mg/dl	64	mean	0.8	0.9	1.1	0.9	r	.08	.12
		std.dev.	0.1	0.3	0.4	0.2	p-value	.5321	.3630
Alkaline Phosphatase in u/l	64	mean	73.6	64.4	65.0	63.3	r	-.11	-.09
		std.dev.	6.8	16.1	17.1	14.8	p-value	.3758	.4747
GGT in u/l	64	mean	25.8	38.1	26.8	32.7	r	.03	.10
		std.dev.	4.8	22.0	12.9	13.6	p-value	.7942	.4255
AST (SGOT) in u/l	64	mean	18.2	19.3	20.9	18.7	r	-.06	.04
		std.dev.	1.5	6.2	6.6	5.4	p-value	.6348	.7737
ALT (SGPT) in u/l	64	mean	22.8	21.6	22.4	21.2	r	-.06	.12
		std.dev.	8.6	10.1	13.5	10.0	p-value	.6112	.3482
Total LDH in u/l	60	mean	157.5	146.8	158.4	149.0	r	-.09	-.12
		std.dev.	12.5	31.2	24.4	26.4	p-value	.4893	.3667
Porphyrin/Creatinine in ug/mg	64	mean	.08	.07	.07	.07	r	-.01	-.12
		std.dev.	.05	.03	.03	.03	p-value	.9184	.3805

*This sample of men excludes those on steroid medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, diabetics, and alcoholic drinks/month.

Appendix Table 5 - Relationship of EUC Job Exposure Score with Liver Biomarkers-Men*

Biomarker	n		non-workers n=5	score 1-71 n=21	score 72-294 n=21	score 295+ n=17	Spearman Correlation		
								Model 1	Model 2
Bilirubin in mg/dl	64	mean	0.8	0.9	1.0	0.9	r	.14	.21
		std.dev.	0.1	0.2	0.3	0.3	p-value	.2744	.1013
Alkaline Phosphatase in u/l	64	mean	73.6	63.5	64.4	64.7	r	-.05	-.03
		std.dev.	6.8	17.6	16.9	12.2	p-value	.7146	.7922
GGT in u/l	64	mean	25.8	32.9	34.3	31.4	r	.07	.17
		std.dev.	4.8	19.5	12.4	15.1	p-value	.6024	.1835
AST (SGOT) in u/l	64	mean	18.2	19.0	21.3	18.2	r	-.06	.09
		std.dev.	1.5	6.0	6.1	5.7	p-value	.6310	.4716
ALT (SGPT) in u/l	64	mean	22.8	20.5	25.4	18.7	r	-.11	.18
		std.dev.	8.6	10.5	11.9	10.5	p-value	.4027	.1696
Total LDH in u/l	60	mean	157.5	152.4	148.0	154.9	r	-.05	-.11
		std.dev.	12.5	29.6	22.9	28.9	p-value	.6946	.4331
Porphyrin/Creatinine in ug/mg	64	mean	.08	.07	.06	.08	r	.11	-.03
		std.dev.	.05	.03	.02	.03	p-value	.3959	.8066

*This sample of men excludes those on steroid medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, diabetes, and alcoholic drinks/month.

Appendix Table 6 - Relationship of EUC Quarters Worked with Lipid Biomarkers-Women*

Biomarker	n		non-EUC workers n=12	1-4 qrts n=12	5-24 qrts n=26	25+ qrts n=29	Spearman Correlation		
								Model 1	Model 2
Triglycerides in mg/dl	**79**	**mean**	121.7	141.0	151.5	159.5	r	.22	.22
		std.dev.	85.5	89.9	64.7	79.9	p-value	.0495	.0549
Total Cholesterol in mg/dl	79	mean	225.1	262.8	236.7	233.3	r	-.03	-.04
		std.dev.	32.0	58.7	36.8	42.4	p-value	.7796	.7659
HDL Cholesterol in mg/dl	79	mean	53.9	51.8	50.0	48.6	r	-.13	-.10
		std.dev.	16.3	13.6	12.4	11.3	p-value	.2423	.3750
LDL Cholesterol in mg/dl	78	mean	146.8	182.8	156.5	153.7	r	-.02	-.04
		std.dev.	32.9	61.0	31.1	41.7	p-value	.8708	.7441
Total Chol/HDLC	79	mean	4.5	5.5	5.0	5.0	r	.07	.04
		std.dev.	1.3	2.2	1.4	1.5	p-value	.5685	.7396

*This sample of women excludes pre-menopausal women, diabetics and those on estrogen-related, steroid, and anti-lipidemic medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, current smoking status, alcoholic drinks/month, and thyroid meds.

Appendix Table 7 - Relationship of EUC Job Exposure Score with Lipid Biomarkers-Women*

Biomarker	n		non-workers n=12	score 1-71 n=20	score 72-294 n=22	score 295+ n=25	Spearman Correlation		
								Model 1	Model 2
Triglycerides in mg/dl	79	mean	121.7	142.9	169.2	147.1	r	.17	.17
		std.dev.	85.5	74.5	91.0	60.3	p-value	.1387	.1571
Total Cholesterol in mg/dl	79	mean	225.1	249.3	244.2	228.6	r	-.04	-.04
		std.dev.	32.0	49.0	43.8	40.1	p-value	.7444	.7501
HDL Cholesterol in mg/dl	79	mean	53.9	49.2	50.1	49.8	r	-.05	-.02
		std.dev.	16.3	11.9	12.8	11.9	p-value	.6690	.8495
LDL Cholesterol in mg/dl	78	mean	146.8	171.6	161.9	149.4	r	-.03	-.06
		std.dev.	32.9	50.9	38.5	38.4	p-value	.7626	.6345
Total Chol/HDLC	79	mean	4.5	5.4	5.2	4.8	r	-.00	-.03
		std.dev.	1.3	1.9	1.5	1.4	p-value	.9754	.7753

*This sample of women excludes pre-menopausal women, diabetics and those on estrogen-related, steroid, and anti-lipidemic medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, current smoking status, alcoholic drinks/month, and thyroid meds.

Appendix Table 8 - Relationship of EUC Quarters Worked Exposure with Lipid Biomarkers-Men*

Biomarker	n		non-workers n=5	1-4 qrts n=13	5-24 qrts n=15	25+ qrts n=19	Spearman Correlation		
								Model 1	Model 2
Triglycerides in mg/dl	52	mean	193.6	132.1	140.7	151.2	r	.06	.13
		std.dev.	147.1	72.4	83.3	66.9	p-value	.6822	.3830
Total Cholesterol in mg/dl	52	mean	201.8	200.0	201.4	220.2	r	.20	.27
		std.dev.	58.9	36.0	39.6	29.1	p-value	.1472	.0642
HDL Cholesterol in mg/dl	52	mean	40.6	43.1	40.9	41.7	r	-.08	-.15
		std.dev.	8.8	14.4	10.4	13.9	p-value	.5965	.3233
LDL Cholesterol in mg/dl	**51**	**mean**	115.3	130.5	132.3	148.3	r	.26	.32
		std.dev.	40.9	36.2	38.0	27.3	p-value	.0642	.0285
Total Chol/HDLC	52	mean	5.4	5.1	5.3	5.8	r	.13	.21
		std.dev.	2.5	1.8	1.9	1.9	p-value	.3451	.1515

*This sample of men excludes diabetics and those on steroid, thyroid, and anti-lipidemic medications.
Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.
Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, current smoking status, and alcoholic drinks/month.

Appendix Table 9 - Relationship of EUC Job Exposure Score with Lipid Biomarkers-Men*

Biomarker	n		non-workers n=5	score 1-71 n=19	score 72-294 n=16	score 295+ n=12	Spearman Correlation		
								Model 1	Model 2
Triglycerides in mg/dl	52	mean	193.6	147.9	144.1	131.9	r	-.10	-.01
		std.dev.	147.1	78.1	75.8	64.2	p-value	.4797	.9617
Total Cholesterol in mg/dl	52	mean	201.8	209.9	204.4	212.2	r	-.00	.08
		std.dev.	58.9	39.9	30.3	35.7	p-value	.9771	.5830
HDL Cholesterol in mg/dl	52	mean	40.6	40.7	42.5	42.7	r	.06	-.04
		std.dev.	8.8	12.7	14.5	11.3	p-value	.6533	.7644
LDL Cholesterol in mg/dl	51	mean	115.3	139.6	133.0	143.1	r	.06	.14
		std.dev.	40.9	39.7	29.3	31.0	p-value	.6892	.3480
Total Chol/HDLC	52	mean	5.4	5.6	5.3	5.3	r	-.06	.04
		std.dev.	2.5	1.9	1.9	1.8	p-value	.6626	.7822

*This sample of men excludes diabetics and those on steroid, thyroid, and anti-lipidemic medications.
Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.
Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, current smoking status, and alcoholic drinks/month.

Appendix Table 10 - Relationship of EUC Quarters Worked with Hormone Levels-Women*

Biomarker	n		non-workers n=13	1-4 qrts n=12	5-24 qrts n=27	25+ qrts n=30	Spearman Correlation		
								Model 1	Model 2
TSH Ultra Sens. in mciu/ml	82	mean	3.1	1.7	4.3	2.5	r	-.03	-.05
		std.dev.	2.8	1.4	5.9	2.4	p-value	.7697	.6895
Triiodothyronine in ng/dl	79	mean	113.4	130.2	131.2	121.3	r	.01	-.01
		std.dev.	15.9	14.3	18.2	19.0	p-value	.9626	.9266
T_3 Uptake in %	**82**	**mean**	**31.9**	**29.5**	**28.1**	**29.3**	**r**	**-.24**	**-.24**
		std.dev.	**2.0**	**2.6**	**3.1**	**3.5**	**p-value**	**.0311**	**.0387**
Total T_4 in mcg/dl	82	mean	7.8	8.4	8.2	8.1	r	.02	.04
		std.dev.	1.3	1.8	1.9	1.6	p-value	.8723	.7059
Free T_4 Index	82	mean	2.5	2.4	2.3	2.4	r	-.08	-.04
		std.dev.	0.4	0.5	0.5	0.5	p-value	.4485	.7316
SHBG in nmol/L	**82**	**mean**	**103.2**	**85.9**	**66.8**	**61.3**	**r**	**-.40**	**-.48**
		std.dev.	**59.9**	**26.0**	**40.8**	**51.9**	**p-value**	**.0002**	**.0001**
DHEA Sulfate in umol/L	82	mean	4.3	3.6	3.3	2.6	r	-.20	-.08
		std.dev.	3.5	2.2	1.8	1.8	p-value	.0702	.4820
Cortisol in nmol/L	82	mean	515.9	462.9	549.1	522.8	r	.06	.08
		std.dev.	180.0	226.7	188.8	214.7	p-value	.5674	.5153
Estradiol (E2) in pmol/L	82	mean	66.2	97.3	78.8	70.0	r	.05	.02
		std.dev.	30.8	118.8	34.6	32.3	p-value	.6518	.8405
FSH in mIU/ml	**82**	**mean**	**64.1**	**46.3**	**51.1**	**42.3**	**r**	**-.31**	**-.30**
		std.dev.	**27.2**	**19.6**	**21.4**	**16.4**	**p-value**	**.0053**	**.0084**
% of E2 bound to SHBG	**82**	**mean**	**38.9**	**38.1**	**31.4**	**31.5**	**r**	**-.28**	**-.36**
		std.dev.	**9.3**	**8.3**	**9.4**	**9.6**	**p-value**	**.0117**	**.0013**
Conc. E2 bound to SHBG in pmol/L	82	mean	26.2	37.1	25.0	22.2	r	-.04	-.08
		std.dev.	17.3	46.3	15.6	12.1	p-value	.7192	.4840
Insulin in uIU/mL	**81**	**mean**	**7.4**	**10.1**	**10.5**	**13.6**	**r**	**.25**	**.23**
		std.dev.	**2.6**	**3.3**	**5.7**	**10.7**	**p-value**	**.0250**	**.0483**

Biomarker	n		non-workers n=13	1-4 qrts n=12	5-24 qrts n=27	25+ qrts n=30	Spearman Correlation		
								Model 1	Model 2
2-OHE_1/Creatinine	**79**	**mean**	**11.2**	**9.1**	**9.2**	**8.2**	**r**	-.19	**-.23**
		std.dev.	**9.3**	**2.8**	**5.3**	**5.7**	**p-value**	.0917	**.0488**
16α-OHE_1/Creatinine	79	mean	5.8	6.4	6.2	4.8	r	-.14	-.16
		std.dev.	3.3	3.5	3.8	2.3	p-value	.2181	.1802
2-OHE_1/16α-OHE_1	79	mean	1.9	1.6	1.7	1.8	r	-.03	-.04
		std.dev.	0.7	0.6	1.0	0.9	p-value	.7806	.7346

*This sample of women excludes pre-menopausal women, diabetics, and those on steroid and estrogen-related medications.
Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.
Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, current smoking status, alcoholic drinks/month, and thyroid meds.

Appendix Table 11 - Relationship of EUC Job Exposure Score with Hormone Levels-Women*

Biomarker	n		non-workers n=13	score 1-71 n=20	score 72-294 n=23	score 295+ n=26	Spearman Correlation		
								Model 1	Model 2
TSH Ultra Sens. in mciu/ml	82	mean	3.1	2.8	4.2	2.2	r	-.06	-.08
		std.dev.	2.8	2.9	6.4	1.6	p-value	.6212	.5049
Triiodothyronine in ng/dl	79	mean	113.4	134.4	123.5	123.2	r	.02	-.02
		std.dev.	15.9	17.9	16.2	19.4	p-value	.8403	.8732
T_3 Uptake in %	82	mean	31.9	28.6	28.2	29.7	r	-.16	-.14
		std.dev.	2.0	2.9	2.7	3.7	p-value	.1577	.2295
Total T_4 in mcg/dl	82	mean	7.8	8.5	7.9	8.3	r	.04	.06
		std.dev.	1.3	2.1	1.5	1.6	p-value	.6928	.6203
Free T_4 Index	82	mean	2.5	2.4	2.2	2.5	r	-.02	.03
		std.dev.	0.4	0.5	0.4	0.5	p-value	.8727	.7963
SHBG in nmol/L	**82**	**mean**	103.2	77.6	65.2	62.4	r	-.36	-.36
		std.dev.	59.9	35.0	41.8	52.8	p-value	.0009	.0014
DHEA Sulfate in umol/L	**82**	**mean**	4.3	4.1	2.5	2.7	r	-.24	-.13
		std.dev.	3.5	2.1	1.3	1.9	p-value	.0334	.2577
Cortisol in nmol/L	82	mean	515.9	501.9	488.9	568.5	r	.13	.16
		std.dev.	180.0	226.9	203.5	191.0	p-value	.2343	.1677
Estradiol (E2) in pmol/L	82	mean	66.2	84.8	75.1	75.9	r	.11	.05
		std.dev.	30.8	93.1	30.9	37.9	p-value	.3289	.6422
FSH in mIU/ml	**82**	**mean**	64.1	48.7	46.2	45.0	r	-.24	-.19
		std.dev.	27.2	22.3	18.3	18.0	p-value	.0308	.0920
% of E2 bound to SHBG	**82**	**mean**	38.9	34.1	32.2	31.8	r	-.20	-.21
		std.dev.	9.3	9.7	9.9	9.2	p-value	.0687	.0686
Conc. E2 bound to SHBG in pmol/L	82	mean	26.2	29.2	24.9	24.1	r	.05	.01
		std.dev.	17.3	36.8	15.4	13.6	p-value	.6822	.9355
Insulin in uIU/mL	81	mean	7.4	10.5	12.6	12.2	r	.18	.05
		std.dev.	2.6	4.5	9.5	9.2	p-value	.1143	.6386

Biomarker	n		non-workers n=13	score 1-71 n=20	score 72-294 n=23	score 295+ n=26	Spearman Correlation		
								Model 1	Model 2
2-OHE_1/Creatinine	79	mean	11.2	8.7	9.6	8.0	r	-.18	-.22
		std.dev.	9.3	3.2	5.8	5.7	p-value	.1111	.0652
16α-OHE_1/Creatinine	79	mean	5.8	6.2	5.7	5.1	r	-.14	-.14
		std.dev.	3.3	3.6	2.5	3.4	p-value	.2333	.2239
2-OHE_1/16α-OHE_1	79	mean	1.9	1.7	1.8	1.8	r	-.03	-.05
		std.dev.	0.7	0.9	0.9	0.9	p-value	.7934	.6813

*This sample of women excludes pre-menopausal women, diabetics, and those on steroid and estrogen-related medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, current smoking status, alcoholic drinks/month, and thyroid meds.

Appendix Table 12 - Relationship of EUC Quarters Worked with Hormone Levels-Men*

Biomarker	n		non-workers n=5	1-4 qrts n=13	5-24 qrts n=17	25+ qrts n=19	Spearman Correlation		
								Model 1	Model 2
TSH Ultra Sens. in mciu/ml	**54**	**mean**	2.7	2.2	2.9	1.6	r	-.36	-.35
		std.dev.	1.2	1.2	4.7	0.8	p-value	.0080	.0115
Triiodothyronine in ng/dl	53	mean	124.4	131.1	121.4	131.2	r	-.03	-.00
		std.dev.	22.9	13.7	15.9	23.7	p-value	.8042	.9904
T_3-Uptake in %	**54**	**mean**	33.0	32.0	31.1	29.8	r	-.29	-.35
		std.dev.	4.8	3.5	2.6	3.7	p-value	.0312	.0124
Total T_4 in mcg/dl	54	mean	6.1	7.9	7.2	8.1	r	.22	.21
		std.dev.	1.2	1.3	1.0	2.0	p-value	.1167	.1480
Free T_4 Index	54	mean	2.0	2.5	2.2	2.4	r	.05	-.00
		std.dev.	0.1	0.3	0.2	0.4	p-value	.7164	.9977
SHBG in nmol/L	54	mean	42.5	36.3	67.1	46.1	r	.03	-.03
		std.dev.	22.2	14.5	51.1	31.9	p-value	.8452	.8236
DHEA Sulfate in umol/L	54	mean	6.5	6.6	7.6	8.0	r	.03	.06
		std.dev.	2.5	3.8	4.8	6.2	p-value	.8224	.6742
Cortisol in nmol/L	**54**	**mean**	440.6	451.6	594.3	606.7	r	.31	.29
		std.dev.	151.7	245.4	221.2	219.7	p-value	.0232	.0431
Estradiol (E2) in pmol/L	54	mean	134.2	131.9	134.2	126.9	r	-.05	-.01
		std.dev.	35.0	43.7	38.5	26.2	p-value	.6954	.9440
LH in mIU/ml	54	mean	3.6	5.2	7.5	6.7	r	.14	.07
		std.dev.	2.2	1.9	6.8	7.1	p-value	.3078	.6126

Biomarker	n		non-workers n=5	1-4 qrts n=13	5-24 qrts n=17	25+ qrts n=19	Spearman Correlation		
								Model 1	Model 2
Testosterone (T) in nmol/L	54	mean	21.1	19.5	24.8	19.6	r	-.00	-.03
		std.dev.	8.0	4.6	12.5	6.5	p-value	.9787	.8356
% of T bound to SHBG	54	mean	28.4	29.9	30.1	30.4	r	.06	-.04
		std.dev.	6.2	6.5	7.7	7.1	p-value	.6890	.7883
Conc. T bound to SHBG in nmol/L	54	mean	6.3	5.9	7.8	6.0	r	-.02	-.07
		std.dev.	3.7	2.0	4.9	2.7	p-value	.8601	.6208
Insulin in uIU/mL	54	std.dev.	17.6	11.6	9.7	12.1	r	-.05	.07
		mean	9.3	5.0	5.4	4.8	p-value	.6954	.6297
2-OHE_1/Creatinine	53	mean	5.0	5.3	7.9	5.8	r	.06	.01
		std.dev.	3.2	2.6	5.3	3.7	p-value	.6641	.9646
16α-OHE_1/Creatinine	53	mean	3.8	3.6	5.0	4.2	r	.01	-.05
		std.dev.	1.1	1.6	3.2	2.6	p-value	.9708	.7335
2-OHE_1/16α-OHE_1	53	mean	1.4	1.7	1.6	1.5	r	-.13	-.12
		std.dev.	0.6	0.6	0.6	0.7	p-value	.3580	.4017

*This sample of men excludes diabetics and those on steroid and thyroid medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, current smoking status, and alcoholic drinks/month.

Appendix Table 13 - Relationship of EUC Job Exposure Score with Hormone Levels-Men*

Biomarker	n		non-workers n=5	score 1-71 n=19	score 72-294 n=18	score 295+ n=12	Spearman Correlation		
								Model 1	Model 2
TSH Ultra Sens. in mcIu/ml	**54**	**mean**	**2.7**	**2.1**	**2.8**	**1.6**	**r**	**-.35**	**-.34**
		std.dev.	**1.2**	**1.0**	**4.6**	**0.4**	**p-value**	**.0094**	**.0162**
Triiodothyronine in ng/dl	53	mean	124.4	127.0	124.9	132.9	r	-.04	.08
		std.dev.	22.9	13.9	16.1	28.8	p-value	.7864	.5850
T_3-Uptake in %	**54**	**mean**	**33.0**	**31.8**	**30.3**	**30.2**	**r**	**-.23**	**-.32**
		std.dev.	**4.8**	**3.3**	**3.5**	**3.2**	**p-value**	**.0958**	**.0251**
Total T_4 in mcg/dl	54	mean	6.1	7.6	7.5	8.3	r	.24	.26
		std.dev.	1.2	1.1	1.2	2.4	p-value	.0849	.0654
Free T_4 Index	54	mean	2.0	2.4	2.2	2.4	r	.11	.09
		std.dev.	0.1	0.3	0.3	0.5	p-value	.4166	.5372
SHBG in nmol/L	54	mean	42.5	40.9	50.2	67.4	r	.16	.06
		std.dev.	22.2	17.2	43.4	50.1	p-value	.2344	.6712
DHEA Sulfate in umol/L	54	mean	6.5	7.2	8.9	5.9	r	-.07	.01
		std.dev.	2.5	4.3	6.0	4.6	p-value	.6343	.9247
Cortisol in nmol/L	54	mean	440.6	494.1	658.9	521.1	r	.19	.17
		std.dev.	151.7	237.6	228.2	193.2	p-value	.1756	.2446
Estradiol (E2) in pmol/L	54	mean	134.2	133.1	138.3	115.8	r	-.11	-.09
		std.dev.	35.0	43.2	25.8	31.2	p-value	.4368	.5364
LH in mIU/ml	54	mean	3.6	5.4	5.9	9.4	r	.15	.05
		std.dev.	2.2	2.0	2.9	11.2	p-value	.2854	.7077

Biomarker	n		non-workers n=5	score 1-71 n=19	score 72-294 n=18	score 295+ n=12	Spearman Correlation		
								Model 1	Model 2
Testosterone (T) in nmol/L	54	mean	21.0	20.8	23.3	19.5	r	.04	.01
		std.dev.	8.0	9.6	8.1	9.2	p-value	.7720	.9214
% of T bound to SHBG	**54**	**mean**	**28.4**	**28.8**	**28.3**	**35.0**	**r**	**-.28**	.15
		std.dev.	**6.2**	**7.1**	**7.2**	**4.4**	**p-value**	**.0430**	.2848
Conc. T bound to SHBG in nmol/L	54	mean	6.3	6.2	6.9	6.7	r	.10	.05
		std.dev.	3.7	3.9	3.6	3.2	p-value	.4799	.7352
Insulin in uIU/mL	54	mean	17.6	11.4	11.5	10.1	r	-.16	-.02
		std.dev.	9.3	5.5	5.3	3.9	p-value	.2494	.9120
2-OHE_1/Creatinine	53	mean	5.0	6.1	6.4	7.1	r	.14	.07
		std.dev.	3.2	3.7	5.1	3.8	p-value	.3278	.6352
16α-OHE_1/Creatinine	53	mean	3.8	4.0	3.9	5.5	r	.09	.01
		std.dev.	1.1	1.9	2.7	3.4	p-value	.5318	.9263
2-OHE_1/16α-OHE_1	53	mean	1.4	1.7	1.7	1.3	r	-.15	-.13
		std.dev.	0.6	0.6	0.8	0.5	p-value	.2696	.3699

*This sample of men excludes diabetics and those on steriod and thyroid medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, current smoking status, and alcoholic drinks/month.

Appendix Table 14 - Relationship of EUC Quarters Worked with Immune Biomarkers-Women*

Biomarker	n		non-workers n=19	1-4 qrts n=24	5-24 qrts n=46	25+ qrts n=57	Spearman Correlation		
								Model 1	Model 2
IgG in mg/dl	143	mean	1107.0	1098.4	1177.0	1165.7	r	.03	.03
		std.dev.	259.0	180.9	297.6	359.3	p-value	.7049	.7142
IgA in mg/dl	143	mean	222.5	244.0	281.8	266.2	r	.10	.05
		std.dev.	109.9	93.6	140.9	126.7	p-value	.2418	.5700
IgM in mg/dl	143	mean	129.9	160.8	158.1	155.4	r	-.04	.03
		std.dev.	64.4	77.3	120.7	151.9	p-value	.6391	.7451
C-reactive protein in mg/dl	**143**	**mean**	**0.4**	**0.5**	**0.5**	**0.7**	**r**	**.17**	.08
		std.dev.	**0.5**	**0.8**	**0.6**	**0.9**	**p-value**	**.0388**	.3795
T-cells as % of Lymphocytes	144	mean	73.2	71.5	70.0	72.9	r	.01	-.01
		std.dev.	7.7	7.2	12.0	6.6	p-value	.8952	.9159
CD4-cells as % of Lymphocytes	144	mean	47.9	51.8	49.7	52.5	r	.15	.10
		std.dev.	9.4	6.9	10.5	9.3	p-value	.0703	.2389
CD8-cells as % of Lymphocytes	144	mean	32.3	27.8	28.0	27.1	r	-.15	-.11
		std.dev.	10.1	6.7	10.0	10.6	p-value	.0685	.2207
CD4-cells/CD8-cells	144	mean	1.7	2.0	2.0	2.4	r	.16	.11
		std.dev.	0.8	0.7	0.7	1.4	p-value	.0547	.1947
B-cells as % of Lymphocytes	144	mean	11.4	13.7	14.7	13.0	r	.04	.08
		std.dev.	5.2	6.2	10.9	5.5	p-value	.5939	.3574
NK-cells as % of Lymphocytes	144	mean	11.9	11.8	12.0	10.7	r	-.12	-.12
		std.dev.	4.5	5.3	6.4	5.5	p-value	.1468	.1710
CD5B-cells	144	mean	4.1	5.3	5.7	4.8	r	.03	.06
		std.dev.	2.9	3.2	10.6	3.1	p-value	.6893	.4581
White Blood Cell count in thous/μl	146	mean	6.2	7.2	6.9	6.7	r	.05	-.02
		std.dev.	2.0	2.6	2.0	1.9	p-value	.5664	.8070
Absolute Neutrophils in cells/μl	146	mean	3511.3	4352.1	4035.9	4040.4	r	.09	.03
		std.dev.	1223.8	2267.6	1459.3	1484.9	p-value	.3074	.7328

Biomarker	n		non-workers n=19	1-4 qrts n=24	5-24 qrts n=46	25+ qrts n=57	Spearman Correlation		
								Model 1	Model 2
Neutrophils in %	146	mean	56.3	58.8	57.8	59.3	r	.11	.08
		std.dev.	5.6	10.8	9.0	9.4	p-value	.1839	.3249
Absolute Lymphocytes in cells/μl	146	mean	1937.1	2107.5	2152.2	1970.2	r	-.03	-.05
		std.dev.	649.8	891.1	989.7	703.0	p-value	.7308	.5289
Lymphocytes in %	146	mean	31.4	30.1	31.5	30.0	r	-.06	-.04
		std.dev.	5.6	9.5	8.5	8.7	p-value	.4373	.6218
Absolute Monocytes in cells/μl	146	mean	495.3	513.3	458.2	460.3	r	-.05	-.06
		std.dev.	202.7	176.1	150.3	128.0	p-value	.5775	.4876
Monocytes in %	146	mean	7.9	7.4	6.9	7.0	r	-.11	-.08
		std.dev.	1.6	2.1	2.1	1.7	p-value	.1736	.3681
Absolute Eosinophils in cells/μl	146	mean	229.4	200.1	226.6	195.2	r	-.02	-.06
		std.dev.	133.4	134.5	163.8	104.2	p-value	.7792	.4620
Eosinophils in %	146	mean	3.6	3.0	3.2	3.0	r	-.05	-.06
		std.dev.	1.7	2.1	1.7	1.6	p-value	.5356	.4926
Absolute Basophils in cells/μl	146	mean	48.1	56.2	46.9	46.5	r	-.02	-.05
		std.dev.	23.6	46.6	24.0	23.6	p-value	.7915	.5381

Biomarker	n		non-workers n=19	1-4 qrts n=24	5-24 qrts n=46	25+ qrts n=57	Spearman Correlation		
								Model 1	Model 2
Basophils in %	146	mean	0.8	0.8	0.7	0.7	r	-.04	-.04
		std.dev.	0.3	0.4	0.3	0.3	p-value	.6432	.6535

*This sample of women excludes those on steroid and oral contraceptive medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, diabetes, current smoking status, alcoholic drinks/month, estrogen related medications, and menopausal status.

Appendix Table 15 - Relationships of EUC Job Exposure Score with Immune Biomarkers-Women*

Biomarker	n		non-workers n=19	score 1-71 n=39	score 72-294 n=43	score 295+ n=44	Spearman Correlation		
								Model 1	Model 2
IgG in mg/dl	143	mean	1107.0	1107.4	1190.2	1169.5	r	.02	.02
		std.dev.	259.0	218.2	293.7	383.3	p-value	.8304	.8250
IgA in mg/dl	143	mean	222.5	254.6	270.0	276.9	r	.13	.07
		std.dev.	109.9	95.6	157.6	119.5	p-value	.1164	.3917
IgM in mg/dl	143	mean	129.9	165.6	147.0	159.8	r	-.04	.03
		std.dev.	64.4	108.9	95.6	167.1	p-value	.5994	.6987
C-reactive protein in mg/dl	**143**	**mean**	**0.4**	**0.4**	**0.6**	**0.7**	**r**	**.22**	.11
		std.dev.	**0.5**	**0.6**	**0.7**	**1.0**	**p-value**	**.0097**	.2061
T-cells as % of Lymphocytes	144	mean	73.2	70.9	70.0	73.6	r	.06	.08
		std.dev.	7.7	7.7	11.8	6.5	p-value	.4862	.3749
CD4-cells as % of Lymphocytes	**144**	**mean**	**47.9**	**50.2**	**51.3**	**52.4**	**r**	**.18**	.15
		std.dev.	**9.4**	**6.8**	**11.1**	**9.7**	**p-value**	**.0308**	.0873
CD8-cells as % of Lymphocytes	144	mean	32.3	28.7	25.9	28.1	r	-.16	-.10
		std.dev.	10.1	6.2	10.6	11.1	p-value	.0634	.2636
CD4-cells/CD8-cells	**144**	**mean**	**1.7**	**1.9**	**2.3**	**2.3**	**r**	**.18**	.13
		std.dev.	**0.8**	**0.6**	**1.1**	**1.3**	**p-value**	**.0285**	.1220
B-cells as % of Lymphocytes	144	mean	11.4	14.1	15.2	12.0	r	-.04	-.02
		std.dev.	5.2	5.6	11.5	4.8	p-value	.6677	.7768
NK-cells as % of Lymphocytes	144	mean	11.9	12.0	11.5	10.7	r	-.11	-.14
		std.dev.	4.5	5.5	6.7	5.3	p-value	.1792	.1004
CD5B-cells	144	mean	4.1	5.0	6.3	4.3	r	-.02	-.02
		std.dev.	2.9	2.7	11.2	2.3	p-value	.8328	.8324
White Blood Cell count in thous/μl	146	mean	6.2	7.0	6.9	6.8	r	.09	.07
		std.dev.	2.0	2.4	1.9	2.0	p-value	.2983	.4295
Absolute Neutrophils in cells/μl	146	mean	3511.3	4264.6	3927.2	4115.8	r	.10	.09
		std.dev.	1223.8	2100.7	1164.6	1598.8	p-value	.2132	.2995

Biomarker	n		non-workers n=19	score 1-71 n=39	score 72-294 n=43	score 295+ n=44	Spearman Correlation		
								Model 1	Model 2
Neutrophils in %	146	mean	56.3	59.5	57.4	59.2	r	.07	.05
		std.dev.	5.6	10.7	8.5	9.3	p-value	.3728	.5323
Absolute Lymphocytes in cells/μl	146	mean	1937.1	1998.4	2203.5	1982.1	r	.04	.03
		std.dev.	649.8	749.7	1095.7	636.6	p-value	.6675	.7477
Lymphocytes in %	146	mean	31.4	30.2	31.5	29.9	r	-.06	-.04
		std.dev.	5.6	9.4	8.2	8.8	p-value	.4747	.6198
Absolute Monocytes in cells/μl	146	mean	495.3	455.2	466.5	485.0	r	.08	.08
		std.dev.	202.7	160.1	130.9	150.2	p-value	.3530	.3233
Monocytes in %	146	mean	7.9	6.8	7.0	7.3	r	-.03	-.01
		std.dev.	1.6	2.0	1.9	1.9	p-value	.7019	.9031
Absolute Eosinophils in cells/μl	146	mean	229.4	188.8	227.5	204.6	r	.04	.02
		std.dev.	133.4	118.8	166.3	109.7	p-value	.6724	.8097
Eosinophils in %	146	mean	3.6	2.8	3.3	3.0	r	-.03	-.02
		std.dev.	1.7	1.7	1.9	1.6	p-value	.7568	.8129
Absolute Basophils in cells/μl	146	mean	48.1	49.5	50.0	46.1	r	.01	-.03
		std.dev.	23.6	39.1	23.9	24.4	p-value	.8933	.7652

Biomarker	n		non-workers n=19	score 1-71 n=39	score 72-294 n=43	score 295+ n=44	Spearman Correlation		
								Model 1	Model 2
Basophils in %	146	mean	0.8	0.7	0.7	0.7	r	-.04	-.07
		std.dev.	0.3	0.3	0.3	0.3	p-value	.6372	.4216

*This sample of women excludes those on steroid and oral contraceptive medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, diabetes, current smoking status, alcoholic drinks/month, estrogen related medications, and menopausal status.

Appendix Table 16 - Relationship of EUC Quarters Worked with Immune Biomarkers-Men*

Biomarker	n		non-workers n=6	1-4 qrts n=13	5-24 qrts n=21	25+ qrts n=20	Spearman Correlation		
								Model 1	Model 2
IgG in mg/dl	64	mean	1149.4	1136.1	1186.0	1100.5	r	-.10	-.14
		std.dev.	157.9	169.1	228.1	256.5	p-value	.4316	.2758
IgA in mg/dl	64	mean	251.0	267.7	239.5	255.7	r	.06	.07
		std.dev.	90.0	135.8	84.3	103.7	p-value	.6482	.5822
IgM in mg/dl	64	mean	128.0	95.7	111.5	101.2	r	-.02	.00
		std.dev.	70.7	42.3	54.4	49.9	p-value	.8543	.9855
C-reactive protein in mg/dl	64	mean	0.3	0.2	0.2	0.4	r	.01	-.03
		std.dev.	0.3	0.4	0.4	0.6	p-value	.9569	.7934
T-cells as % of Lymphocytes	62	mean	56.3	70.4	68.7	69.1	r	-.07	-.13
		std.dev.	33.1	7.6	8.1	7.5	p-value	.6140	.3322
CD4-cells as % of Lymphocytes	62	mean	34.0	49.9	48.2	47.4	r	-.00	-.01
		std.dev.	19.7	6.8	10.3	10.1	p-value	.9962	.9137
CD8-cells as % of Lymphocytes	62	mean	29.3	30.6	30.9	31.0	r	-.03	-.00
		std.dev.	17.3	9.8	8.4	10.7	p-value	.8211	.9911
CD4-cells/CD8-cells	62	mean	1.2	1.8	1.8	1.8	r	.06	.05
		std.dev.	0.3	0.8	1.1	1.0	p-value	.6691	.7030
B-cells as % of Lymphocytes	62	mean	29.8	12.5	12.5	10.9	r	-.17	-.11
		std.dev.	36.1	5.2	4.7	5.4	p-value	.1952	.4163
NK-cells as % of Lymphocytes	**62**	**mean**	**10.0**	**11.9**	**15.2**	**16.1**	**r**	**.24**	**.29**
		std.dev.	**5.0**	**5.2**	**5.7**	**7.6**	**p-value**	**.0626**	**.0302**
CD5B-cells	62	mean	26.0	4.4	4.9	3.7	r	-.22	-.13
		std.dev.	39.9	2.8	2.7	2.5	p-value	.0887	.3454
White Blood Cell count in thous/μl	64	mean	8.2	7.0	5.9	7.0	r	-.01	-.09
		std.dev.	4.2	1.3	1.2	1.9	p-value	.9483	.4850
Absolute Neutrophils in cells/μl	64	mean	3899.6	4340.8	3624.1	4405.5	r	.05	.00
		std.dev.	1053.6	1420.7	890.8	1517.4	p-value	.7206	.9889

Biomarker	n		non-workers n=6	1-4 qrts n=13	5-24 qrts n=21	25+ qrts n=20	Spearman Correlation		
								Model 1	Model 2
Neutrophils in %	64	mean	52.7	61.1	60.8	61.9	r	.16	.19
		std.dev.	14.4	8.9	5.4	7.4	p-value	.2162	.1560
Absolute Lymphocytes in cells/μl	64	mean	3673.4	1806.6	1548.1	1771.2	r	-.08	-.13
		std.dev.	3884.3	340.3	439.5	413.9	p-value	.5402	.3367
Lymphocytes in %	64	mean	37.9	27.0	26.2	26.1	r	-.18	-.18
		std.dev.	17.7	7.4	5.5	6.0	p-value	.1497	.1709
Absolute Monocytes in cells/μl	64	mean	387.2	559.4	500.5	561.0	r	.19	.13
		std.dev.	137.3	169.8	121.5	162.1	p-value	.1427	.3295
Monocytes in %	64	mean	5.5	8.4	8.6	8.1	r	.13	.11
		std.dev.	2.6	3.3	1.9	1.9	p-value	.3241	.4167
Absolute Eosinophils in cells/μl	64	mean	231.6	204.9	222.0	216.8	r	.02	-.03
		std.dev.	215.7	136.6	100.1	146.2	p-value	.8646	.8243
Eosinophils in %	64	mean	3.3	2.9	3.8	3.2	r	-.04	-.07
		std.dev.	2.3	1.6	1.8	2.2	p-value	.7626	.5759
Absolute Basophils in cells/μl	64	mean	28.0	46.1	38.8	49.7	r	.24	.25
		std.dev.	17.5	17.1	15.5	20.8	p-value	.0583	.0573

Biomarker	n		non-workers n=6	1-4 qrts n=13	5-24 qrts n=21	25+ qrts n=20	Spearman Correlation		
								Model 1	Model 2
Basophils in %	64	mean	0.5	0.7	0.7	0.7	r	.18	.21
		std.dev.	0.3	0.2	0.3	0.2	p-value	.1665	.1026

*This sample of men excludes those on steroid medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, diabetes, current smoking status, and alcoholic drinks/month.

Appendix Table 17 - Relationship of EUC Job Exposure Score with Immune Biomarkers-Men*

Biomarker	n		non-workers n=6	score 1-71 n=18	score 72-294 n=18	score 295+ n=18	Spearman Correlation		
								Model 1	Model 2
IgG in mg/dl	64	mean	1149.4	1145.3	1126.1	1148.4	r	-.00	-.06
		std.dev.	157.9	183.0	220.1	291.8	p-value	.9884	.6359
IgA in mg/dl	64	mean	251.0	246.8	237.3	279.3	r	.17	.18
		std.dev.	90.0	122.6	88.1	100.9	p-value	.1770	.1742
IgM in mg/dl	64	mean	128.0	103.2	101.0	107.1	r	-.06	-.04
		std.dev.	70.7	46.7	37.9	64.8	p-value	.6589	.7695
C-reactive protein in mg/dl	64	mean	0.3	0.2	0.4	0.3	r	-.01	-.05
		std.dev.	0.3	0.4	0.6	0.5	p-value	.9264	.7552
T-cells as % of Lymphocytes	62	mean	56.3	71.5	67.7	68.5	r	-.17	-.25
		std.dev.	33.1	7.6	6.8	8.5	p-value	.1978	.0569
CD4-cells as % of Lymphocytes	62	mean	34.0	51.7	47.6	45.0	r	-.16	-.18
		std.dev.	19.7	8.4	9.3	9.7	p-value	.2059	.1889
CD8-cells as % of Lymphocytes	62	mean	29.3	29.9	29.7	33.5	r	.08	.12
		std.dev.	17.3	9.4	9.1	10.3	p-value	.5482	.3572
CD4-cells/CD8-cells	62	mean	1.2	2.0	1.8	1.6	r	-.08	-.07
		std.dev.	0.3	1.1	0.9	0.9	p-value	.5685	.5940
B-cells as % of Lymphocytes	62	mean	29.8	11.9	13.7	9.5	r	-.20	-.10
		std.dev.	36.1	4.5	5.1	5.0	p-value	.1203	.4813
NK-cells as % of Lymphocytes	**62**	**mean**	**10.0**	**12.2**	**14.6**	**18.0**	**r**	**.35**	**.40**
		std.dev.	**5.0**	**5.1**	**5.6**	**8.0**	**p-value**	**.0054**	**.0020**
CD5B-cells	62	mean	26.0	4.2	5.4	3.1	r	-.24	-.11
		std.dev.	39.9	2.6	2.7	2.2	p-value	.0620	.4220
White Blood Cell count in thous/μl	64	mean	8.2	6.8	6.2	6.8	r	-.07	-.15
		std.dev.	4.2	1.4	1.7	1.7	p-value	.5842	.2681
Absolute Neutrophils in cells/μl	64	mean	3899.6	4190.4	3957.6	4205.8	r	-.01	-.02
		std.dev.	1053.6	1312.3	1355.6	1389.6	p-value	.9113	.8688

Biomarker	n		non-workers n=6	score 1-71 n=18	score 72-294 n=18	score 295+ n=18	Spearman Correlation		
								Model 1	Model 2
Neutrophils in %	64	mean	52.7	60.7	62.6	60.5	r	.13	.22
		std.dev.	14.4	7.4	6.3	7.7	p-value	.3142	.1011
Absolute Lymphocytes in cells/μl	64	mean	3673.4	1813.1	1520.0	1783.4	r	-.15	-.23
		std.dev.	3884.3	385.8	402.2	418.0	p-value	.2293	.0784
Lymphocytes in %	**64**	**mean**	**37.9**	**27.5**	**24.8**	**26.7**	**r**	-.22	**-.27**
		std.dev.	**17.7**	**6.2**	**5.5**	**6.5**	**p-value**	.0774	**.0356**
Absolute Monocytes in cells/μl	64	mean	387.2	534.8	522.2	565.2	r	.21	.16
		std.dev.	137.3	152.1	142.4	165.2	p-value	.1027	.2181
Monocytes in %	64	mean	5.5	8.2	8.5	8.3	r	.20	.18
		std.dev.	2.6	2.9	1.8	2.0	p-value	.1152	.1741
Absolute Eosinophils in cells/μl	64	mean	231.6	203.8	205.0	244.2	r	.11	.06
		std.dev.	215.7	123.2	106.6	155.5	p-value	.3901	.6637
Eosinophils in %	64	mean	3.3	3.0	3.4	3.7	r	.08	.03
		std.dev.	2.3	1.5	1.9	2.4	p-value	.5282	.7960
Absolute Basophils in cells/μl	64	mean	28.0	44.0	43.0	48.5	r	.17	.20
		std.dev.	17.5	17.0	16.0	23.3	p-value	.1763	.1269

Biomarker	n		non-workers n=6	score 1-71 n=18	score 72-294 n=18	score 295+ n=18	Spearman Correlation		
								Model 1	Model 2
Basophils in %	64	mean	0.5	0.7	0.7	0.7	r	.17	.20
		std.dev.	0.3	0.3	0.2	0.2	p-value	.1850	.1235

*This sample of men excludes those on steroid medications.

Model 1: Spearman rank correlation between continuous biomarker and ordinal exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and ordinal exposure variable when the effect of the following confounders are removed: age, BMI, diabetes, current smoking status, alcoholic drinks/month.

Appendix Table 18 - Relationship of EUC Exposure with Other Biomarkers-Women*

Biomarker	n		PCB		Lipid PCB		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Urea Nitrogen (Bun) in mg/dl	**146**	**r**	**.18**	-.01	.16	-.01	.15	.03	.16	.04
		p-value	**.0345**	.8773	.0539	.8747	.0763	.7289	.0526	.6319
Creatinine in mg/dl	146	r	.07	-.05	.07	-.03	.03	-.03	.01	-.05
		p-value	.4029	.5794	.3885	.6875	.6842	.7441	.9009	.5923
Bun/Creatinine	**146**	**r**	**.19**	.05	**.17**	.04	.16	.06	**.18**	.08
		p-value	**.0240**	.5422	**.0441**	.6474	.0600	.4790	**.0320**	.3679
Sodium in meq/l	**146**	**r**	-.15	**-.22**	-.11	-.16	-.10	-.13	-.09	-.12
		p-value	.0637	**.0089**	.1694	.0608	.2467	.1353	.2852	.1740
Potassium in meq/l	140	r	-.04	-.09	-.02	-.05	.04	.03	.04	.05
		p-value	.6419	.3011	.7730	.5376	.6306	.7263	.6537	.5752
Chloride in meq/l	**146**	**r**	**-.32**	**-.25**	**-.29**	**-.20**	**-.21**	-.13	**-.21**	-.12
		p-value	**.0001**	**.0037**	**.0004**	**.0184**	**.0116**	.1201	**.0098**	.1802
Magnesium in meq/l	146	r	.03	.03	.01	.01	.02	.04	-.03	.01
		p-value	.7254	.7484	.9359	.9238	.7795	.6327	.7547	.9090
Calcium in mg/dl	140	r	.09	.14	.06	.10	-.04	-.03	-.05	-.04
		p-value	.2868	.1139	.5012	.2628	.6212	.7424	.5746	.6554
Inorganic Phosphorus in mg/dl	146	r	-.10	-.09	-.10	-.09	-.03	.00	-.01	.02
		p-value	.2284	.2770	.2072	.3080	.7230	.9825	.9072	.7842

Biomarker	n		PCB		Lipid PCB		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Total Protein in g/dl	**146**	**r**	.09	.17	.05	.12	.02	.06	.04	.07
		p-value	.3015	.0473	.5524	.1513	.7824	.4800	.6697	.3967
Albumin in g/dl	**146**	**r**	-.21	-.01	-.22	-.02	-.18	-.03	-.18	-.02
		p-value	.0092	.8966	.0089	.7804	.0265	.7717	.0337	.7963
Globulin in g/dl	**146**	**r**	.20	.18	.16	.13	.11	.06	.11	.07
		p-value	.0163	.0369	.0566	.1223	.1951	.4878	.1852	.4408
Albumin/Globulin	**146**	**r**	-.27	-.17	-.23	-.12	-.16	-.04	-.16	-.05
		p-value	.0008	.0471	.0046	.1493	.0512	.6571	.0484	.5806
Uric Acid in mg/dl	146	r	.14	.08	.08	.02	.16	.11	.17	.12
		p-value	.0990	.3324	.3509	.7811	.0589	.2134	.0361	.1666
Total Iron in mcg/dl	146	r	-.07	-.14	-.10	-.15	-.21	-.26	-.23	-.27
		p-value	.3743	.1127	.2532	.0770	.0100	.0025	.0059	.0014
Iron Binding Capacity in mcg/dl	146	r	-.03	.09	-.04	.06	-.07	.00	-.04	.02
		p-value	.7371	.3083	.6118	.4970	.4085	.9918	.5986	.8296
% Saturation	**146**	**r**	-.07	-.16	-.07	-.16	-.18	-.25	-.21	-.27
		p-value	.4286	.0605	.3691	.0627	.0283	.0036	.0113	.0014
Red Blood Cell count in mill/μl	146	r	.01	-.02	-.01	-.04	-.02	-.07	-.03	-.11
		p-value	.8767	.8244	.9339	.6846	.8536	.3986	.7617	.1868
Hemoglobin in g/dl	146	r	.07	.02	.05	.01	.02	-.06	-.02	-.12
		p-value	.3747	.7879	.5486	.9138	.8542	.4853	.8365	.1597
Hematocrit in %	146	r	.07	.01	.05	-.00	.05	-.02	.02	-.09
		p-value	.3725	.8850	.5656	.9543	.5681	.7731	.8462	.3131
MCV in fl	146	r	.03	-.03	.01	-.03	.06	.07	.05	.06
		p-value	.7520	.6912	.8864	.6991	.4394	.4419	.5844	.5160
MCH in pg	146	r	.01	-.02	.01	-.02	.01	.01	-.01	-.01
		p-value	.8750	.7820	.9330	.8263	.8930	.9027	.8680	.9518
MCHC in %	146	r	-.04	-.00	-.02	.02	-.09	-.08	-.10	-.09
		p-value	.6602	.9826	.8244	.8402	.2836	.3696	.2128	.3126

Biomarker	n		PCB		Lipid PCB		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Platelet Count in thous/μL	146	r	.02	.10	.03	.11	.10	.17	.14	.23
		p-value	.8051	.2255	.6798	.1935	.2482	.0508	.1023	.0078

*This sample of women excludes those on steroid and oral contraceptive medications.

Model 1: Spearman rank correlation between continuous biomarker and continuous exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and continuous exposure variables when the effect of the following confounders are removed: age, BMI, diabetes, current smoking status, alcoholic drinks/month, menopausal status, and estrogen related, anti-lipidemic,and thyroid medications.

Appendix Table 19 - Relationship of EUC Exposure with Other Biomarkers-Men*

Biomarker	n		PCB		Lipid PCB		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Urea Nitrogen (Bun) in mg/dl	59	r	.16	.09	.15	.09	.21	.18	.10	.05
		p-value	.2377	.5111	.2592	.5233	.1102	.2050	.4738	.7093
Creatinine in mg/dl	59	r	-.12	-.10	-.08	-.06	-.07	-.05	-.11	-.09
		p-value	.3769	.4662	.5235	.6566	.5848	.7379	.4116	.5023
Bun/Creatinine	59	r	.23	.14	.20	.11	.24	.18	.13	.06
		p-value	.0750	.3161	.1282	.4364	.0677	.1916	.3313	.6418
Sodium in meq/l	59	r	.14	.17	.12	.14	.02	.06	.09	.12
		p-value	.2883	.2130	.3695	.2987	.8524	.6852	.5097	.3955
Potassium in meq/l	57	r	.10	.00	.07	-.02	-.09	-.18	-.07	-.14
		p-value	.4684	.9926	.6111	.8919	.4932	.1951	.6026	.3357
Chloride in meq/l	59	r	-.18	-.01	-.15	.01	-.15	-.05	-.07	.03
		p-value	.1710	.9265	.2550	.9560	.2529	.6877	.6181	.8337
Magnesium in meq/l	59	r	.11	.14	.09	.12	.18	.22	.13	.17
		p-value	.3956	.3079	.4893	.3884	.1804	.1112	.3209	.2228
Calcium in mg/dl	57	r	.14	.12	.09	.06	.05	.05	-.03	-.03
		p-value	.3008	.4059	.5254	.6783	.6947	.7253	.8566	.8601
Inorganic Phosphorus in mg/dl	59	r	-.12	-.14	-.10	-.12	-.12	-.13	-.10	-.11
		p-value	.3515	.3079	.4471	.4076	.3457	.3395	.4381	.4415
Total Protein in g/dl	59	r	.13	.10	.04	.01	.00	.03	-.08	-.04
		p-value	.3388	.4737	.7635	.9346	.9812	.8358	.5360	.7530
Albumin in g/dl	59	r	.05	.07	.02	.03	.08	.17	.02	.08
		p-value	.6866	.5919	.8742	.8196	.5249	.2273	.8650	.5458
Globulin in g/dl	59	r	.12	.06	.03	-.03	-.07	-.09	-.13	-.13
		p-value	.3856	.6579	.8449	.8470	.6114	.5291	.3269	.3323
Albumin/Globulin	59	r	-.07	.00	-.01	.06	.09	.15	.12	.17
		p-value	.6020	.9787	.9637	.6866	.5175	.2821	.3503	.2289

Biomarker	n		PCB		Lipid PCB		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Uric Acid in mg/dl	59	r	.04	.08	.00	.04	-.01	.04	-.08	-.04
		p-value	.7923	.5691	.9995	.7576	.9485	.7760	.5395	.7707
Total Iron in mcg/dl	59	r	.08	.04	.07	.04	.00	-.03	-.01	-.04
		p-value	.5529	.7526	.5956	.7965	.9928	.8542	.9354	.7748
Iron Binding Capacity in mcg/dl	59	r	.10	.21	.10	.23	.03	.16	.04	.19
		p-value	.4588	.1214	.4330	.0912	.8356	.2408	.7658	.1604
% Saturation	59	r	-.01	-.09	-.02	-.10	-.03	-.11	-.06	-.14
		p-value	.9385	.5306	.9003	.4881	.8175	.4487	.6686	.3091
Red Blood Cell count in mill/μl	59	r	.13	.18	.13	.19	.09	.17	.10	.19
		p-value	.3097	.1988	.3123	.1701	.4894	.2288	.4671	.1639
Hemoglobin in g/dl	59	r	.10	.17	.11	.18	-.03	.02	-.00	.06
		p-value	.4386	.2225	.4192	.1876	.8219	.8920	.9737	.6556
Hematocrit in %	59	r	.11	.15	.14	.19	-.01	.01	.02	.06
		p-value	.3899	.2883	.2860	.1724	.9410	.9349	.8666	.6576
MCV in fl	59	r	.05	.03	.08	.06	-.03	-.11	.02	-.06
		p-value	.7093	.8461	.5319	.6607	.8184	.4206	.8940	.6516
MCH in pg	59	r	.00	.00	.00	.00	-.06	-.10	-.04	-.08
		p-value	.9843	.9905	.9893	.9918	.6737	.4819	.7787	.5677
MCHC in %	59	r	-.07	-.03	-.12	-.09	-.06	-.02	-.11	-.07
		p-value	.6189	.8189	.3550	.5154	.6768	.8825	.4215	.6278

Biomarker	n		PCB		Lipid PCB		Quarters Worked		Total Job Score	
			Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Platelet Count in thousands/μl	59	r	-.09	.01	-.14	-.05	-.07	.04	-.16	-.06
		p-value	.4995	.9688	.2927	.7341	.5944	.7758	.2302	.6928

*This sample of men excludes those on steroid, anti-lipidemic, and thyroid medications.

Model 1: Spearman rank correlation between continuous biomarker and continuous exposure variable.

Model 2: Partial Spearman rank correlation between continuous biomarker and continuous exposure variables when the effect of the following confounders are removed: age, BMI, diabetes, current smoking status, and alcoholic drinks/month.