Neurotoxicology and Teratology 38 (2013) 13–20

Contents lists available at SciVerse ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Structural Magnetic Resonance Imaging in an adult cohort following prenatal and early postnatal exposure to tetrachloroethylene (PCE)-contaminated drinking water

Patricia A. Janulewicz [a,*], Ronald J. Killiany [b], Roberta F. White [c,f], Brett M. Martin [d], Michael R. Winter [d], Janice M. Weinberg [e], Ann Aschengrau [a]

[a] Department of Epidemiology, Boston University Schools of Public Health and Medicine, Boston, MA 02118, USA
[b] Department of Anatomy and Neurobiology, Boston University Schools of Public Health and Medicine, Boston, MA 02118, USA
[c] Department of Environmental Health, Boston University Schools of Public Health and Medicine, Boston, MA 02118, USA
[d] Department of Data Coordinating Center, Boston University Schools of Public Health and Medicine, Boston, MA 02118, USA
[e] Department of Biostatistics, Boston University Schools of Public Health and Medicine, Boston, MA 02118, USA
[f] Department of Neurology, Boston University Schools of Public Health and Medicine, Boston, MA 02118, USA

ARTICLE INFO

Article history:
Received 19 April 2012
Received in revised form 21 March 2013
Accepted 22 March 2013
Available online 6 April 2013

Keywords:
Tetrachloroethylene
PCE
Development
Structural Magnetic Resonance Imaging

ABSTRACT

This population-based retrospective cohort study examined Structural Magnetic Resonance Imaging (MRI) of the brain in relation to prenatal and early postnatal exposure to tetrachloroethylene (PCE)-contaminated drinking water on Cape Cod, Massachusetts. Subjects were identified through birth records from 1969 through 1983. Exposure was modeled using pipe network information from town water departments, a PCE leaching and transport algorithm, EPANet water flow modeling software, and Geographic Information System (GIS) methodology. Brain imaging was performed on 26 exposed and 16 unexposed subjects. Scans were acquired on a Philips 3T whole body scanner using the ADNI T1-weighted MP-RAGE scan. The scans were processed by FreeSurfer version 4.3.1 software to obtain measurements of specific brain regions. There were no statistically significant differences between exposed and unexposed subjects on the measures of white matter hypointensities (β: 127.5 mm^3, 95% CI: −259.1, 1514.0), white matter volumes (e.g. total cerebral white matter: β: 21230.0 mm^3, 95% CI: −4512.6, 46971.7) or gray matter volumes (e.g. total cerebral gray matter: β: 11976.0 mm^3, 95% CI: −13657.2, 37609.3). The results of this study suggest that exposure to PCE during gestation and early childhood, at the levels observed in this population, is not associated with alterations in the brain structures studied.

1. Introduction

Tetrachloroethylene (PCE, Perc or perchloroethylene) is a manufactured colorless solvent commonly used for dry cleaning fabrics and degreasing metals. It is one of the most frequently detected solvents in groundwater (Moran et al., 2007) and at the United States Environmental Protection Agency (USEPA) Superfund sites (EPA, 2008). PCE and its main metabolite dichloroacetylene (DCA) are recognized human and animal neurotoxicants (Feldman, 1999; Klaassen, 2001; Stevens and Eisenmann, 1997; TOXICS, 1994a, 1994b). These fat soluble substances have a high affinity for the lipophilic tissues of the central nervous system (Altmann et al., 1995) and readily cross both the placental and blood brain barriers (Klaassen, 2001).

Most of the epidemiological literature on the neurotoxic effects of solvents such as PCE has focused on neurobehavioral sequelae among adults with occupational exposures to mixtures of organic solvents. Cognitive and visual dysfunction have been observed, as having mood changes (Bockelmann et al., 2002; Bowler et al., 2001; Condray et al., 2000; Daniell et al., 1999; Fiedler et al., 2003; Grosch et al., 1996; Ichihara et al., 2004; Kilburn, 2002; Klaassen, 2001; Morrow et al., 2000; Morrow and Scott, 2002; Morrow et al., 1997; Pauling and Ogden, 1996; Reif et al., 2003; Rosenberg et al., 2002; Tsai et al., 1997; White et al., 1995; Wood and Liossi, 2005). The cognitive sequelae associated with mixed organic solvent exposures have included diminished performance on measures of memory, visuospatial abilities, attention/executive function, and motor skills.

The few studies examining adult occupational exposures to PCE alone have produced mixed results. Some studies found diminished performance on the measures of attention/executive function (Grosch et al., 1996; TOXICS, 1994a, 1994b), while others have not found any adverse neuropsychological effects (Daniell et al., 1999; Grosch et al., 1996). All studies that focused on visuospatial abilities have reported diminished performance associated with PCE exposure (Daniell et al., 1999; TOXICS, 1994a, 1994b).

* Corresponding author at: Department of Epidemiology, Boston University SPH, 715 Albany Street, Boston, MA 02118, USA. Tel.: +1 617 638 5764; fax: +1 617 638 4857.
E-mail address: paj@bu.edu (P.A. Janulewicz).

0892-0362/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ntt.2013.03.060

The published literature examining neurobehavioral effects among children with prenatal and childhood exposure is comparatively small, and is also mixed. Three studies found no decrements in cognitive or behavioral function in disorders of attention and learning (Eskenazi et al., 1988; Janulewicz et al., 2008; NYSDOH, 2005), while two found lower test scores and more behavioral problems among children with prenatal or early childhood exposure to organic solvents, including PCE (Laslo-Baker et al., 2004; Till et al., 2001).

Studies using structural MRI in populations of adults with solvent encephalopathy have reported diffuse atrophy in the frontal and parietal cortices, cerebellum and brainstem regions (Keski-Santti et al., 2009; Thuomas et al., 1996). To date, there have been no published MRI studies of individuals with subtle toxicant-induced brain changes due to solvent exposure during adulthood or early life.

The present study examined an unusual scenario involving environmental exposure to PCE. In early 1980, elevated levels of PCE were discovered in the drinking water supplies of many New England towns. Investigations revealed that the public water distribution systems in these towns had installed vinyl-lined asbestos-cement (VL/AC) pipes to address alkalinity problems. Approximately 660 miles of VL/AC pipes was installed in Massachusetts from 1968 through early 1980; a large proportion was installed in eight towns in the Cape Cod region (Barnstable, Bourne, Falmouth, Mashpee, Sandwich, Brewster, Chatham, and Provincetown) (Larson et al., 1983). The pipe manufacturing process involved spraying a mixture of vinyl toluene resin and PCE onto the interior of the pipe. It was believed that the PCE would volatilize before the pipes were installed; however, substantial quantities remained. PCE measurements taken in 1980 from Cape Cod public drinking water supplies ranged from 1.5 μg/L to 7750 μg/L (Demond, 1982). State officials began a program of flushing and bleeding the affected pipes in order to reduce the PCE concentrations to 40 μg/L, the action level at the time. The current United States Environmental Protection Agency (USEPA) maximum contaminant level (MCL) is 5 μg/L (TOXICS, 1994a, 1994b).

Before remediation efforts were completed, tens of thousands of Cape Cod residents, including pregnant women and their children, were exposed to PCE-contaminated drinking water. The present population-based retrospective cohort study was undertaken to examine the long-term neurotoxic effects of prenatal and early childhood exposure to this water. The parent study that generated these data was undertaken to examine a wide range of neurotoxic effects following prenatal and early postnatal exposure to PCE contaminated drinking water. The outcomes that were examined included risky behaviors (Aschengrau et al., 2011); mental illness (Aschengrau et al., 2012); clinical and behavioral problems and learning disabilities based on questionnaire data (Janulewicz et al., 2008); and subtle functional changes assessed with neuropsychological (Janulewicz et al., 2012) and vision tests (Getz et al., 2012); overt structural brain changes using MRIs. The current paper focuses only on the structural MRI results.

Currently, very little is known about the relationship between PCE exposure and structural changes that can be detected using brain imaging methodology. While not the most sensitive measure of neurotoxicant effects, structural MRI findings are important to understanding the full range of exposure-related brain damage. PCE is a well-known lipophilic solvent that is thought to act mechanistically through action on the myelin sheaths of white matter (Feldman, 1999; Kyrklund et al., 1990). For this reason, we hypothesized that early life exposure would be associated with increases in white matter hypointensities and decreases in total white matter measures on structural MRI. White matter hypointensities reflect an abnormal pallor of the white matter as visualized using T1 weighted sequences with MRI. The hypointensities are often interpreted as disruption to the structure of the white matter as a consequence of disease, inflammation, infection, or toxic exposure.

2. Material and methods

2.1. Study population selection

Subjects were eligible if they were born between 1969 and 1983 to mothers who lived in one of eight Cape Cod towns with VL/AC water distribution pipes. These towns were Barnstable, Brewster, Bourne, Chatham, Falmouth, Mashpee, Provincetown, and Sandwich. Birth certificates were manually reviewed and the maternal addresses on the certificate were cross-matched with a database of all street locations with VL/AC pipes in order to tentatively designate subjects as “exposed” or “unexposed”. The database also contained information on the installation year and diameter of the pipes. This tentative designation was based on visual inspection of the maps of water pipes in the immediate vicinity of the birth residence (Janulewicz et al., 2008).

The study was approved by the Institutional Review Boards (IRBs) 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.

2.2. Follow-up and enrollment

Based on initial exposure assessment, two groups of children were selected: 1) children who were tentatively designated as “exposed” to PCE, and 2) children who were tentatively designated as “unexposed” to PCE. Children designated as “unexposed” were randomly selected and frequency matched to exposed children on the month and year of birth. More extensive exposure assessments were conducted following the return of self-administered questionnaires that included residential histories as well as information on drinking water sources.

Follow-up and enrollment of subjects took place between 2006 and 2010. Subjects were traced to obtain their current addresses and telephone numbers using Massachusetts residence lists; death, marriage, divorce, credit bureau and alumni records, and telephone books, directory assistance, and the Internet White Pages. Recruitment letters explaining the purpose of the study and accompanying self-administered questionnaires were sent to all traced subjects. In all, 619 exposed and 626 unexposed subjects returned the study questionnaire.

As shown in Table 1, 27.9% percent of the subjects resided outside of our testing area, 23.5% were missing key data from maternal questionnaires, and 6.3% had only postnatal exposure and thus were excluded from brain imaging. Based on the information collected from the self-administered questionnaires, another 22.7% of subjects were excluded for one or more of the following reasons: had a neurological condition, experienced lead or carbon monoxide poisoning, suffered a head injury with a loss of consciousness >5 min, used 3 or more illicit drugs, or drank excessive amounts of alcoholic beverages (average daily volume > 3 drinks). An additional 1.8% of the subjects were excluded because they were a twin or triplet. The exclusion percentages were similar for both the exposed and unexposed groups.

Following the exclusions, a total of 219 subjects were available for brain imaging. As shown in Table 1, 22.4% refused to participate and 58.4% of subjects were located but never responded to any contact attempts, which included 3 letters and multiple telephone calls, leaving 42 subjects who underwent structural MRI.

There were no meaningful differences in the characteristics of eligible subjects who participated in structural MRI testing and those who did not. Participants and non-participants were similar with regard to birth year, gender, race, education and the prevalence of low birth weight and prematurity. However, non-participants were more likely than participants to have self-reported learning problems (22.5% vs. 10.8%) and to have used self-service dry cleaners (9.8% vs. 0%). These differences held true for both exposed and