FINAL PROGRESS REPORT

Project Title:	**TRICHLOROETHYLENE AND PARKINSON'S DISEASE**
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LIST OF TERMS/ABBREVIATIONS

CCl4: carbon tetrachloride
CEI: cumulative exposure index
CI: confidence interval
GSTM1: glutathione-S-transferase M1
NAS/NRC: National Academy of Sciences/National Research Council
NCIRE: Northern California Institute for Research & Education
OR: odds ratio
PD: Parkinson's Disease
PERC: tetrachloroethylene; perchloroethylene
SEARCH: Study of Environmental Association and Risk of Parkinsonism using Case-Control Historical Interviews
TCE: trichloroethylene
UPDRS: Unified Parkinson's Disease Rating Scale

ABSTRACT

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The purpose of this study was to investigate the association of occupational exposures to the solvents trichloroethylene (TCE) and tetrachloroethylene (perchloroethylene, PERC) and risk of Parkinson's disease (PD). The basis for this investigation was founded on three prior observations: 1) In 2008 a cluster of PD was reported in a small manufacturing facility in Kentucky where a large vapor-degreasing vat of TCE had been present in an enclosed area for several years; 2) Subsequently, TCE was shown to produce an animal model of parkinsonism that recapitulated the primary behavioral and pathological characteristics of PD. 3) This prompted our group to conduct the first analytic study of TCE in a cohort of twins who were discordant for

PD, in which we found a significant 6-fold increased risk of PD among persons who had worked with TCE, and a . The present study aimed to replicate these findings in an independent study population, and test the hypothesis that variation in genes related to TCE metabolism or genes related to PD risk might modify the risk from TCE.

We collected lifetime detailed job-task histories from 519 PD and 511 control subjects. We reviewed a total of 9,369 individual job histories and estimated exposure likelihood, intensity and duration to the solvents TCE, PERC, and carbon tetrachloride (CCl_4) for each job. We also calculated a cumulative exposure estimate for each compound. Solvent exposures were rare in this cohort, with only 37 (7.1%) cases and 47 (9.2%) controls exposed to any of TCE, PERC or CCl4. 12 case and 10 control subjects were judged to have had an occupational exposure to TCE, our solvent of primary interest. PD risk associated with “high” cumulative exposure to TCE was slightly but non-significantly elevated: odds ratio 1.8 (95%CI 0.5-5.2). We conducted a pooled analysis that combined the current data with data from our prior study in twins. In this pooled analysis, we found a significantly increased risk from TCE: odds ratio 4.2 (95%CI 1.2-15.3). Our ability to assess exposure risk in persons with specific genetic variants was limited due to small numbers. We found a significant interaction between occupational use of CCl4 and the metabolic enzyme GSTM1 among men: persons with active glutathione-S-transferase-M1 enzyme were at higher risk from TCE exposure ($p=0.037$) than persons with inactive enzyme. No other significant interactions were found, but risk associated with TCE exposure was somewhat higher in persons with function glutathione-S-transferase-M1 enzyme. Additionally, though not statistically significant, risk associated with TCE exposure was higher in smokers and in persons who sustained a prior head injury.

Overall, this work adds to current data suggesting that occupational exposure to TCE is a risk factor for PD. Though statistical power was low, possible genetic and environmental interactions were suggested, consistent with the hypothesis that some workers may be particularly susceptible to solvent toxicity. Future studies would benefit from larger numbers of exposed subjects, ideally with objective estimates of exposure to these specific solvents.

SECTION 1

Significant/Key Findings

The current project had three primary aims. The first aim was to determine if we could replicate our prior observation of markedly increased risk of Parkinson's disease associated with occupational exposure to the solvents TCE, PERC or CCl4. To this end, we collected lifetime detailed job-task histories from 519 PD and 511 control subjects. An academic industrial hygienist and/or occupational medicine physician reviewed 9,369 individual job histories, unaware of disease status, and estimated exposure likelihood, intensity and duration to the TCE, PERC, and CCl_4 for each job. We derived a cumulative exposure estimate for each compound based on these determinants. In multivariable analyses adjusted for age, sex, race and smoking, we considered PD associations with ever/never exposure as well as with cumulative exposures, and assessed dose-reponse relationships.

Solvent exposures were rare in this cohort, with only 37 (7.1%) cases and 47 (9.2%) controls exposed to any of TCE, PERC or CCl4. 12 case and 10 control subjects were judged to have had an occupational exposure to TCE, our solvent of primary interest. Ever having worked with TCE was associated with slight but non-significant increased PD risk: OR 1.33 (95%CI 0.55-3.22). Risk was not increased for PERC or CCl4, nor for anaylses considering the 3 solvent exposures pooled. In analyses of cumulative exposures, "high" cumulative exposure to TCE was modestly but non-significantly elevated: OR 1.7 (95%CI 0.5-5.2) and for CCl4: OR 1.3 (0.6-3.0), but was actually inversely associated with PERC: OR 0.4 (95CI 0.1-1.9).

We conducted a pooled analysis that combined the data from the present study with data from our prior study in twins. We used generalized estimating equations that adjusted for study, twin-relatedness, age and smoking. In this pooled analysis, we found a significantly increased risk from high TCE exposure: OR 4.2 (95%CI 1.2-15.3).

Our second aim was to assess whether associations with TCE, PERC or CCl4 were modified by polymorphic variants in genes encoding solvent metabolizing enzymes, or PD-associated genes. Our ability to assess gene-solvent interactions was limited due to small numbers of exposed individuals in combination with the rarity of most genetic variants. An exception to this is for *GSTM1* which encodes the enzyme glutathione-M-transferase 1, for which approximately 40% of the population lacks any functional enzyme due to homozygous large deletions. We found a significant interaction between occupational use of CCl4 and the metabolic enzyme GSTM1 among men: persons with active glutathione-S-transferase-M1 enzyme were at higher risk from CCl4 exposure (p=0.037) than persons with inactive enzyme. No other significant interactions were found, but risk associated with TCE exposure was also higher in persons with functional glutathione-S-transferase-M1 enzyme.

Our third aim was to assess whether risk associated with solvent exposure was modified by other environmental exposures known to be associated with PD risk. Risk associated with TCE exposure was found to be greater in smokers than in non-smokers (OR_{int} 1.6). This interaction tended toward significance in persons with high cumulative TCE exposure (OR in smokers 3.6, 95%CI 0.7-18, p-interaction 0.12). Risk

associated with either TCE or CCl4 exposure was also modestly non-significantly higher in persons who had sustained a prior head injury.

Overall, despite the small number of exposed subjects, this work adds to current data suggesting that occupational exposure to TCE is a risk factor for PD. Novel findings suggest that risk may be greater in persons with active glutathione-M-transferase and in those who smoke or sustained a prior head injury. Future studies of TCE, PERC and CCl4 should target larger numbers of exposed subjects, ideally with objective estimates of exposure.

Translation of Findings

Though analytic power was limited due to the small number of exposed subjects, this work, in combination with our prior findings in twins adds to evidence that TCE exposure is a risk factor for Parkinson's disease. The use of TCE in the workplace should be reduced through product substitutions, and if not possible, through use of engineering controls and personal protective equipment. Dissemination of these findings has been achieved through presentation of results at professional meetings. A manuscript is in preparation. These results are also providing key preliminary data for a pending grant application in another cohort.

Research Outcomes/Impact

Potential outcomes. These findings add to evidence that occupational exposure to TCE and CCl4 may increase worker risk for Parkinson's disease many years later. The primary occupations most frequently associated with TCE exposure in the current study population included Aircraft Mechanics, Electricians, and Mechanic/Auto Body, and the mean duration between last estimated exposure and PD diagnosis was 28 years (SD 19 years). The occupations most frequently associated with CCl4 exposure included Electricians, Mechanic/Auto Body, Artist, and Industrial Machinery Repair. Although these results are very preliminary, worker exposure to these chlorinated solvents should be minimized as much as possible. Future work should attempt to identify highly exposed cohorts and follow them for development of PD and other neurodegenerative diseases as primary outcomes.

SECTION 2: SCIENTIFIC REPORT

Overview:

The purpose of this study was to investigate the association of occupational exposures to the solvents trichloroethylene (TCE) and tetrachloroethylene (perchloroethylene, PERC) and risk of Parkinson's disease. The basis for this investigation was founded on three prior observations. In 2008 a cluster of PD was reported in a small manufacturing facility in Kentucky where a large vapor-degreasing vat of TCE had been present in an enclosed area for several years. Subsequently, TCE was shown to produce an animal model of parkinsonism that recapitulated the primary behavioral and pathological characteristics of PD. This prompted our group to conduct the first analytic study of TCE and the chemically (and industrially) similar compound PERC in a cohort of twins who were discordant for PD (the TWINS study)

The present work had 3 primary aims. First, we sought to replicate our prior associations in an independent cohort. Additionally, we hypothesized that polymorphic genetic variants related to solvent metabolism and/or to PD might modify the associations. And finally, we hypothesized that other PD-related exposures might modify the solvent associations. To do this, we took advantage of existing data from the Study of Environmental Association and Risk of Parkinsonism using Case-Control Historical Interviews study (SEARCH), a study of over 500 PD cases and 1:1 matched controls from 8 North American movement disorders centers. Occupational interviews had previously collected information about industry/tasks/processes/materials for all jobs held at least 6 months since age 10. Initially, we had proposed to conduct variant analyses of select genes of interest using existing DNA that had been previously collected and stored in -80 freezers at the original granting institution, the Parkinson's Institute in Sunnyvale, CA. However, during 2014, our research group moved from the Parkinson's Institute to the University of California-San Francisco, and the grant was transferred to the Northern California Institute for Research & Education (NCIRE). Despite our best efforts to collaborate, the Parkinson's Institute refused to provide us access to the DNA specimens. Fortunately, we had previously conducted analyses of 110 genes of interest for 590 of the 1030 SEARCH subjects using a custom-designed Illumina SNP array, and were able to use these data to test many of our a priori hypotheses of interest. Unfortunately, in addition to including only 590 of the 1030 SEARCH subjects, this Illumina GoldenGate array did not include the gene *CYP2E1*, one of the key enzymes involved in TCE metabolism.

We conducted all analyses within the SEARCH study independently, and then pooled results with those of the prior TWINS study, in which we had used identical exposure assessment and genotyping methods. These are described in detail below.

Exposure Assessments:

Using methods successfully implemented in TWINS, we estimated TCE, PERC and CCl_4 exposures for 1030 SEARCH subjects, utilizing data from the 52 already-administered job-task-based questionnaire modules (See Job Module table below). A

total of 8342 individual job modules and 1027 job overviews were considered (9369 total). A computerized algorithm was implemented to identify those modules with potential exposures of relevance and requiring further review. Jobs held until the diagnosis date of PD (or similar index date for control) were considered. A total of 4085 individual modules were evaluated for potential exposure events encompassing a total of 185 relevant variables. Ultimately, after staged reviews, Dr. Goldman (experienced in occupational medicine) and Ms. Quinlan (industrial hygienist) manually reviewed 937 potential exposure events while blinded to case status, and estimated exposures using extensive probability databases (Siemiatycki, unpublished data) and multiple reference sources. 307 of the 937 exposures were reviewed by *both* Dr. Goldman and Ms. Quinlan and exposures assigned by consensus. A 5% subset were independently re-rated to assess consistency. For each job and each compound, exposures were rated for exposure probability (none, possible, probable, definite, unable to rate), degree/intensity (low, medium, high, unable to rate), hours per year, and years exposed (see Exposure Rating Sheet, below). Exposures to each compound were summed within and across all job modules to derive a cumulative exposure for each job, and summed across all jobs. A total of 937 exposure events to compounds of interest were identified and rated.

A *cumulative exposure index* was derived as follows:

For each exposure event:

1) Probability was valued at 3 levels: none=0, possible=1, definite/probable=5
2) Degree was valued at 2 levels: low=2, medium=5 (no high degree exposures were identified)
3) Generate probability*degree*years score for each exposure for each job
4) Generate a summary variable for each subject*compound by summing the probability*degree*years variable across all jobs for each of TCE, PERC and CCl4
5) Generate a “summary” summary variable for TCE or PERC, and for TCE or PERC or CCl4

Job Module List

AM **Aircraft Mechanic:** weld, solder, paint/varnish(1), clean/degrease (V/P), machine parts
AR **Artist/Photographer/Art Teacher:** weld, solder, clean/degrease (V/P)
BA **Barber/Hairdresser**
BS **Brick/Stone Mason**
CA **Cabinet Maker/Bench Carpenter/Hobby Carpenter:** paint/varnish(2), glues, paint-stripping, wood**
CL* **Carpet layer:** Glues, part of clean/degrease
CR **Carpenter:** paint/varnish(2), glues, paint-stripping, wood**
CT **Concrete or Terrazo Worker**
DC **Dry Cleaner or Launderer**
EG **Engineer**
EL **Electrician/Repairer of Transformers, Electrical, or Electronic Equipment:** weld, solder, machine parts, clean/degrease (V/P), glues
FF **Firefighter**
FM **Farmer/Farmworker:** weld, solder, paint/varnish(2), woodwork, paint-stripping, s-pest

FS **Fisherman**
GA **Gardener/Groundskeeper/Landscaper:** paint/varnish(2)**, s-pest
GS **Gas Station Attendant**
HC **Heavy Construction Worker/Laborer:** weld, solder, clean/degrease (V/P)
HW **Health Worker**
IM **Industrial Machinery Repairer:** weld, solder, machine parts, paint/varnish(1), clean/degrease (V/P), glues
IN **Insulator:** weld, solder, glues, clean/degrease (V/P)**
IW **Industrial Worker or Manufacturer:** clean/degrease (V/P)
JA **Janitor:** paint/varnish(2)
KN **Knitter/Textile Worker/Garment Worker**
LAB **Laboratory Technician, Teacher, or Scientist**
MA **Machinist/Metal Worker:** weld, solder, clean/degrease (V/P), machining parts, wood**
ME **Mechanic/Autobody Worker:** weld, paint/varnish(1), clean/degrease (V/P)
MIL* **Military personnel**
MIN **Miner/Quarry Worker**
PA **Painter: Construction, Industrial/Maintenance:** paint/varnish(1,2), paint-stripping
PF **Packaging/Filling Machine Operator:** Glues**, IM (weld, solder, machine, paint(1), clean, glue)
PI **Production Inspector**
POL* **Police**
PL **Plumber, Pipe Fitter, or Steamfitter:** weld, solder, machine parts, clean/degrease (V/P)
PR* **Printer/lithographer:** part of clean/degrease
RO **Roofer:** paint/varnish(2)
SH **Shoemaker/Repairer:** glues, clean/degrease (V/P)
SM **Sheet Metal Worker:** weld, solder, machine parts, clean/degrease (V/P)
ST **Steel Worker:** Metal/manganese questions
TC **Traffic Clerk/Forklift Operator/Shipping/Receiving/Stock/Inventory/Freight/Storage**
TD **Truck Driver**
TO **Tool and Die Worker:** weld, solder, clean/degrease (V/P), machine parts, paint/varnish(2), woodwork, glues
WE **Welder/Cutter/Burner:** weld, solder, clean/degrease (V/P), machine parts

SUBMODULES:
S-weld
S-solder
S-clean (solvent V/P)
S-mach (machine parts)
S-wood
S-glue
S-strip (paint stripping)
S-paint 1 (industrial)
S-paint 2 (non-industrials)
S-pesticide

Exposure Rating Sheet (one for each module; multiple modules per job)

ID_____ Job#_____ JM_____ submod_____ MD Rev Date _____ IH Rev Date _____

COMPOUND	Data Code	0=not exposed 1=yes, V 2=yes, P 8=miss/no ask 9=DK	Probability 0=no 1=poss 2=prob 3=def 9=DK	Degree 1=low 2=med/high 9=DK	Hours/year 8888=missing 9999=DK	First date	Last date
TCE/PERC Indeterminate	10						
TCE1	11						
TCE2	12						
TCE3	13						
PERC1	21						
PERC2	22						
PERC3	23						
CCl1	31						
CCl2	32						
CCl3	33						
Methylene chloride	41						
Chloroform	51						
Trichloroethane	61						
OTHER Halogenated Hydrocarbon							
Specify:							

RESULTS

Demographic results are presented in Table 1. To summarize, a total of 519 case and 511 control lifetime occupational histories were reviewed, including 9369 interview components. 937 histories were considered to have had possible exposures that warranted hands-on manual review. Subject demographic characteristics and relevant covariates are summarized in Table 1, “SEARCH Subject Descriptives.” As expected, smoking was inversely associated with PD risk. Case subjects were well-matched to controls on matching variables. Mean PD duration at enrollment was quite low at only 2.8 years.

Table 1. SEARCH Subject Descriptives

	Case (n=519)	Control (n=511)	Significant differences
Sex			
Female	210 (40.5%)	209 (40.9%)	
Male	309 (59.5%)	302 (59.1%)	
Non-Hispanic White	473 (91.7%)	472 (93.3%)	
Highschool or less education	105 (20.2%)	84 (16.4%)	

Smoking			P=0.002
Never	58.5%	50.3%	
Former	37.7%	42.3%	
Current	3.8%	7.4%	
Head injury ever	24.4%	20.6%	
Proportion employed at enrollment	40.5%	43.8%	
PD duration at enrollment, mean years (SD), range	2.8 (2.0), 0-8		
Age at diagnosis	61.6 (10.2), 30-88		
UPDRS Motor score	19.2 (11.2), 0-73		

Solvent exposures were rare in this cohort, as summarized in Table 2, "Exposure Descriptives and Univariate Odds Ratios", with only 37 (7.1%) cases and 47 (9.2%) controls exposed to any of TCE, PERC or CCl4. Only 12 case and 10 control subjects were judged to have had an occupational exposure to TCE, our solvent of primary interest. This is a considerably lower frequency than we observed in the prior TWINS study, and far lower than we anticipated in our power estimates for this project. A possible explanation for this low frequency is that the SEARCH study was not a population-based study, rather subjects were recruited from 8 North American specialty movement disorders centers, whose patient populations may have had a higher proportion of white collar occupations. Supporting this possibility, the education level of the study cohort was very high, with 82% reporting greater than a highschool education. For TCE, years since last exposure until index age averaged 27.9 years (SD 18.9), range 0-62 years. Exposure durations were relatively similar in exposed cases and controls, though a trend toward longer exposure durations were seen for TCE among cases (p=0.2). The low exposure frequency negatively impacted our ability to detect associated risk differences, and particularly limited our ability to assess gene x environment interactions.

Table 2. Exposure Descriptives & Univariate Odds Ratios (OR).

Exposure	**Case (n=519)**	**Control (n=511)**	**OR (95%CI)**
TCE ever/never	12 (2.3%)	10 (2.0%)	1.18 (0.51-2.75)
TCE Probability			
Probable	11	8	
Possible	1	2	
TCE Degree			
Med/High	6	2	
Low	6	8	
TCE Exposure Duration (among exposed), mean years, median, range	mean 11.3 median 9.0 range 1-36	Mean 9.9 Median 3.5 Range 0.33-55	Wilcoxon p=0.2
PERC ever/never	8 (1.5%)	11 (2.2%)	0.71 (0.28-1.78)
PERC Probability			

Probable	7	10	
Possible	1	1	
PERC Degree			
Med/High	2	8	
Low	5	3	
PERC Exposure Duration (among exposed), mean years, median, range	Mean 8.4 median 1.5 range 0.17-45	Mean 8.5 Median 4.0 Range 0.25-27	ns
TCE or PERC*	22 (4.2%)	23 (4.3%)	0.94 (0.52-1.71)
TCE/PERC Probability			
Probable	20	21	
Possible	2	2	
TCE/PERC Degree			
Med/High	9	9	
Low	12	14	
CCl4	24 (4.6%)	30 (5.9%)	0.78 (0.45-1.35)
CCl4 Probability			
Probable	24	29	
Possible	0	1	
CCl4 Degree			
Med/High	12	8	
Low	12	21	
CCl4 Exposure Duration (among exposed), mean years, medians, range	Mean 10.3 Median 7.5 Range 0.25-49	Mean 9.3 Median 4.0 Range 0.5-35	ns
TCE or PERC or CCl4	37 (7.1%)	47 (9.2%)	0.76 (0.48-1.19)

*n is larger than for TCE n + PERC n because for some subjects we were only able to classify them as *either* TCE or PERC

In analyses adjusted for age, sex, race and smoking (Table 3), we found non-significant modest increases in PD risk associated with TCE exposure, OR 1.33 (95%CI 0.55-3.22), and modest non-significant lower risk in PERC exposed subjects, OR 0.77 (95%CI 0.30-1.97).

Table 3. Adjusted ORs [adjusted for age, sex, race (white non-hispanic or other), smoking (never, former, current)]. Total n=967

Exposure	**OR (95%CI)**
TCE ever/never	1.33 (0.55-3.22)
PERC ever/never	0.77 (0.30-1.97)
TCE or PERC	1.06 (0.57-2.0)
CCl4	0.89 (0.50-1.59)
TCE or PERC or CCl4	0.82 (0.52-1.31)

In analyses of cumulative exposure (Table 4), risk for "high" exposure to TCE was 1.67 (0.54-5.20), while risk for high exposure for PERC was 0.36 (0.07-1.87) and for CCl4 was 1.34 (0.59-3.02). Notably, when we reclassified subjects for whom exposure to TCE/PERC was indeterminate (i.e., we judged subjects to have been exposed, but we felt we could not reliably determine whether that exposure had been to TCE or to PERC) as TCE-exposed, risk was somewhat higher though still non-significant at 2.16 (0.53-8.78).

Table 4. Cumulative Exposure Index (CEI) Tertile Analyses

Exposure	Case	Control	Adjusted OR (95%CI)
TCE CEI			
None (reference)	505	496	1.0
Middle	4	5	1.01
High	8	5	1.67 (0.54-5.20)
TCE inclusive CEI*			
None (reference)	505	496	1.0
Middle	4	5	1.00
High	8	5	2.16 (0.53-8.78)
PERC CEI			
None (reference)	509	496	1.0
Middle	5	5	0.98
High	2	6	0.36 (0.07-1.87)
CCL4 CEI			
None (reference)	495	481	1.0
Middle	10	16	0.76 (0.33-1.75)
High	14	11	1.34 (0.59-3.02)

*TCE/PERC indeterminates reclassified as TCE-exposed

Gene x environment analyes were severely limited due to the small number of exposed subjects, compounded by low variant allele frequencies for most of the genes available. An exception is provided by gluathione-S-transferases M1 and T1, for which homozygous null deletions are present in approximately 50% and 20% of Caucasian populations, respectively. Select GST*solvent analyses are presented in Table 5 "Select Gene X Environment Analyses", below. Of note, though results were not significant in any cell, greater risk from TCE was observed in the presence of active GSTM1. The lone signficant interaction was found for GSTM1*CCl4 in analyses restricted to men. In addition to those presented here, we conducted a wide range of analyses in several hundred SNPs in both metabolic genes (ABCB1, ABCC1, ABCC5, CYP1A1, CYP1A2, CYP2D6, CYP3A4, EPHX1) and PD-associated genes (LRRK2, MAPT, SNCA), as specified in Aims 1 & 2. Though we were able to assess these for main effects, except for GSTM1 and GSTT1 we had insufficient power to assess these for gene-environment interaction.

Table 5. Select Gene x Environment Analyses (Case n=407, control n=169)

Exposure	Gene	Unadjusted OR (95%CI)	p-interaction
TCE ever	GSTM1 present (47.8%)	2.09 (0.24-18.2)	0.3
	GSTM1 absent (52.2%)	0.67 (0.16-2.9)	
TCE ever	GSTT1 present (82.1%)	0.84 (0.25-2.8)	0.35
	GSTT1 absent (17.9%)	Not calculable (2 cases, 0 controls)	
CCl4 ever	GSTM1 present	1.56 (0.42-5.76)	0.09
	GSTM1 absent	0.39 (0.14-1.08)	
CCl4 ever, men only	GSTM1 present	2.65 (0.57-12.4)	**0.037**
	GSTM1 absent	0.39 (0.13-1.16)	

Solvent x environment interactions. We tested whether associations of solvents with PD are modified by common environmental risk factors for PD, specifically smoking and head injury (Table 6). We were unable to test interactions with pesticides due to small numbers. Risk associated with TCE exposure was higher in smokers. Among smokers, this tended toward significance for the high tertile of TCE cumulative exposure (p-interaction 0.12). Similar non-significant trends toward increased risk were observed among both TCE and CCl4-exposed subjects who had sustained a prior head injury.

In stratified analyses among smokers (Table 7), the OR for ever exposure to TCE was 1.77 (0.55-5.75).

Table 6. Solvent x Environment Analyses

Exposure	Exposure	Unadjusted OR (95%CI)	p-interaction
TCE ever	Never Smoker	1.05 (0.28-3.95)	ns
	Smoker	1.67 (0.52-5.35)	
	No Head injury	1.30 (0.51-3.34)	ns
	Head injury	1.66 (0.15-18.5)	
TCE high CEI	Never Smoker	0.56 (0.1-3.4)	0.12
	Smoker	3.6 (0.72-17.9)	
CCl4 ever	No Head injury	0.75 (0.4-1.37)	0.23
	Head injury	2.13 (0.4-11.2)	

Table 7. Adjusted analyses restricted to former or current smokers. [adjusted for age, sex, race (white non-hispanic or other)]. Total n=438

Exposure	OR (95%CI)
TCE ever/never	1.77 (0.55-5.75)
PERC ever/never	0.68 (0.16-2.87)
TCE or PERC	1.19 (0.52-2.73)
CCl4	0.77 (0.37-1.61)
TCE or PERC or CCl4	0.70 (0.37-1.33)

Pooling of results from TWINS and SEARCH.

Given the very limited power of analyses in SEARCH, we conducted analyses that pooled results from both TWINS and SEARCH, independent studies which used identical interview and exposure analysis methods. Briefly, the TWINS study was a population-based study of PD conducted in the 32,000 member NAS/NRC World War II Twins cohort, which had been assembled by the National Academies from military records of Caucasian male twins born between 1917-1927. We conducted cohort-wide screens in 1992-3 and again in 1997-8 and conducted in-person exams to ascertain approximately 220 twin pairs with PD in at least 1 twin (198 discordant, 22 concordant pairs). Lifetime occupational histories and exposure assessments were completed for 155 twins with PD and 117 co-twin controls without PD. Pooled TWINS and SEARCH analyses (restricted to men only) used generalized estimating equations that adjusted for study, twin-relatedness, age and smoking. These results are presented in Table 8 "Pooled Analysis of TCE exposure in SEARCH & TWINS." In pooled analyses, PD risk was higher for TCE exposure (OR 1.8, 95%CI 0.9-3.7). In cumulative tertile pooled analyses restricted to men, relative to no exposure, OR for TCE exposure was 1.0 (0.4-2.4) for low (n= 12 in SEARCH, 9 in TWINS) and 4.2 (1.2-15.3) (n= 9 in SEARCH, 6 in TWINS) for high exposure (p-trend 0.033).

Table 8. Pooled Analysis of TCE exposure in SEARCH & TWINS. OR (95%CIs) adjusted for study, twin-relatedness, age, smoking.

TCE Exposure tertile	Pooled
None	1.0 (ref)
Low	1.0 (0.4-2.4)
High	4.2 (1.2-15.3)
p-trend	0.033

Summary of Significant Findings: In SEARCH, TCE exposure was associated with a modest, non-significant increased risk of PD. When pooled with results of the prior TWNS study, in analyses of cumulative tertiles, relative to no exposure, risk associated with TCE exposure was 1.0 (0.4-2.4) in the low-exposure group, and 4.2 (1.2-15.3) for the high exposure group (p-trend 0.033). Analyses of gene-environment interaction were constrained by very limited power. We found non-significant but consistent associations of increased risk for TCE and CCl4 associated with presence (vs. absence) of functional glutathione-S-transferase M1 (*GSTM1*). We also found non-significant but consistently increased solvent-associated risk in smokers and in subjects who had sustained a prior head injury.

Publications

Proceedings

S. Goldman, P. Quinlan, C. Meng, K. Comyns, G.W. Ross, K. Marek, C. Tanner. Occupational trichloroethylene exposure and Parkinson's disease risk [abstract]. *Mov Disord.* 2017; 32 (suppl 2). http://www.mdsabstracts.org/abstract/occupational-trichloroethylene-exposure-and-parkinsons-disease-risk/. International Parkinsonism and Movement Disorder Society 21st International Congress, 2017, Vancouver, Canada.

View Burden Statement

PHS Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

OMB Number: 0925-0001 and 0925-0002
Expiration Date: 10/31/2018

***Study Title (must be unique):** TRICHLOROETHYLENE AND PARKINSON'S DISEASE

* Delayed Onset Study? ☐ Yes ☒ No

If study is not delayed onset, the following selections are required:

Enrollment Type ☐ Planned ☒ Cumulative (Actual)

Using an Existing Dataset or Resource ☒ Yes ☐ No

Enrollment Location ☒ Domestic ☐ Foreign

Clinical Trial ☐ Yes ☒ No **NIH-Defined Phase III Clinical Trial** ☐ Yes ☒ No

Comments:

Racial Categories	Ethnic Categories									
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			Total
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	6	8	0	0	0	0	0	0	0	14
Asian	7	17	0	0	0	0	0	0	0	24
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	5	8	0	0	0	0	0	0	0	13
White	370	559	0	18	24	0	7	11	0	989
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	6	210	0	0	0	0	0	0	0	216
Total	394	802	0	18	24	0	7	11	0	1,256

Inclusion of Children

No children were included in this study for two reasons. First, Parkinson's disease is a disease of aging and is exceedingly uncommon under age 18. Second, this was a pre-existing study cohort that did not contain children.

Materials Available for Other Investigators

Requests for access to de-identified study data by qualified academic researchers should be sent to Principal Investigator, Dr. Samuel M. Goldman: Samuel.goldman@ucsf.edu