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Neurobehavioral effects of exposure to trichloroethylene through a municipal water supply ☆

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Abstract

We studied a population-based sample of 143 residents of a community in which the municipal water supply had been contaminated with trichloroethylene (TCE) and related chemicals from several adjacent hazardous waste sites between 1981 and 1986. A hydraulic simulation model was used in conjunction with a geographic information system (GIS) to estimate residential water supply exposures to TCE; 80% of the participants had potential TCE exposure exceeding the maximum contaminant level (5 ppb). The Neurobehavioral Core Test Battery (NCTB), tests of visual contrast sensitivity, and the profile of mood states (POMS) were administered approximately 6 years following peak concentrations of TCE in municipal drinking water. Multivariate analysis of variance adjusted for potential confounders was used to compare mean test scores of residents classified by estimated TCE exposure (≤ 5, >5–10, >10–15, >15 ppb). TCE exposure >15 ppb was associated with poorer performance on the digit symbol, contrast sensitivity C test, and contrast sensitivity D test and higher mean scores for confusion, depression, and tension. We found evidence of a strong interaction between exposure to TCE and alcohol consumption; the associations for the NCTB and POMS among persons in the high-exposure group who also consumed alcohol were stronger and were statistically significant for the Benton, digit symbol, digit span, and simple reaction time tests, as well as for confusion, depression, and tension. This study adds to the evidence that long-term exposure to low concentrations of TCE is associated with neurobehavioral deficits and demonstrates the usefulness of GIS-based modeling in exposure assessment.

Keywords: Alcohol; Epidemiology; Geographic information system; Neurobehavioral testing; Solvents; Trichloroethylene

1. Introduction

Trichloroethylene (TCE) and related solvents are found at approximately 40% of the hazardous waste sites on the US Environmental Protection Agency's National Priorities list (ATSDR, 1997). TCE frequently contaminates ground water, leading to human exposure through the municipal water distribution system. At high concentrations, TCE is neurotoxic and the effects can be persistent. There is also evidence that chronic, low-dose exposure to TCE can result in neurobehavioral impairment (ATSDR, 1997).

In 1981, the US Environmental Protection Agency (EPA) detected TCE during a random sampling of municipal wells serving a population in northeast Denver, Colorado that resided in the vicinity of several hazardous waste sites (US EPA, 1991). TCE, perchloroethylene (PCE), and other degradation products continued to be detected in the alluvial aquifer during the years that followed, peaking at most well locations between 1985 and 1987. At that time, TCE and PCE were present throughout much of the local water district (LWD). The district served 30,000 customers and

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obtained about 85% of the supply from the alluvial aquifer. TCE contamination of ground water in the study area resulted from multiple sources of release (ESE, 1988; US EPA, 1991).

We conducted a series of evaluations to assess potential health effects associated with residence in the vicinity of hazardous waste sites in this part of metropolitan Denver (ATSDR, 1993, 1996a, b). During the course of these studies, we performed neurobehavioral testing and administered questionnaires to 204 adults who lived in the exposure area. We then applied a novel methodology that incorporated a geographic information system (GIS) and a hydrologic simulation model designed for water distribution systems to assign individual exposure to TCE. The EPANET computer simulation model was developed by the US EPA (Rossman, 1994) for hydraulic and water quality system characterization. It and similar models have been successfully applied in exposure assessment for contaminants in a municipal water supply in other studies (Aral et al., 1996; Gallagher et al., 1998; Maslia et al., 2000). TCE was selected as the marker contaminant for exposure assessment because of its neurotoxicant properties and widespread distribution through the municipal water system. The primary purpose of this paper is to report the results of neurobehavioral testing in a population-based sample of persons who resided in the area at the time of peak contamination of their municipal water distribution system with TCE and related chemicals. This study also demonstrates the utility of geographic information systems and computer simulation modeling in reconstructing environmental data for use in exposure assessment.

2. Methods

2.1. Study population

In 1988, we initiated a cross-sectional study of exposure to arsenic, mercury, chlorinated pesticides, and other chemicals among residents living in the vicinity of the Rocky Mountain Arsenal (RMA) (ATSDR, 1993, 1996a). A population-based sample of persons who had lived at their current residence for at least 2 years was obtained in 1989 by conducting a door-to-door census in communities within 1 mile of the northern, northwestern, and western boundaries of the RMA Superfund site (ATSDR, 1993) and in a comparison community 15 miles distant. The area directly west of the RMA was densely settled; therefore, blocks were randomly chosen for the census in that area. A total of 3393 persons was identified through the census, from which an age- and gender-stratified sample of 1267 eligible individuals who had lived at their current residence for at least 2 years was drawn. Random selection was then used to identify 585 persons from within the age–gender strata, of whom 472 persons aged 2–86 provided samples for biomonitoring (ATSDR, 1993).

A second study was conducted in 1991 to assess symptom frequency, neurobehavioral performance, and reproductive outcome among residents who lived near the RMA and in the comparison area (ATSDR, 1996b). During the course of this study, we interviewed and conducted neurobehavioral testing of 204 adults who lived in the RMA exposure area for a minimum of 2 years. All subjects were originally identified through the population-based census and random selection techniques described above. The participation rate for adults in the neurobehavioral component of the original study was 78% (ATSDR, 1996b). Approximately 20% of participants were Hispanic or nonWhite; 79% had 12 years of education or less and 41% reported family income of less than $20,000. The socioeconomic profile of the participants closely resembled that of the census tracts encompassing the study area. Among the 204 persons who were tested, 184 (90.2%) lived within the boundaries of the LWD and were originally considered eligible for the current analysis (ATSDR, 2001).

The LWD obtained water from wells in the South Platte alluvial aquifer, in which TCE contamination was discovered in 1981 (ESE, 1988), and from wells in the Arapaho formation, a confined bedrock aquifer without evidence of contamination. During the1980s, the district obtained about 85% of its water from seven alluvial aquifer wells located in well fields distributed across the water district. Each well field pumped directly into the water distribution system without water treatment other than chlorination. TCE, PCE, and other compounds continued to be detected in the system after 1981, peaking in most of these alluvial wells between late 1984 and mid-1986. Treatment to remove organic chemical contamination from the water supply was initiated in 1986 (US EPA, 1991). Therefore, participants who reported moving into the LWD after 1985 were excluded from the total of 184, leaving 143 persons available for analysis.

2.2. Exposure estimation

A GIS-based exposure assessment for TCE contamination in the water district was performed using ARC-INFO and ArcView Software (Environmental Systems Research Institute; Redlands, CA, USA), and a water distribution system model, EPANET (Rossman, 1994). The EPANET model was used to reconstruct hydraulic and water quality conditions in the water district's distribution system.

The levels of TCE reported in the supply wells for the LWD during the period 1981–1986 were reviewed. Based on an analysis of the relative hydraulic and

TCE contribution of each alluvial well or well field during this period, we determined that 1985 was representative of hydraulic parameters and TCE levels across the distribution system for most of the study period (ATSDR, 2001). We also found that estimated TCE concentrations in the water distribution system at that point in time would most likely represent the peak potential exposure for the study population. Data for July and August 1985 were chosen for modeling and exposure classification because of the availability of both TCE concentrations and hydraulic parameters in the distribution system and the capability to validate the hydraulic component of the model for this time period.

To quantify the exposure metric, a digitized map of pipe segments 10 in. in diameter or larger, nodes (pipe junctions), pumps, valves, and storage tanks in the distribution system was compiled using the GIS. EPANET simulations were then performed using the pipe network configuration, flow inputs from pumps, network water demand estimation, flow scaling coefficients to simulate diurnal fluctuations, and well head TCE concentrations as inputs to the model. A simulation of the hydraulic performance of the system over 48 h was calibrated and validated using July and August 1985 flow and pressure records, respectively. The pattern coefficients for water demand developed for each of 48 nodes in the July 1985 calibration model were applied to the August 1985 simulation input file. The success of the validation was measured by comparing predicted versus total flow volume for the entire water distribution system and predicted versus designed water pressure over the modeling period at the nodes. Predicted water volume pumped into the system was within 1.3–2.6% of the recorded volume by the LWD for the 48 h simulation period, and predicted water pressures were within design specifications (75 psi $\pm$15%). Based on these results, we concluded that the 48 h simulation period adequately represented the transport component of our TCE exposure model for the LWD. We used the hydraulic model to determine the fate and transport of TCE from the alluvial wells across the water distribution system. We based the simulation on concentrations that were measured in August 1985 at each of the wells, and estimated concentrations at each of the 48 nodes. We used a water demand estimation procedure (Cesario, 1995; Nuckols et al., 2001) to estimate the geographic area of the water district represented by each node in the model in terms of hydraulics and water quality. Using the GIS, we found the intersection between these geographic areas served by each node and census blocks in the study area. We then assigned mean TCE concentrations estimated from the final 24 h of the EPANET simulation as exposure concentrations to participants based on the census block of their residence during the study period (Fig. 1).

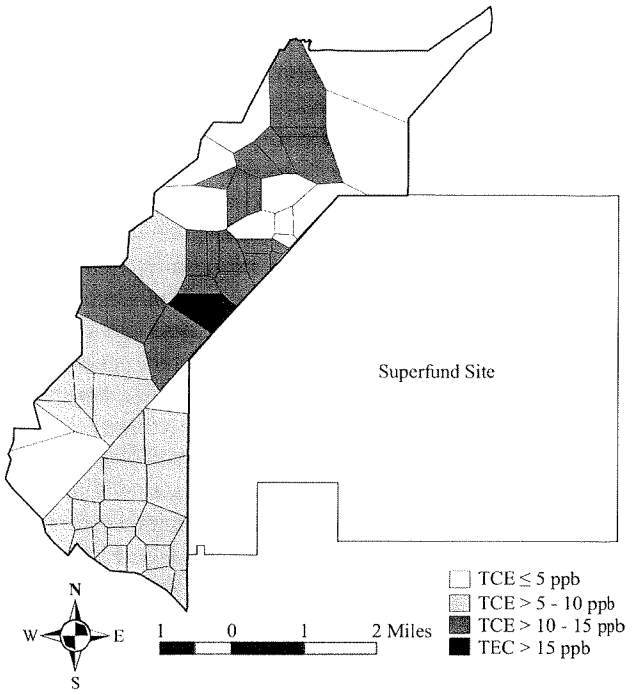

Fig. 1. Estimated concentrations of TCE in the water distribution system by census block (August, 1985).

Additional analyses were performed to evaluate how representative the August 1985 predicted TCE concentrations were over the study period. The modeling effort was repeated using source well TCE concentrations from August 1984, another period with relatively high reported TCE concentrations in at least one well. To accomplish this, 1985 water demand patterns were held constant but the pumpage and water quality data for each well were changed to reflect August 1984 conditions. This analysis indicated that due to differences in relative pumpage and TCE concentrations in the wells between 1984 and 1985, estimated TCE levels in the distribution system in 1984 were approximately 30–50% lower than those predicted for 1985. However, the relative concentration at specific nodes within the system remained essentially constant, validating our assumption that the 1985 simulation period was representative of hydraulic parameters and relative TCE levels across the distribution system for other years in the study period.

2.3. *Neurobehavioral tests*

The World Health Organization (WHO)-recommended Neurobehavioral Core Test Battery (NCTB) was administered to assess potential neurotoxic effects of drinking water contamination, including psychomotor skills, memory, and learning (Anger et al., 1993, 2000). The NCTB consists of seven neurobehavioral

tests: (1) Santa Ana; (2) aiming; (3) simple reaction time; (4) digit symbol; (5) Benton visual retention test; and (6) digit span. The final NCTB test is the profile of mood states (POMS), which assesses affect measured by six scales: (1) tension/anxiety; (2) depression/dejection; (3) vigor; (4) anger/hostility; (5) fatigue; and (6) confusion. Two additional tests of visual perception, contrast sensitivity C and D, were also included in the test battery due to their sensitivity to solvents (Frennette and Mergler, 1991). Data were obtained for a total of 19 endpoints, 13 measuring behavioral performance (coordination, reaction time, memory, contrast vision, etc.) and 6 tests of affect. Tests were administered by three trained interviewers (one bilingual in Spanish) in the participants' homes by prearranged scheduling according to the WHO NCTB Operational Guide (unpublished: but available from the authors).

2.4. Statistical analysis

Prior to exploring associations between neurobehavioral test results and estimated exposure to TCE, we conducted a univariate screening for 78 questionnaire items that could have been potential confounders using a χ^2 test with a cutoff of $P<0.10$ for inclusion in further analyses. The questionnaire contained information for demographic variables including age, gender, race, education, household income, tobacco, alcohol and drug use, hobbies, residential history, occupational history, and self-reported exposures to chemicals. We also included questions regarding the participant's level of concern about their health and environmental chemicals in their neighborhood and in the water supply at their residence to assess potential recall bias and stress associated with residence near a hazardous waste site (Roht et al., 1985). For example, we asked "How worried are you about environmental or chemical hazards in your neighborhood?" The variables were analyzed according to the estimated TCE exposure for each individual. Environmental concern, race, drug use, and duration of residence were not associated with estimated exposure to TCE. Four variables were associated with TCE exposure at $P<0.10$: consumption of seafood once a week or more, years of education, current or previous smoking, and alcohol consumption. These four variables were included in a multivariate analysis of variance using the generalized linear model in SAS. Least-squares means for each neurobehavioral test were calculated across four categories of estimated TCE exposure based on the August 1985 exposure assessment model. These categories were $\leqslant 5$ ppb, >5–10 ppb, >10–15 ppb, and >15 ppb. These values were assumed to represent peak exposure to participants between 1981 and 1985. Mean scores in the high-TCE-exposure group were compared by the least-significant-differences statistic to those in the referent group, which was defined as those with estimated TCE concentrations at or below the Safe Drinking Water Act's maximum contaminant level (MCL) of 5 ppb for TCE (US EPA, 2001). Because alcohol consumption could be responsible for decrements in neurobehavioral function and therefore act as an effect modifier as well as a confounder, we analyzed the data further in stratified analyses to explore the joint effects of alcohol and estimated exposure to TCE.

3. Results

The distribution of age, race, gender, education, years of residency within the study area, smoking, alcohol consumption, and seafood ingestion are presented in Table 1 for 143 participants in the four categories of estimated TCE exposure. Based on our modeled estimates, approximately 80% of the participants were exposed to TCE levels exceeding the MCL of 5 ppb and 14.0% had estimated TCE exposures exceeding 15 ppb for some portion of the study period. During 1985, the

Table 1
Distribution of participant demographic characteristics among municipal water supply TCE exposure categories

Estimated peak TCE level	*N*	%	Mean age (years)	Number males (%)	Number hispanic or nonWhite (%)	Mean education (years)	Mean residence (years)	Number consuming alcoholic beverages[a] (%)	Number smoking cigarettes[a] (%)	Number consuming seafood $\geqslant 1$ time per week (%)
Highest TCE (>15 ppb)	20	14	55.8 ± 18.5	11(55)	4(20)	10.7 ± 3.2	24.7 ± 12.6	8(40)	6(32)	7(35)
High TCE (10–15 ppb)	62	43	51.5 ± 20.8	31(50)	12(19)	10.7 ± 2.8	18.8 ± 10.3	36(58)	13(21)	14(23)
Medium TCE (5–10 ppb)	33	23	48.6 ± 18.2	17(52)	7(21)	11.8 ± 2.3	20.5 ± 10.8	22(67)	10(30)	17(52)
Low TCE (<5 ppb)	28	20	50.8 ± 17.6	16(57)	5(18)	12.3 ± 2.8	20.6 ± 9.3	21(75)	9(32)	6(21)

[a] Missing data for one participant.

Table 2
Adjusted mean[a] neurobehavioral test results by estimated TCE exposure levels in a municipal water supply

Test	Estimated peak TCE concentration (ppb)				Difference ≤5 vs. >15 (%)	P value[b]
	≤5	>5–10	>10–15	>15		
Aiming	120.5	124.1	107.1	105.0	−13	0.26
Benton	8.3	7.8	8.0	7.5	−10	0.15
Contrast sensitivity C	5.0	5.1	5.2	3.9	−22	0.06
Contrast sensitivity D	5.0	5.0	5.0	4.0	−20	0.07
Digit symbol	48.4	45.5	43.6	39.7	−18	0.07
Digit span (total)	13.0	12.9	12.5	11.6	−11	0.24
Digit span (backward)	6.0	5.4	5.6	5.4	−10	0.29
Digit span (forward)	6.9	7.4	6.9	6.2	−10	0.29
Santa Ana (nonpreferred)	26.9	26.8	26.5	26.8	−0.4	0.96
Santa Ana (preferred)	28.9	28.2	28.1	28.3	−2	0.77
Santa Ana (total)	55.9	54.8	54.8	55.7	−0.4	0.96
Simple reaction time	301	283	291	316	+5	0.42

[a] Least-squares means adjusted for education, seafood consumption, cigarette smoking, and alcohol consumption.
[b] P value for highest category of estimated exposure (>15 ppb) vs. referent category (≤5 ppb).

Table 3
Adjusted mean[a] profile of mood state scores by estimated TCE exposure levels in a municipal water supply

Test	Estimated peak TCE concentration (ppb)				Difference ≤5 vs. >15 (%)	P value[b]
	≤5	>5–10	>10–15	>15		
Anger/hostility	7.3	8.6	7.6	9.2	+26	0.43
Confusion/bewilderment	5.9	6.7	7.3	8.1	+37	0.14
Depression/dejection	7.1	9.0	9.3	13.0	+83	0.08
Fatigue/inertia	7.9	6.2	8.3	9.6	+22	0.35
Tension/anxiety	8.5	10.3	10.3	10.9	+28	0.24
Vigor/activity	16.6	16.3	16.5	15.6	−6	0.58

[a] Least-squares means adjusted for education, seafood consumption, cigarette smoking, and alcohol consumption.
[b] P value for highest category of estimated exposure (>15 ppb) vs. referent category (≤5 ppb).

highest mean predicted concentration of TCE at a distribution system node was 19.1 ppb; the highest measured concentration at a source well was reported in August as 51.9 ppb. The maximum reported concentration for the period 1981–1985 was 56.7 ppb in May of 1984 (same well location). There were no statistically significant differences in age, gender, race, or years of residence among participants across categories of estimated exposure to TCE. There were also no associations between estimated exposure to TCE and a variety of occupational and lifestyle variables obtained from the questionnaire data. As described above, we found associations between estimated exposure to TCE and self-reported consumption of seafood once a week or more, years of education, current or previous smoking, and alcohol consumption at $P<0.10$ and included these variables in all multivariate models as potential confounders. The results of preliminary analyses in which age, gender, and years of education were included a priori (Anger et al., 1997) were similar to the adjusted results shown in Tables 2 and 3.

The results of multivariate statistical analyses of neurobehavioral test scores among subjects with different levels of estimated TCE exposure are presented in Table 2. Adjusted mean scores were approximately 10–20% lower among persons in the highest category of estimated exposure to TCE compared to those in the reference group (≤5 ppb) for several neurobehavioral tests, including the aiming-Benton, digit span (forward, backward, and total), and digit symbol tests. The reduction in performance on the digit symbol test among those with estimated exposures to TCE >15 ppb approached statistical significance ($P = 0.07$). Adjusted mean scores for sensory measures were also lower among those with estimated TCE concentrations greater than 15 ppb; the differences between the high- and low-exposure groups approached statistical significance for contrast sensitivity C ($P = 0.06$) and contrast sensitivity D ($P = 0.07$).

There was also evidence of changes in affect among individuals with high estimated TCE exposures (Table 3). The adjusted mean for the POMS scale of depression/dejection was greater in the high-estimated TCE exposure group than the mean score in the comparison group, although the difference was not statistically significant after adjustment for other risk

Table 4
Adjusted mean[a] neurobehavioral test results by estimated TCE exposure levels in a municipal water supply, stratified by alcohol consumption

Test and alcohol consumption[b] (no or yes)	Estimated peak TCE concentration (ppb)				Difference ≤5 vs. >15 (%)	P value[c]
	≤5	>5–10	>10–15	>15		
Aiming						
No	89.9	137.4	103.1	103.8	+15	0.51
Yes	132.4	118.3	110.6	104.7	−21	0.13
Benton						
No	7.7	7.1	7.9	7.8	+1	0.85
Yes	8.6	8.3	8.1	7.0	−19	0.02
Contrast sensitivity C						
No	4.2	5.3	5.0	3.2	−24	0.26
Yes	5.4	5.1	5.5	4.7	−13	0.36
Contrast sensitivity D						
No	4.6	5.0	4.7	3.2	−30	0.11
Yes	5.3	5.2	5.3	4.8	−9	0.51
Digit symbol						
No	38.8	46.2	42.2	39.4	+2	0.92
Yes	52.7	46.1	45.0	39.2	−26	0.03
Digit span (total)						
No	12.2	12.8	12.4	13.5	+11	0.46
Yes	13.1	12.8	12.4	9.2	−30	0.02
Digit span (backward)						
No	6.1	5.5	5.5	6.2	+20	0.88
Yes	5.9	5.2	5.5	4.5	−24	0.08
Digit span (forward)						
No	6.1	7.2	6.9	7.3	+20	0.29
Yes	7.2	7.5	6.8	4.7	−35	0.01
Santa Ana (preferred)						
No	27.1	28.4	26.4	27.6	+2	0.90
Yes	30.1	28.5	29.6	28.7	−5	0.65
Santa Ana (nonpreferred)						
No	23.4	25.2	25.3	25.7	+10	0.50
Yes	29.2	28.4	27.8	27.7	−5	0.63
Santa Ana (total)						
No	50.7	52.8	52.3	53.9	+6	0.62
Yes	59.5	57.1	57.3	57.2	−4	0.70
Simple reaction time						
No	321	287	302	296	−8	0.42
Yes	293	280	283	347	18	0.04

[a] Least-squares means adjusted for education, seafood consumption, and cigarette smoking.
[b] Alcoholic beverage consumption.
[c] P value for highest category of estimated exposure (>15 ppb) vs. referent category (≤5 ppb).

factors ($P = 0.08$). A tendency toward higher scores among subjects with high estimated exposure to TCE was also noted for the POMS scales for confusion/bewilderment ($P = 0.14$) and tension/anxiety ($P = 0.24$).

When we repeated the analyses with the data stratified by current alcohol consumption; 55 did not consume alcohol, 84 consumed at least one drink per month, and data were missing for four individuals. Alcohol was an effect modifier; all of the significant effects associated with exposure to TCE occurred among persons who reported current consumption of alcohol at the time they were tested and the associations were generally much stronger than they were in the entire study group (Table 4). Statistically significant decrements were found

Table 5
Adjusted mean[a] profile of mood state scores by estimated TCE exposure levels in a municipal water supply, stratified by alcohol consumption

Test and alcohol consumption[b] (no or yes)	Estimated peak TCE concentration (ppb)				Difference ≤5 vs. >15 (%)	P value[c]
	≤5	>5–10	>10–15	>15		
Anger/hostility						
No	9.1	8.5	7.7	6.3	−25	0.47
Yes	7.2	8.9	7.8	12.9	76	0.07
Confusion/bewilderment						
No	7.3	6.6	8.9	5.9	−21	0.54
Yes	5.5	6.7	6.3	11.2	100	<0.01
Depression/dejection						
No	12.3	7.4	8.7	7.7	−38	0.35
Yes	6.2	10.3	10.2	20.4	204	<0.01
Fatigue/inertia						
No	9.5	3.7	8.6	8.0	−19	0.56
Yes	8.0	7.8	8.4	11.9	59	0.10
Tension/anxiety						
No	11.4	9.6	11.2	9.6	−15	0.56
Yes	7.4	10.4	9.7	12.7	71	0.05
Vigor/activity						
No	3.4	17.0	16.2	16.7	26	0.29
Yes	17.6	16.0	16.7	14.1	−18	0.16

[a] Least-squares means adjusted for education, seafood consumption, and cigarette smoking.
[b] Alcoholic beverage consumption.
[c] P value for highest category of estimated exposure (>15 ppb) vs. referent category (≤5 ppb).

for the Benton ($P = 0.02$), digit symbol ($P = 0.03$), digit span total and forward ($P = 0.02$ and 0.01), and simple reaction time ($P = 0.04$) tests. The differences observed for contrast sensitivity C and contrast sensitivity D in the entire group, on the other hand, were not seen in the stratified analyses. No statistically significant associations were found among persons who did not consume alcohol.

Alcohol consumption also modified the effect of TCE exposure for the POMS scores (Table 5). The associations were broader and more robust. Significantly increased scores on tests of affect were observed among persons consuming alcohol for confusion/bewilderment ($P<0.01$) and depression/dejection ($P<0.01$); the association with tension/anxiety was marginally significant ($P = 0.05$). Similarly, no significant observations for POMS scores were found among persons who did not consume alcohol.

4. Discussion

A major impediment to assessing health outcomes at hazardous waste sites is nondifferential misclassification of exposure. The effect of mixing exposed and unexposed subsets of the population nondifferentially with respect to outcome is generally to obscure potential effects, driving risk estimates toward the null (Copeland et al., 1977). Here, the GIS-based modeling of exposure to a specific neurotoxicant was associated with statistically significant decrements in neurobehavioral function and affect among persons who consumed alcohol.

Our findings are compatible with the work of others showing that TCE and related solvents act as neurotoxicants among persons exposed occupationally or residentially. Feldman et al. (1985), for example, described neurologic effects up to 16 years after acute TCE intoxication. The effects of TCE on cranial nerves have been demonstrated through electrophysiological measurement of the blink reflex in occupationally exposed workers (Feldman et al., 1993). These effects are also seen at lower concentrations found in community exposures. Deficits on neuropsychological tests and blink reflex latency were reported in Woburn, MA, USA, residents drinking water from two municipal wells contaminated with TCE (267 ppb) and other solvents, notably PCE (Byers et al., 1988; Lagakos et al., 1986). Although the prevalence of reported neurological disorders among the Woburn population was not elevated, several individuals from this population showed residual damage to the facial and trigeminal

cranial nerves, as measured by a decreased blink reflex 6 years postexposure (Feldman et al., 1988).

Neurobehavioral markers were used in a study of residents in Tucson, AZ, USA, exposed to TCE (6–500 ppb) and other chemicals in drinking water. Significant decreases in blink reflex, eye closure, reaction time, and intelligence test scores, as well as increases in mood disorders, were reported to occur in exposed persons (Kilburn and Warshaw, 1993). Kilburn (2002) reported similar changes for individuals who lived near electronic manufacturing plants and were exposed to chlorinated solvents directly by inhalation and through out-gassing from well water. The latter group of residents was reported to have neurobehavioral impairment as well as elevated scores on the POMS and an increased frequency of self-reported symptoms compared to regional and distant referent groups.

The decrements on NCTB neurobehavioral tests and contrast sensitivity shown in the current study are compatible with those reported previously for exposures to solvents (Eskelinen et al., 1986; Lindstrom, 1980; White et al., 1995). Neurobehavioral tests have been shown to be sensitive to the neurotoxicity of organic chemical constituents in studies conducted worldwide (e.g., Baker et al., 1985; Broadwell et al., 1995; Colvin et al., 1993; Fidler et al., 1987; Foo et al., 1994; Gamberale, 1985; Kyrklund, 1992; Morrow et al., 1992; Ng et al., 1990; Spurgeon et al., 1992). TCE has been specifically linked with neurobehavioral effects following extended exposures to a municipal water distribution system that obtained its water from a contaminated groundwater source (White et al., 1997) and to industrial solvents in microelectronics workers (Bowler et al., 1991). Of the two tests common to the present study and the reports of White et al. and Bowler et al., evidence of an effect on the digit symbol test was shown in all three studies. This is arguably the most generally sensitive test of nervous system deficits (Anger et al., 1998, 2003), perhaps because it requires the integrity of so many different neuropsychological functions in the cognitive and motor domains (Lezak, 1995). Evidence of impaired contrast vision, as measured by the visual contrast sensitivity C and D tests, was seen in the group with estimated exposure to TCE above 15 ppb. Contrast sensitivity is reportedly reduced significantly in workers exposed to styrene (Campagna et al., 1995a) and mixtures of organic solvents (Frennette and Mergler, 1991; Mergler et al., 1991).

Mean scores for POMS confusion/ bewilderment and depression/dejection scales in the high-TCE-exposure group were 37–83% greater than those in the comparison group. Mood state alterations have been frequently described as an outcome of chronic exposure to solvents, including TCE, and are considered to be early signs of neurotoxicity (White and Proctor, 1997). For example, Campagna et al. (1995b) reported a decrement in five of the six POMS scales (tension/ anxiety, depression, anger/hostility, confusion, and fatigue) among laboratory workers exposed to organic solvents, and emotional disturbances have also been described among factory workers exposed to styrene (Cherry et al., 1980; Flodin et al., 1989).

The most striking and potentially important finding in this analysis is the evidence of an interaction between alcohol consumption and exposure to TCE. Alcohol consumption appeared to potentiate the effects of exposure to TCE; the decrements on the NCTB were more profound and extensive in the analyses stratified on alcohol consumption than in the analyses of the total sample. Similarly, differences in affective status were larger and involved a wider range of mood states when alcohol consumption was used to stratify participants. Several investigators have reported similar findings documenting an interaction with alcohol, especially among persons with occupational exposures to solvents. An increased risk of organic dementia, cerebral atrophy, or psycho-organic syndrome was found in hospitalized patients with occupational solvent exposure and alcohol intake compared with matched patients hospitalized due to other diagnoses (Cherry et al., 1992). Alternatively, solvent exposure may be diagnosed as alcoholism and vice versa (White, 1995). Massioui et al. (1990) reported that auditory and visual evoked electrophysiologic potential changes in solvent-exposed workers are potentiated by chronic alcohol consumption. Cherry (1993) summarized the results of three studies that showed an increased risk of alcohol-induced psychiatric disorders among men with occupational solvent exposure. Valic et al. (1997) reported a significant loss of color vision in persons who consumed more than 250 g of alcohol a week and were simultaneously exposed to solvents, including TCE and PCE. These studies suggest synergy between solvents and alcohol intake, although the mechanism for the phenomenon remains unclear. When given as a bolus under experimental conditions, alcohol slows the metabolism and clearance of styrene (Wilson et al., 1983) or toluene (Waldron et al., 1983). However, field studies show that moderate alcohol consumption stimulates the elimination of solvents such as toluene more quickly, perhaps through enzyme induction. In heavy drinkers, on the other hand, hepatocellular damage may interfere with clearance (Cherry, 1993).

TCE was selected as the marker chemical for this study, although the LWD wells were also contaminated in 1985 with a mixture of organic compounds, including tetrachloroethylene, 1,1,1-trichloroethane, and 1,1-dichloroethylene. TCE was the primary contaminant measured and was present at relatively high concentrations; however, the specific role of TCE in inducing neurobehavioral effects cannot be evaluated. At the time of the 1985 sampling, the highest TCE levels measured

at the LWD wells were in the range of 50–60 ppb (Camp, Dresser and Mckee, 1991). Due to the limited frequency of sampling at the wells, it was not possible to determine whether the reported values represented the true peak concentrations in the contaminant plume. If so, these concentrations were substantially lower than the concentrations of TCE measured at other sites where health effects were evaluated (Byers et al., 1988, Kilburn and Warshaw, 1993; Lagakos et al., 1986).

Several classes of chemicals found in the workplace and in the environment have the potential to induce neurologic damage (e.g., Anger et al., 2000). In addition to the organic solvents represented by TCE, heavy metals and some pesticides may induce similar effects and thus have the potential to cause confounding. Our analyses adjusted for reported occupational and residential exposures to a variety of chemicals. We found that consumption of seafood was associated with estimated exposure to TCE, raising the possibility of exposure to mercury. Using our historical data, we found that only 16 of the study subjects had a measurable concentration of urinary mercury at a detection limit of 5 ppb and urinary mercury was not associated with seafood consumption. Nonetheless, we adjusted the data for seafood consumption. Although the population in the current study was derived from a limited geographic area, we screened our data for associations between TCE distribution and 78 questionnaire items, including race, socioeconomic status, environmental concern, drug use, and alcohol consumption. Variables associated with TCE were included in all multivariate analyses. However, the possibility that residual confounding from other, unmeasured exposures exists cannot be ruled out. We were unable to assess the potential effect of selective out-migration from the study area prior to the initiation of neurobehavioral testing in 1991. It is conceivable that persons with symptoms, disease, or concern about their health status may have moved selectively, but the effect of such migration cannot be measured.

The modeling approach used in our study to estimate the concentrations of TCE at the residences of participants is subject to uncertainty. Short-term exposure assessment was used to estimate chronic exposures. The possibility that exposures to TCE fluctuated over the period of interest cannot be discounted. However, a comparison of the model's results between 1984 and 1985 indicated that the relative ranking of subjects with high, medium, and low estimated TCE exposure was not likely to have changed during the years that the LWD's source wells were contaminated. This assumption was further substantiated by an analysis of pumpage and TCE concentrations for the source wells over the period 1981–1986 (data not shown).

There were few private wells and limited consumption of bottled water in the study area when the neurobehavioral tests were performed (ATSDR, 1996b). However, we had no information regarding the use of bottled water or other sources of water for the period prior to 1991. We also lacked information about individual water consumption and showering/bathing patterns. The latter are a significant source of exposure to TCE and other volatile solvents via inhalation and dermal absorption (US EPA, 2001). There was also uncertainty regarding the period of latency and timing of exposure for the outcomes measured in 1991. The exposure assessment used data from 1985 when contamination in the LWD was documented and complete data were available. All participants in this study lived in the study area prior to 1986 when water treatment was initiated, and the mean duration of residency ranged from approximately 20–25 years among subjects across TCE exposure categories. However, it was not possible to ascertain the cumulative dose each person might have received with the data available.

In our earlier studies of the same population (ATSDR, 1996a, b), we used proximity to one of the hazardous waste sites as an exposure metric, with much lower specificity. We found no evidence of an association between exposure and neurobehavioral deficits. This study demonstrates that GIS-based simulation modeling can be used to refine exposure for epidemiologic investigations with adequate specificity to reveal adverse effects in the nervous system.

In summary, this study adds to the evidence that long-term exposure to low concentrations of TCE is associated with neurobehavioral deficits in humans. The finding of a strong interaction between exposure to a chlorinated solvent and alcohol consumption in the induction of neurobehavioral deficits is of potential public health significance.

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