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Association of Prenatal and Early Life Exposure to Tetrachloroethylene (PCE) with Polycystic Ovary Syndrome and Other Reproductive Disorders in the Cape Cod Health Study: A Retrospective Cohort Study

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Abstract

Background—Tetrachloroethylene (PCE) is an organic lipophilic solvent with possible neuroendocrine toxicity. The objective of this study was to determine the association of prenatal and early childhood exposure to PCE-contaminated drinking water and development of adult-onset Polycystic Ovary Syndrome (PCOS), endometriosis, difficulty conceiving and miscarriage.

Methods—Five-hundred exposed and 331 unexposed female participants born between 1969 and 1983 completed questionnaires on demographic and lifestyle characteristics, and reproductive disorders. Residential locations from the prenatal period through five years of age were used to estimate early life PCE exposure with water modeling software.

Results—For any early life exposure to PCE, the adjusted risk ratio for PCOS was 0.9 (95% CI: 0.5–1.6). No statistically significant associations were observed for increasing levels of exposure with PCOS or the other reproductive disorders.

Conclusion—No meaningful associations were found among adult women with early life exposure to PCE-contaminated drinking water and adult-onset reproductive disorders.

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Competing Interests

None

Authors' contributions

AA conceived the study and its design, coordinated data collection and analysis. SM drafted the initial manuscript. MRW participated in the data collection and conducted the data analyses. All authors read and approved the final manuscript.

Keywords

drinking water; tetrachloroethylene; polycystic ovary syndrome; prenatal exposures

Introduction

Tetrachloroethylene (PCE) is an organic lipophilic solvent commonly used in dry cleaning of fabric, degreasing of metals, and in the synthesis of other chemicals. Commonly found in chemical waste, it can easily evaporate and aerosolize, and may leach into contact solutions, such as drinking water [1]. Before harmful health effects were known, PCE was used to apply a vinyl lining to asbestos-cement (AC) water distribution pipes in the Cape Cod area of Massachusetts. The vinyl lining was introduced as a barrier to unacceptable taste and odor problems and to minimize corrosion associated with conventional AC water mains [2]. It was assumed that the PCE solvent would completely evaporate prior to the installation of the pipes carrying drinking water for human use. However, in 1980 Massachusetts officials found that PCE was leaching into public drinking water supplies from the vinyl liner (VL) that had been applied to the AC pipes [3]. There were two distinct features of this exposure setting: (1) an irregular pattern of exposure corresponding to the pattern of VL/AC pipe installation, and (2) a wide range of PCE levels in the water. In one town, exposure levels ranged from undetectable to 80 µg/L in high flow pipes compared to 1,600 to 7,750 µg/L in low flow pipes, such as those found on dead end streets [4].

Polycystic Ovary Syndrome (PCOS) is a multifactorial disorder affecting the hypothalamic-pituitary-ovarian axis that presents with a combination of the following: oligomenorrhea, clinical or biochemical evidence of hyperandrogenism, and ultrasonographic evidence of polycystic ovary morphology. There is a paucity of literature on PCE and reproductive physiology. Tri- and tetrachloroethylene are noted to cross the placenta after inhalational exposure in a murine model [5]. Other organic solvents, such as chlorinated hydrocarbons are secreted into breastmilk among women with and without occupational exposure [6, 7], and benzene is detectable in the follicular fluid surrounding the oocyte among *in vitro* fertilization (IVF) patients at the time of egg retrieval [8]. Prenatal exposure to organic solvents during brain formation can trigger substantial cell death, potentially leading to structural damage of the neuroendocrine axis [9]. There is literature demonstrating modest associations between organic solvent exposures and adverse reproductive effects. One cross-sectional study in China among occupational petrochemical workers exposed to organic solvents (benzene, styrene, toluene, or xylene) demonstrated menstrual cycle prolongation with adjusted odds ratios for each additional year of work with exposure and for 3 or more years of exposure compared to no exposure were 1.07 (95% CI: 1.00–1.14) and 1.53 (95% CI: 1.00–2.34) respectively [10]. Another study of females with occupational exposure to organic solvents in the pharmaceutical industry demonstrated an increased odds of menstrual disturbances in highly exposed women (OR: 9.7, $p=0.001$) [11]. A cross-sectional study of female liquid crystal display-manufacturing workers (with exposure to acetone and ethanol) noted a higher prevalence of short menstrual cycle with an adjusted odd ratio of 7.68 (95% CI: 1.51–39.15) [12]. Three studies reported on reduced fertility and subfertility after exposure to organic solvents [13–16]. In a retrospective time-to-pregnancy study, those with

daily or high exposure to organic solvents had reduced fecundability with an adjusted incidence density ratio of clinical pregnancies of 0.41 (95 % CI: 0.27–0.62) [13]. Among female workers at a semi-conductor manufacturing plant, high ethylene glycol exposure conferred an increased risk of miscarriage (RR: 2.8, 95 % CI: 1.4–5.6) and subfertility (RR: 4.6, 95% CI: 1.6–13.3) [15]. In a prospective cohort study in women with occupational exposure to organic solvent, the occurrence of a major fetal malformation was increased among women with a risk ratio of 13 (95% CI: 1.8–99.5) [17]. Additionally, associations have been previously reported from this cohort between prenatal PCE exposure and neurological outcomes such as color vision deficits, diminished performance on neuropsychological tests of visuospatial functioning, learning and memory, motor, attention and mood [18–20], stillbirths (RR: 2.38, 95% CI: 1.01–5.59), placental abruption (RR: 1.35, 95% CI: 0.68–2.67) [21], central nervous system birth defects (OR: 3.1, 95% CI: 0.9–11.0) and oral clefts (OR: 3.2, 95% CI: 0.7–15) [22]. However, few studies have assessed the association of prenatal PCE exposure and PCOS, as well as other adult onset reproductive disorders in women.

The objective of this retrospective cohort study was to determine the association of prenatal and early childhood exposure to PCE-contaminated drinking water and later onset of PCOS and other reproductive disorders including endometriosis, difficulty conceiving, and miscarriage.

Methods

Selection of Study Population

The Cape Cod Health Study is a closed two-stage trans-generational retrospective cohort study. The mother's cohort was comprised of married women who resided in the Cape Cod area of Massachusetts from 1969 through 1983 in one of eight towns with VL/AC water distribution pipes and who had at least one birth (termed index birth) during this time period. Enrollment methods have been previously described [18] and are summarized here. Eligible mothers were identified by reviewing birth certificates and cross-matching the address on the birth certificate with information collected from water companies on the location and installation year of VL/AC pipes. Mothers were enrolled in 2002–2003 and completed a self-administered questionnaire. Exposure status of the mother's index birth was initially assigned by visually inspecting maps depicting the pipe distribution network in the vicinity of the birth address. Index births were tentatively designated as “exposed” when their residence was either directly adjacent to a VL/AC pipe or indirectly adjacent to a pipe connected to a VL/AC pipe with the only possible water flow through a VL/AC pipe (N=1,910). Births who were initially designated as “unexposed” were randomly selected from the remaining resident births during this time period and frequency matched to exposed subjects on month and year of birth (N=1,928). In addition, 1,202 older siblings of exposed and unexposed index subjects were identified if they were born in Massachusetts during 1969–1983. These older siblings were initially considered unexposed because they were born before the family moved to an affected Cape Cod residence. The initial exposure status of all subjects was considered tentative until more extensive exposure assessments were completed, as described below.

The survey administered to the mothers collected information on reproductive and developmental disorders, confounding variables, and the family's residential history. Data collected included the mother's demographic characteristics, menstrual abnormalities, delayed time to conception, pregnancy outcomes, breastfeeding practices, medical conditions, environmental and occupational exposures, use of tap and bottled water, dry cleaning for clothing, residence near dry cleaning facilities, and a residential history since 1969.

The study was approved by the Institutional Review Boards of the Massachusetts Department of Public Health and Boston University Medical Center and by the 24A/B/11B Review Committee at the Massachusetts Department of Public Health.

Follow-Up and Enrollment

Follow-up and enrollment of index children and their siblings occurred during 2006–2008. A self-administered questionnaire was sent to all successfully traced subjects (40.5% of those selected) to gather information on their health status including height and weight (to estimate body mass index), reproductive disorders such as polycystic ovary syndrome, endometriosis, difficulty conceiving, miscarriage, and chronic conditions. In addition, these surveys gathered information on current demographic characteristics; lifestyle characteristics (smoking, alcohol, caffeine consumption, and recreational drugs); history of chronic illnesses, medications, family medical history; occupational and non-occupational sources of solvent exposure and residential locations from birth through 1990, including the exact street address and calendar years of residence for all Cape Cod residences. All disease-related questions asked if a doctor or health care provider had ever stated that the participant had a particular condition and what year the condition was diagnosed.

Reproductive Disorder Assessment

The survey administered to female children included the following questions reported here by diagnosis.

Polycystic Ovary Syndrome—"Has a doctor or health care provider ever said that you had polycystic ovarian disease?" If the daughter said, "yes," she was asked, "In what year were you diagnosed with polycystic ovarian disease?"

Endometriosis—"Has a doctor or health care provider ever said that you had endometriosis?" If the daughter said, "yes," she was asked, "In what year were you diagnosed with endometriosis?"

Difficulty Conceiving—"Have you or your partner ever visited a doctor, clinic, or hospital because of a problem becoming pregnant or to seek help in becoming pregnant?"

Miscarriage—"Have you or your partner ever had a miscarriage?"

Geocoding of Residential Addresses

As previously described,[18] approximately 95% of reported addresses were successfully geocoded using ArcGIS 8. Addresses that could not be geocoded to a specific corresponding street segment (parcel) were geocoded to the closest parcel by street number. For addresses lacking a street number in a street less than a mile long, the address was geocoded to the middle of the street. For streets one mile or longer, the address was geocoded to the intersection of the street with the cross-street provided in the survey.

PCE Exposure Assessment

As previously described [18], initial exposure status was assigned to each subject by visually inspecting maps of the pipe distribution network in the area surrounding the birth residence. The final exposure designation was determined by models for leaching and transport. These models were used to estimate the mass of PCE delivered to each residence from the prenatal period through five years of age. The period of time from prenatal to five years of age is also referred to as the prenatal and early childhood period, or the early life period.

The Webler-Brown model, developed for our prior epidemiological studies [23, 24], estimates the quantity of PCE entering the drinking water using the following pipe characteristics: (1) the initial amount of PCE in the liner (based on the pipe diameter and length), (2) the age of the pipe, and (3) the leaching rate of PCE from the liner into the water, which demonstrated an exponential decline relationship in lab experiments [4].

EPANET is a water transport algorithm developed by the United States Environmental Protection Agency (EPA) for water monitoring programs and utilized in epidemiologic studies evaluating the health effects of drinking water contaminants [25, 26]. It estimates water flow dynamics (rate and direction) using inputs of the pipe configuration and number of water users throughout a town's entire public water distribution network. To include PCE leaching dynamics into the exposure model, the Webler-Brown algorithm was incorporated into the publicly available source code of EPANET water distribution modeling software [27].

Exposure assessment incorporating a geographic information system (GIS) was performed in a step-wise method layering the leaching and transport modeling over a base layer of key characteristics including mapped subject residences, water sources, pipe characteristics, and nodes. Nodes represent points of water consumption along the pipe. The GIS layer represented the pipe configuration in the period around 1980. Data on the location, installation date, and diameter of VL/AC pipes was obtained from local water companies and the Massachusetts Department of Environmental Protection.

EPANET was used to simulate the instantaneous water flow through each town's network and to estimate the annual mass of PCE delivered to each node and all subject residences associated with the node. The assumptions of this exposure assessment model were that (1) all land parcels represented water users, (2) all water users in the network drew the same quantity of water, and (3) water sources did not change over the study period. These assumptions are supported by observations that the study area was mainly comprised of

residences, and the distribution system changed little between the late 1960s and late 1980s, when some water sources were added to accommodate population growth.

Only annual PCE exposures were calculated because only move-in and pipe installation years were available. PCE exposure during the prenatal period was estimated by multiplying the annual mass of PCE that entered the subject's residence during their birth year by $\frac{9}{12}$. Cumulative exposure during early childhood was calculated by summing the estimated mass of PCE that entered their residences from the month and year following birth through the month and year of the fifth birthday. Simple proportions were used to account for partial years. PCE exposure levels were estimated only for subjects who had complete geocoded residential histories from birth through age five.

Of maternal responders, 1,920 were exposed to PCE during at least one pregnancy. Children with prenatal and early childhood exposure to PCE and a comparable group of unexposed children were then approached, as described above. A total of 1,689 index children and their older siblings returned the questionnaire. After excluding 177 because of incomplete exposure ascertainment, there were 1512 subjects available for the analysis. Among these, there were a total of 500 exposed and 331 unexposed female children comprising the final analytic sample.

Statistical Analysis

We compared the occurrence of polycystic ovary syndrome, endometriosis, difficulty conceiving, and miscarriage among subjects with combined prenatal and early childhood exposure to unexposed subjects. First, we examined the impact of any PCE exposure and then divided the exposure at the median to examine whether risk was related to higher or lower level of exposure.

The risk ratio (RR) was used to estimate the strength of the association between PCE exposure and the occurrence of each condition. Ninety-five percent confidence intervals were used to assess the precision of the risk ratios. Generalized estimating equation (GEE) analyses were performed to account for non-independent outcomes arising from several children from the same family [28, 29]. The log link was used while assuming equal correlation between birth outcomes from the same mother.

Adjusted GEE analyses were conducted to assess the influence of confounding. Variables considered for these analyses were: demographic, medical, family characteristics, and non-drinking water sources of solvent exposure. These variables included the subject's gender, race, age, educational level, employment status, and marital status; cigarette smoking, alcoholic beverage consumption and illicit drug use; history of solvent-related jobs and hobbies; and maternal characteristics and behaviors during the subject's pregnancy. Each of these variables was added to the GEE model one at a time to assess the presence of confounding. Most of the potential confounding variables had few missing data and so individuals with missing data were dropped from the analyses. Only age had a meaningful impact (>10% change) in the crude estimates of associations and so this was the only variable included in the final adjusted GEE model [30].

Results

Cohort characteristics for the full cohort were described previously [18]. As shown in Table 1, the characteristics of the exposed and unexposed female subjects were quite similar. Subjects were predominantly white, college-educated, employed, in their late 30s, and married or cohabitating when they completed the study questionnaires. There were slightly more exposed subjects with possible occupational exposure to solvents compared to unexposed subjects (12.0% vs. 9.4%). Many had potential exposure from hobbies (79.2% vs. 80.7%). Birthweight and gestational length were similar across groups. Breastfeeding was similar among mothers of exposed and unexposed subjects (49.4% vs. 54.7%). Family history of relevant illnesses, parental characteristics (including parental age at subject birth), and the frequency of cigarette smoking and alcoholic beverage consumption was also similar across groups. However, the frequency of maternal medical or obstetrical complications (16.4% vs. 20.8%) and multiple pregnancy (2.0% vs. 4.8%) was higher among unexposed subjects, whereas the frequency of illicit drug use (e.g., crack, cocaine, psychedelics/hallucinogens, club/designer drugs, Ritalin without a prescription, and heroin) was more common among exposed subjects.

The study population was exposed to a wide distribution of PCE exposure levels that covered several orders of magnitude, shown in Table 2. Cumulative prenatal exposure levels were lower than early childhood levels because of their different durations (nine months vs. five years). Mean (SD) exposures were 29.2 (71.1), 92.5 (204.2), and 121.7 (268.4) grams, respectively, for prenatal, early childhood and combined prenatal and early childhood exposure.

The relationship between early life PCE exposure and self-reported polycystic ovary syndrome, endometriosis, miscarriage, and difficulty conceiving is shown in Table 3. There were 47 cases of self-reported PCOS corresponding to a cohort prevalence of PCOS of 5.7%. For any PCE exposure during the prenatal and early childhood window, the adjusted risk ratio was 0.9 (95% CI: 0.5–1.6). There were 38 cases of self-reported endometriosis corresponding to a cohort prevalence of 4.5%. For any early life PCE exposure, the adjusted risk ratio was 1.0 (95% CI: 0.5–1.8) for endometriosis. There were a total of 61 reports of difficulty conceiving and 85 reports of miscarriage. No meaningful associations were observed between early life PCE exposure and difficulty conceiving or miscarriage. No statistically significant associations were observed for levels (≥ median and < median) of PCE exposure with PCOS and of the other reproductive disorders. There were also no major differences in mean age (SD) at diagnosis in years for either PCOS (24.8 (4.6) vs 24.8 (5.9)) or endometriosis (22.0 (4.7) vs 23.9 (6.8)) in the exposed vs. unexposed groups. Age(s) at difficulty conceiving and miscarriage were not obtained.

Conclusions

The results of this study found no meaningful associations between early life PCE exposure and PCOS, endometriosis, miscarriage, and difficulty conceiving. Regardless, ongoing surveillance and monitoring of this and other populations with PCE exposure is critical for assessment of long-term health outcomes.

Prenatal exposure to environmental agents and chemicals (ethanol, phencyclidine, ketamine, nitrous oxide, barbiturates, benzodiazepines, halothane, isoflurane, and propofol) in animal models has been shown to alter neuronal development, including inducing neuronal cell apoptosis via NMDA and GABAergic pathways in developing embryos [9] and in cell models by decreased myelination (1,1,2-trichloroethylene) [31]. Neuroendocrine toxicity is plausible following prenatal and childhood exposure because PCE can cross the placenta in animals [5] and is present in human breast milk among women with and without occupational exposure [6, 7].

However, one study evaluating magnetic resonance imaging on adults with prenatal and early childhood exposure to PCE found no statistically significant differences in white and gray matter volumes and white matter hypointensities [20]. Polycystic ovary syndrome is multifactorial and can be a result of dysfunction at the level of the hypothalamus/pituitary, or ovary. At the level of the ovary, insulin resistance and altered paracrine signaling are proposed to be etiologic factors [32]. At the level of the hypothalamus, central control of the reproductive axis by gonadotropin-releasing hormone neurons and their pulse frequency regulation of the gonadotropes secreting LH and FSH are critical for normal reproductive function [33].

GnRH neurons are located in the hypothalamus. These neurons are in close contact with each other through synapse formation and cell-cell gap junctions [34]. Though no studies have been conducted to test this hypothesis, neuroendocrine toxicity resulting in reduced functionality from reduced synapses and gap junctions thereby affecting pulsatility and surge functions of the GnRH neurons may promote development of disorders of ovulation, such as polycystic ovary syndrome and resultant difficulty conceiving [35].

Endometriosis is a reproductive disorder in which endometrial cells that typically line the endometrial cavity within the uterus are found at other sites. There are several proposed etiologies for endometriosis. These include retrograde menstruation, lymphatic spread, and coelomic metaplasia.[36] Environmental exposures have not been implicated in endometriosis incidence, but one study demonstrated persistence of endometriosis lesions in a monkey models of endometriosis after diesel exhaust exposure [37]. Exposure to PCE during organogenesis may potentially alter signaling pathways and promote erratic cell migration, though no studies are currently available to support this hypothesis.

Miscarriage has a multifactorial etiology and can be a result of genetic causes in the parents transmitted to the gametes, cellular damage of the oocyte/embryo, aneuploidy, uterine structural disease, and hormonal disorders. Cellular changes were noted after exposure to PCE and related solvents in animal models, such as changes in lipid peroxidation, ligand mediated metabolic pathways [38–42], and apoptosis [9]. Thus, it is plausible that cell membrane changes resulting from PCE exposure may promote aneuploidy and predispose to miscarriage after prenatal exposure. A previous study in the parent cohort did not reveal an association between exposures during pregnancy and risk of miscarriage in that pregnancy [43]. Despite potential for biological plausibility, the current study did not find a meaningful associations between early life PCE exposure and later onset PCOS, endometriosis, difficulty conceiving, or miscarriage.

There are several limitations to consider in this study. Despite being the first and largest study of its kind, the small number of reproductive disorders and exposure misclassification may have biased our results towards the null. Exposure misclassification is a concern as PCE exposure was modeled on water distribution conditions in 1980 and was assumed to be representative of the entire exposure period. Furthermore, the exposure assessment predicted the annual mass of PCE delivered to each subject's residence during gestation and early childhood. Despite the concern for exposure misclassification, validation studies indicate reasonable correlation between our exposure estimates and PCE concentrations in historical water samples [44]. Though unmeasured confounding is a concern, the current and previous studies from this cohort noted little or no confounding because of the irregular pattern of contamination [45]. Additionally, all outcomes were self-reported. Though the survey used was developed with input from survey research experts, and previously used for other health outcomes, there was no medical record validation of self-reported reproductive diseases. However, since most subjects did not know their exposure status, inaccurate reporting was likely to be non-differential and so would not have affected the risk ratios from this cohort study [46].

Though the response rate for the study was low, participation was not associated with PCE exposure, and most available characteristics of participants and non-participants were similar, including initial PCE exposure status. As such, the concern for selection bias in this study is negligible. Despite the low response rate, the cohort prevalence of PCOS (5.6%) is comparable to other cohorts, ranging from 5–8% [47–49]. The cohort prevalence of clinically recognized endometriosis (4.5%) is also comparable with other populations [36], though prevalence estimates range widely based on severity of disease, method of diagnosis, and study design.

The current study was performed through a retrospective ascertainment of disease. The young age of the participants and timing of survey administration with temporally close disease onset may result in increased accuracy in self-report of PCOS and endometriosis. PCOS is generally diagnosed in the adolescent period, with rare cases diagnosed in pre-adolescence [50]. The diagnosis of early stage endometriosis varies by practice patterns and geographic location. One study noted that the mean age (SD) at symptom onset was 21.49 (8.28) years, with mean age (SD) at diagnosis was 30.35 (9.19) years in the United States [51]. With regards to difficulty conceiving, this may not accurately represent the clinically defined disease of infertility. Reports of difficulty conceiving and miscarriage may be low in this cohort because some study subjects had not initiated or completed their reproductive years when they responded to the questionnaire. Any cases of the reproductive diseases occurring after the survey administration period were not captured and therefore not evaluated in this analysis. In terms of miscarriage, further information regarding gestational age of the miscarriage or method of detection were unavailable. Any pregnancy loss that occurred before a detectable pregnancy test or that resulted in a slightly delayed menses would not be reported in this study.

In conclusion, while adult exposure to PCE is known to have numerous toxic effects, there is little information on the long-term impact of prenatal and early childhood exposure. We undertook a retrospective cohort study to examine whether early life exposure to PCE-

contaminated drinking water influenced the risk of reproductive disorders (PCOS, endometriosis, difficulty conceiving, and miscarriages) among adults who were born in the Cape Cod area of Massachusetts. Though there were no meaningful associations observed in this study, the relatively young study population should be monitored periodically for any changes in disease risk. Since PCE remains a commonly used commercial solvent that exposes workers and consumers and frequently contaminates drinking water, it is important to determine the long-term impact of early life exposure. Future studies should be improved with medical record validation of disease outcomes including hormonal validation of the diagnosis of PCOS, laparoscopic confirmation of endometriosis, and karyotype screening of couples or the products of conception in cases of miscarriage.

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Abbreviations

CI	Confidence Interval
DEP	Department of Environmental Protection
GEE	Generalized estimating equation
PCE	Tetrachloroethylene
RR	Risk Ratio
VL/AC	vinyl-lined asbestos-cement

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Highlights

- Tetrachloroethylene (PCE) is an organic lipophilic solvent commonly used in dry cleaning of fabric, degreasing of metals, and in the synthesis of other chemicals with possible neuroendocrine toxicity.
- Before harmful health effects were known, PCE was used to apply a vinyl lining to asbestos-cement (AC) water distribution pipes in the Cape Cod area of Massachusetts. The vinyl lining was introduced as a barrier to unacceptable taste and odor problems and to minimize corrosion associated with conventional AC water mains.
- In this retrospective cohort study, no meaningful associations were found among adult women with early life exposure to PCE-contaminated drinking water and adult-onset reproductive disorders.
- Though there were no meaningful associations observed, the relatively young study population should be monitored periodically for any changes in disease risk. Since PCE remains a commonly used commercial solvent that exposes workers and consumers and frequently contaminates drinking water, it is important to determine the long-term impact of early life exposure.

Table 1

Distribution of Selected Characteristics of Subjects and Parents by PCE Exposure Status, Women Only

Characteristic	Exposed (n)	Exposed %	Unexposed (n)	Unexposed %
Subject Characteristics				
Year of birth				
1969–1974	96	19.2	77	23.3
1975–1980	267	53.4	179	54.1
1981–1983	137	27.4	75	22.7
Gender				
Female	500	100.0	331	100.0
White race				
Yes	495	99.0	328	99.1
No	5	1.0	3	0.9
Current educational level				
High School Grad or Less	68	13.6	33	10.0
Some College	113	22.6	85	25.7
4-Year College Grad or Higher	318	63.6	212	64.0
Missing	1	0.2	1	0.3
Currently employed				
Yes	421	84.2	283	85.5
No	69	13.8	44	13.3
Missing	10	2.0	4	1.2
Current marital status				
Single	156	31.2	82	24.8
Married or cohabiting	327	65.4	236	71.3
Other (Separated, Widowed, Divorced)	14	2.8	9	2.7
Missing	3	0.6	4	1.2
Ever had a job with solvent exposure				
Yes	60	12.0	31	9.4
No	427	85.4	291	87.9
Missing	13	2.6	9	2.7
Ever had hobby with solvent exposure				
Yes	396	79.2	267	80.7
No	101	20.2	62	18.7
Missing	3	0.6	2	0.6
Ever smoked cigarettes regularly				
Yes	217	43.4	149	45.0
No	278	55.6	182	55.0
Missing	5	1.0	0	0.0
Drank alcoholic beverages as a teen				

Characteristic	Exposed (n)	Exposed %	Unexposed (n)	Unexposed %
Yes	381	76.2	251	75.8
No	109	21.8	77	23.3
Missing	10	2.0	3	0.9
Drank alcoholic beverages as an adult				
Yes	386	77.2	254	76.7
No	102	20.4	75	22.7
Missing	12	2.4	2	0.6
Used major illicit drugs as a teen				
Yes	127	25.4	58	17.5
No	368	73.6	270	81.6
Missing	5	1.0	3	0.9
Used major illicit drugs as an adult				
Yes	157	31.4	89	26.9
No	336	67.2	241	72.8
Missing	7	1.4	1	0.3
Subject's birth weight (g) (n, mean (sd))	497	3377 (488)	300	3342 (514)
Subject's gestation (weeks) (n, mean (sd))	475	40.3 (2.3)	314	39.9 (2.3)
Parent Characteristics				
Mother's age at subject's birth (years) (n, mean (sd))	500	27.1 (4.8)	331	27.1 (4.1)
Father's age at subject's birth (years) (n, mean (sd))	500	29.8 (5.8)	331	29.6 (5.1)
Mother received prenatal care during subject's gestation				
Yes	476	95.2	316	95.5
No	3	0.6	0	0.0
Missing	21	4.2	15	4.5
Mother smoked cigarettes during subject's gestation				
11+ cigarettes/day	59	11.8	38	11.5
1–10 cigarettes/day	40	8.0	35	10.6
None	290	58.0	194	58.6
Missing	111	22.2	64	19.3
Mother consumed alcohol during subject's gestation				
1+ drinks/week	63	12.6	37	11.2
1–3 drinks/month	104	20.8	75	22.7
None	221	44.2	155	46.8
Missing	112	22.4	64	19.3
Mother smoked marijuana during subject's gestation				
Yes	15	3.0	10	3.0
No	375	75.0	253	76.4
Missing	110	22.0	68	20.5
Mother had medical and obstetrical complications during subject's gestation				

Characteristic	Exposed (n)	Exposed %	Unexposed (n)	Unexposed %
Yes	82	16.4	69	20.8
No	303	60.6	197	59.5
Missing	115	23.0	65	19.6
Breastfed subject				
Yes	247	49.4	181	54.7
No	138	27.6	83	25.1
Missing	115	23.0	67	20.2
Mother had occupational exposure to solvents				
Yes	45	9.0	35	10.6
No	334	66.8	225	68.0
Missing	121	24.2	71	21.5
Multiple pregnancy				
Yes	10	2.0	16	4.8
No	490	98.0	315	95.2

Table 2

Distribution of PCE Exposure (g) Among Exposed Subjects, Women Only

	<i>Prenatal PCE (g) *</i>	<i>Early Childhood PCE (g) *</i>	<i>Prenatal + Early Childhood PCE (g) *</i>
Number	500	500	500
Minimum	2.633E-03	8.448E-03	1.108E-02
10th Percentile	0.3	1.2	1.7
33rd Percentile	1.9	5.5	7.6
25th Percentile	2.9	8.8	13.1
Median	7.1	22.1	32.6
67th Percentile	17.1	52.8	74.9
75th Percentile	25.3	86.4	115.6
90th Percentile	71.7	221.0	287.6
Maximum	702.4	1,645.9	2,333.7
Mean	29.2	92.5	121.7
SD	71.1	204.2	268.4

* Among those with both prenatal and postnatal exposure

Table 3

Crude and Age-adjusted Risk Ratios for Combined Prenatal and Early Childhood PCE Exposure and Reproductive Outcomes.

Outcome	Combined Prenatal and Early Childhood PCE Exposure Category/ Percentile	% Yes (n/N)	Crude GEE RR (95% CI)	Adjusted* GEE RR (95% CI)
Polycystic ovary syndrome vs. No polycystic ovary syndrome	Any	5.5 (27/495)	0.9 (0.5,1.6)	0.9 (0.5,1.6)
	median	5.8 (14/240)	0.9 (0.5,1.9)	0.9 (0.4,1.8)
	> 0 – < median	5.1 (13/255)	0.8 (0.4,1.7)	1.0 (0.5,1.9)
	No exposure	6.1 (20/328)		
Endometriosis vs. No endometriosis	Any	4.5 (22/493)	0.9 (0.5,1.7)	1.0 (0.5,1.8)
	median	4.6 (11/240)	0.9 (0.4,1.9)	0.9 (0.4,1.8)
	> 0 – < median	4.3 (11/253)	0.9 (0.4,1.9)	1.1 (0.5,2.2)
	No exposure	4.9 (16/328)		
Trouble getting pregnant vs. No trouble getting pregnant	Any	8.5 (37/433)	1.0 (0.6,1.6)	1.0 (0.6,1.6)
	median	8.3 (17/205)	0.9 (0.5,1.7)	0.8 (0.5,1.5)
	> 0 – < median	8.8 (20/228)	1.0 (0.6,1.7)	1.2 (0.7,2.1)
	No exposure	8.9 (24/271)		
Miscarriage vs. No miscarriage	Any	11.6 (50/430)	0.9 (0.6,1.4)	0.9 (0.6,1.4)
	median	11.8 (24/204)	0.9 (0.6,1.5)	0.9 (0.5,1.4)
	> 0 – < median	11.5 (26/226)	0.9 (0.6,1.4)	1.0 (0.6,1.7)
	No exposure	12.9 (35/271)		

* Model adjusted for Child's age

Tetrachloroethylene (PCE), Generalized Estimating Equation (GEE), Risk Ratio (RR), Confidence Interval (CI)