



Published in final edited form as:

*Schizophr Res.* 2007 February ; 90(1-3): 251–254. doi:10.1016/j.schres.2006.09.024.

## TETRACHLOROETHYLENE EXPOSURE AND RISK OF SCHIZOPHRENIA: OFFSPRING OF DRY CLEANERS IN A POPULATION BIRTH COHORT, PRELIMINARY FINDINGS

Mary C. Perrin<sup>b</sup>, Mark G. Opler<sup>a,b</sup>, Susan Harlap<sup>b</sup>, Jill Harkavy-Friedman<sup>b</sup>, Karine Kleinhaus<sup>a</sup>, Daniella Nahon, MS<sup>c</sup>, Shmuel Fennig, MD<sup>d</sup>, Ezra S. Susser, MD, DrPH<sup>a,b</sup>, and Dolores Malaspina, MD, MPH<sup>a</sup>

<sup>a</sup>New York State Psychiatric Institute, New York, New York, 10032 United States

<sup>b</sup>Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York, 10032 United States

<sup>c</sup>Mental Health Services Section, Israel Ministry of Health, Tel Aviv, Israel

<sup>d</sup>Shalvata Mental Health Center affiliated with the Department of Psychiatry, Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel.

### Abstract

Tetrachloroethylene is a solvent used in dry cleaning with reported neurotoxic effects. Using proportional hazard methods, we examined the relationship between parental occupation as a dry cleaner and risk for schizophrenia in a prospective population-based cohort of 88,829 offspring born in Jerusalem from 1964 through 1976, followed from birth to age 21–33 years. Of 144 offspring whose parents were dry cleaners, 4 developed schizophrenia. We observed an increased incidence of schizophrenia in offspring of parents who were dry cleaners (RR = 3.4, 95% CI, 1.3–9.2, p=0.01). Tetrachloroethylene exposure warrants further investigation as a risk factor for schizophrenia.

### Keywords

dry cleaning; schizophrenia; tetrachloroethylene; perchloroethylene; perc

### 1. Introduction

Pollution and occupational exposures to manmade chemicals have been evaluated as causes of birth defects, pulmonary disorders and cancer, but have been little studied with respect to the risk for schizophrenia. As in other complex diseases, the causes of schizophrenia may involve environment, gene environment interactions and genetic susceptibility. Research examining the influence of prenatal exposures has centered on nutritional deficiency (Susser and Lin 1992) (St Clair et al. 2005), infections (Brown 2006), and maternal conditions (Cannon

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Address correspondence and reprint requests to MC Perrin, Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th Street, Room 1715, New York, New York 10032 United States. Telephone: 01-212 342-0173. Fax: 01-212-342-5170. mcp20@columbia.edu.

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et al. 2002). However a recent study using a biomarker of prenatal lead exposure (Opler et al. 2004) suggests that environmental exposures may be an important class of risk factors to consider.

A volatile organic solvent, tetrachloroethylene (a.k.a.tetrachloroethene perchloroethylene, PCE, PERC)(ATSDR), is the primary chemical used in dry cleaning since the 1950s (cited in (Mundt et al. 2003)). A primary route of exposure is inhalation (ATSDR). We examined the relationship between parental occupation as a dry cleaner (a surrogate for PCE exposure) and risk of schizophrenia-related disorders (schizophrenia) in offspring.

## 2. Method

### 2.1 Subjects

We relied on an ongoing, population-based cohort study of individuals born in 1964–76 (Harlap et al. 2006; Malaspina et al. 2001). The Jerusalem Perinatal Study included all births to mothers in a defined geographic area, recording demographic data on the parents, including their occupations from the birth certificate. To study schizophrenia, the cohort was linked to Israel's national Psychiatric Registry. This registry, established in 1950, receives psychiatric diagnoses from multiple sources, including inpatient wards in psychiatric and general hospitals, and psychiatric day-care facilities (Malaspina et al. 2001). Diagnoses for individuals with psychosis have been validated (Weiser et al. 2005). We used a broad definition from schizophrenia-related discharge diagnostic codes F20–F29 (ICD-10), hereafter termed “schizophrenia”. The date of onset was taken as the date of first psychiatric admission. Names, identity numbers and other identifying information were removed and the anonymous file was analyzed collaboratively in New York and Israel. The study was approved by Institutional Review Boards in both countries.

### 2.2 Statistical Analyses

Because offspring born in different years were followed for varying durations, we studied time to schizophrenia with proportional hazards methods (Hosmer and Lemeshow 1999). We used SAS's PHREG procedure (version 9.0, SAS Institute Inc). Offspring were followed from birth until diagnosis, death or censoring (December 31, 1997) at which point survivors were aged 21–33. Dry cleaning was coded as a dichotomy (1 if either father or mother had this occupation at the time of the birth, otherwise 0). Variables considered for inclusion in the model were parents' age, father's social class, duration of marriage, rural residence, religion, ethnic origin, parental immigration status, offspring's birth order, sex, birth weight and month of birth. Variables included in the model were those that altered the crude estimate of the hazard rate ratio (relative risk) by more than 10%. We found, however, that confounding was minimal, so the results are presented as a crude relative risk (RR).

## 3. Results

Of 88, 829 offspring born alive, traced and followed to January 1, 1998, 637 were admitted to hospitals with a schizophrenia-related diagnosis. The cumulative incidence of schizophrenia in this cohort is approximately 1% (Malaspina et al. 2001) similar to that reported elsewhere (Mueser and McGurk 2004). We excluded 5 cases of schizophrenia and 769 offspring (0.9%) because of missing information for either parent. In the cohort available for study (N=88,060) there were 144 offspring (63 female, 81 male) with one or more parent a dry cleaner and 4 cases of schizophrenia (2 female, 2 male). The cohort included 120 offspring (3 with schizophrenia) whose fathers were dry cleaners; 20 offspring (one with schizophrenia) whose mothers were dry cleaners; and 4 offspring (none with schizophrenia) with both parents as dry cleaners. The RR for schizophrenia in the offspring of dry cleaners was 3.4 (95% confidence

interval 1.3–9.2  $p=.01$ ). This RR was not appreciably altered by controlling for any of the variables listed in the methods section, including paternal age, an important risk factor for schizophrenia (Malaspina et al. 2001).

#### 4. Comment

This study found that the risk for schizophrenia was more than tripled for offspring whose parents worked in dry cleaning occupations. Although these results are based on only four cases in 144 offspring of dry cleaners, the prospective, longitudinal nature of this population based birth cohort study design lends strengths to the findings. Furthermore, the association was not confounded by parental age, social class, duration of marriage, urban versus rural residence, religion, ethnicity, or immigration status, or by the offspring's birth order, sex, birthweight and month of birth.

We speculate that PCE might affect the risk of schizophrenia through damage to paternal germ cells. Human studies of PCE exposure demonstrate subtle alterations in spermatogenesis (Eskenazi et al. 1991) and wives of dry cleaners seem to have fertility problems and prolonged conception times (Eskenazi et al. 1991). Sperm quality decreases with age and advanced paternal age is a consistent risk factor for schizophrenia (Byrne et al. 2003; Malaspina et al. 2001; Sipos et al. 2004; Tsuchiya et al. 2005; Zammit et al. 2003). Thus, the risk of schizophrenia associated with PCE, if confirmed, might plausibly be due to effects in men.

Another possibility is that exposure to PCE in pregnancy might disrupt fetal neurodevelopment; in animals, PCE is reported to cross the placenta and enter fetal tissues (Ghantous et al. 1986). In humans, there is controversy about its effects on pregnancy outcome, although it has been associated with spontaneous abortions in dry cleaners in one study (Kyyronen et al. 1989). The presence of PCE in drinking water has been associated with small for gestational age infants among older mothers and women with two or more previous fetal losses (Sonnenfeld et al. 2001).

PCE might also affect newborns and children; it is secreted in breast milk (Bagnell and Ellenberger 1977) and it is also a contaminant in the household of dry cleaners (Aggazzotti et al. 1994; Aggazzotti et al. 1994). Thus, the father, pregnant mother, newborn and growing child are all exposed as a consequence of either parent's occupation. As a volatile halogenated hydrocarbon, PCE is soluble in lipids and the brain is a target organ (ATSDR). It has been reported to have neurotoxic effects in animals (Wang et al. 1993). Neurobehavioral deficits have been reported in people living near a dry cleaning facility (Altmann et al. 1995) and PCE exposure may disturb neuronal processing and alter visual function (Altmann et al. 1990).

##### 4.1 Comparison with other studies

To our knowledge, this is the first report of a possible link between schizophrenia and dry cleaning. The principal strength of this study is its prospectively population based design. Ascertainment of occupation was done in a non-biased and uniform manner unrelated to the outcome. As for ascertainment of outcome, Israel's Psychiatric Registry is population-based and protected by law; and access to health care in Israel is universal. Emigration from this cohort is estimated at only 0.7%. Thus, this study avoids biases common in case-control designs. We are limited by the small number of cases, and by the use of occupation as a proxy measure for PCE exposure. In spite of these limitations, a 3.4-fold increase in risk of schizophrenia would not be trivial, particularly in light of the strong evidence supporting biologic plausibility of the association.

## 4.2 Public Health Impact

Further study is warranted to confirm these findings and knowledge about the toxicological mechanisms and potential hazards of PCE to human health is still emerging. Furthermore, our data cannot further elucidate the route or mechanism linking parental dry cleaning occupation with the risk for schizophrenia. These results do suggest that prenatal, perinatal or childhood exposures to PCE might play a meaningful role in the population attributable risk of schizophrenia, particularly in populations with high occupational or environmental exposures to the agent. PCE can be found in ground water and many hazardous waste sites (ATSDR). It is highly volatile, and exposure may also occur from vapor inhalation over contaminated sites, from industrial uses, and from contaminated water (ATSDR).

## 4.3 Implications of the Data

Elucidating a role for environmental contaminants in the etiology of schizophrenia is clearly of interest and should be further studied. Effects of exposure to PCE related to the risk for schizophrenia may occur through paternal germ cells prior to conception or through neurotoxic effects on the offspring.

## Acknowledgments

Supported by grants from the National Institutes of Health, 1R01 MH059114 (DM) and 2 K24 MH001699. We thank the mothers, fathers and offspring of the Jerusalem Perinatal Study for their participation. We also thank Dr. E. Richter for his thoughtful comments and critical appraisal of the manuscript.

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