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Neurobehavioral Evaluation for a Community with Chronic Exposure to Hydrogen Sulfide Gas

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Neurobehavioral evaluation for a community with chronic exposure to hydrogen sulfide gas☆

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Abstract

In May 2000, the Agency for Toxic Substances and Disease Registry of the US government conducted a health investigation in response to community concerns regarding ambient and indoor hydrogen sulfide (H_2S), odor, and health symptoms in Dakota City, Nebraska. The objective was to determine whether adult residents in an area with repeated exposure to H_2S showed poorer performance on neurobehavioral tests than unexposed residents. Study participants were required to meet age ($\geqslant$16 years of age) and length of residency (2 years) eligibility requirements. A battery of computer-assisted standardized neurobehavioral tests was administered in English or Spanish. A questionnaire was used to collect information about participants, demographic and health status. Three hundred forty-five people agreed to participate. After the exclusion of 10 persons, analyses were conducted on 335 participants; 171 residents in the target area and 164 residents in the comparison area. The two groups were comparable in demographic characteristics and various health conditions. Overall, neurobehavioral test results for the target and comparison groups were similar. Residence in the H_2S-exposed area was associated with marginally poorer performance on a test of memory, namely, match to sample score, and a test of grip strength. However, these differences were not significant. Deficits in overall neurobehavioral performance were not associated with exposure to H_2S in this study.

Keywords: Neurobehavioral; Air pollution; Hydrogen sulfide; Neurotoxicology; Air modeling; Nervous system toxicity; Total reduced sulfur compounds; Kriging

1. Introduction

Hydrogen sulfide (H_2S) is a colorless, flammable gas under normal conditions. H_2S is used as a reagent and intermediate in industrial processes. It is a degradation product of human and animal waste, and it is created naturally under certain environmental conditions. H_2S is noted for its offensive "rotten egg" odor. In California alone, annual industrial emissions of H_2S were estimated to be 5.7 million pounds. Hydrogen sulfide was found at 39 of the 1467 current or former Superfund waste sites or industry release sites. Accidental release of H_2S continues to impact public health. A US multistate surveillance program found that from 1993 to 2001 there were 637 H_2S events resulting in 63 public evacuations and 185 people injured (ATSDR, 2002). In 1995, a total of 1407 unintentional H_2S poisonings were reported in the United States (Litovitz et al., 1996). Other opportunities for human exposure include confined animal feeding operations and urban or school encroachment on H_2S sources.

This investigation focused on residents of the cities of Dakota and South Sioux, Nebraska, (hereafter referred to as "Dakota City"). Dakota City, population 13,700,

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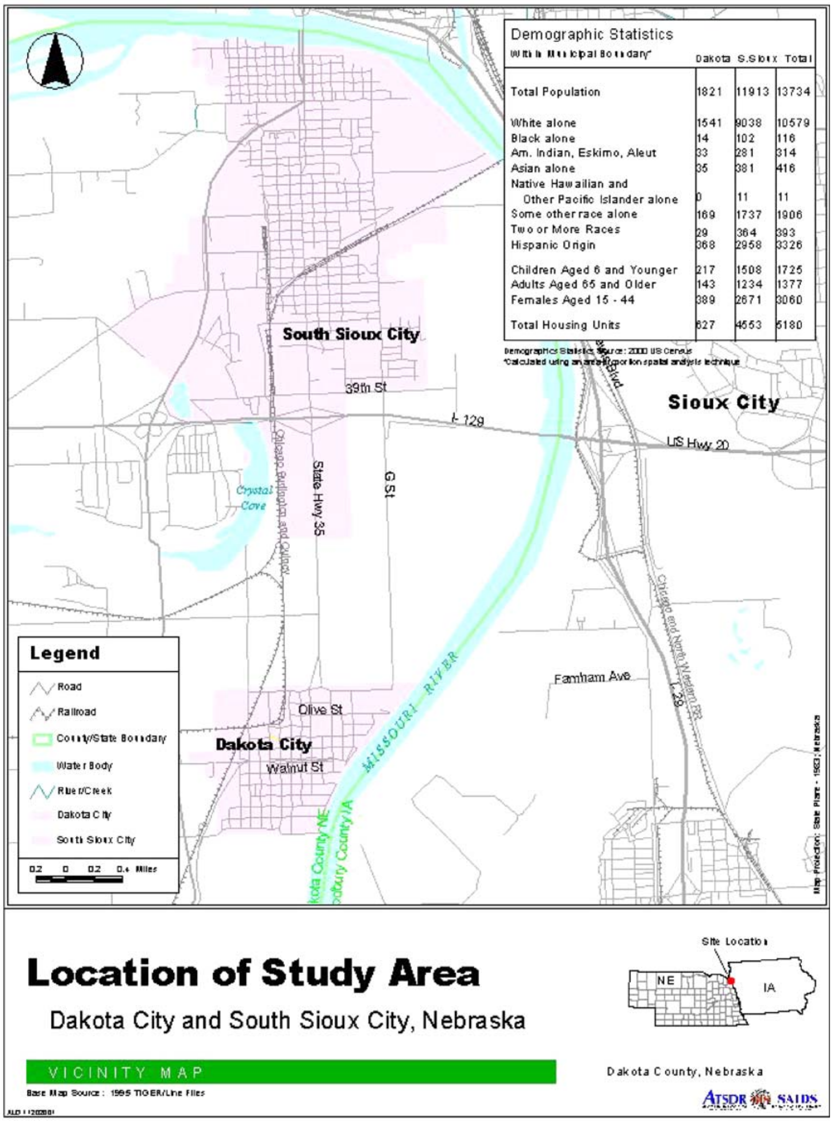

Demographic Statistics

Within Municipal Boundary*	Dakota	S.Sioux	Total
Total Population	1821	11913	13734
White alone	1541	9038	10579
Black alone	14	102	116
Am. Indian, Eskimo, Aleut	33	281	314
Asian alone	35	381	416
Native Hawaiian and Other Pacific Islander alone	0	11	11
Some other race alone	169	1737	1906
Two or More Races	29	364	393
Hispanic Origin	368	2958	3326
Children Aged 6 and Younger	217	1508	1725
Adults Aged 65 and Older	143	1234	1377
Females Aged 15 - 44	389	2671	3060
Total Housing Units	627	4553	5180

Demographics Statistics Source: 2000 US Census
*Calculated using an area-proportion spatial analysis technique

Fig. 1.

is located in northeastern Nebraska and next to Sioux City, Iowa (Fig. 1). Since 1993, residents have complained of respiratory and nervous system symptoms, such as frequent headaches, overwhelming fatigue, paresthesia of extremities, and a mental disorientation-like symptom during intense odor events. In 1997, Nebraska officials identified 13 point sources of H_2S or total reduced sulfur compounds (TRS) in the Dakota City area (ATSDR, 1997). These sources, which vary considerably in size, include a large beef slaughter/leather tanning facility and a nearby sizable wastewater lagoon. This source released an estimated 1 ton of H_2S daily (Deborah Reyher, US Department of Justice, personal communication, 2001). Approximately 1000 people live within 1 mile of this source.

Beginning in the early 1990s, Dakota City residents were repeatedly exposed to potentially toxic levels of H_2S. The highest recorded TRS concentration of 37,000 parts per billion (ppb) was measured in the mid-1990s (Shelley Kaderly, Nebraska Department of Environmental Quality, personal communication, 1997). From September 1995 to November 1999, outdoor measurements of H_2S registered in excess of 1000 ppb on 275 occasions [US Environmental Protection Agency (EPA), 2000]. In 1997, the highest concentration of H_2S or TRS was 1300 ppb. For 1997–1998, peak levels dropped in their frequency and intensity. For the mid-1990s, the local odor hotline received hundreds of odor and health complaints. In response to health and pollution concerns, in 1997 the state adopted the TRS standard of 100 ppb for a highest 30-min rolling average. However, the standard was violated repeatedly in Dakota City, and federal health officials concluded that levels of ambient TRS, along with indoor and outdoor concentrations of H_2S, posed a threat to public health (ATSDR, 1997; EPA, 2000). Ambient and indoor H_2S exposures made it difficult for residents to eliminate or reduce personal exposures.

Reviews of the toxicity of H_2S have been published (ATSDR, 1999; Bhambhani et al., 1997, 1996; Milby, 2000; Milby and Baselt, 1999; Burnett et al., 1977; Campagna et al., 2000). Clinical and research findings indicate that the nervous system is a target of H_2S. At high concentrations, exposure can cause loss of consciousness or death (ATSDR, 1999). Exposure to H_2S is one of the leading causes of occupational sudden death in the United States (NIOSH, 1977; ATSDR, 1999). Breathing H_2S at greater than 500,000 ppb can affect the brain's respiratory center, leading to respiratory failure and death after only a few breaths. At high concentrations, deficits have been measured in memory, balance, and vibration sense and other neurobehavioral tests; at some points permanent neurologic damage has been evident. Fatigue, poor memory, dizziness, and irritability have been observed in workers chronically exposed to H_2S (Beauchamp et al., 1984; Milby, 2000; Tvedt et al., 1991; Kilburn, 1999; Schneider et al., 1998). Although controversial, there is increasing evidence that nonoccupational exposure to low-level H_2S may be associated with nervous system toxicity (ATSDR, 1999; Partti-Pellinen et al., 1996; Bates et al., 1998; Kilburn, 1997).

The objective of this health investigation was to assess whether adult residents of Dakota City, in an area with repeated exposures to elevated ambient H_2S, showed poorer performance on neurobehavioral tests than residents who had not been exposed. By assessing subclinical neurotoxicity, the researchers sought to identify possible subtle adverse changes in neurobehavioral health status.

2. Materials and methods

2.1. Exposure estimates

The classification of H_2S exposure was determined using 9 months (February through October 1999) of real-time communitywide air monitoring data and then modeling of the data. Assumptions and parameters used for design of the air monitoring network included proximity and density of housing in relation to H_2S sources, meteorological/wind data, federal and state air data, and odor complaints. The air monitoring method and characterization are described elsewhere (Inserra et al., 2002; White et al., 1999). Universal kriging, a spatial modeling technique using a statistical interpolation procedure to generate a surface trend estimate (Mulholland et al., 1998; Georgopoulos et al., 1997), was used to estimate H_2S levels between two or more of the nearest monitoring locations. Taking into consideration historical and 1998 air monitoring data for Dakota City, we reviewed the scientific literature for modeling air data. The monthly highest 1-h concentration was used for each of the 14 residential monitoring locations. Air modeling used a total of 99 time-averaged concentrations communitywide. To improve accuracy, the modeled spatial area was restricted to up to 500 m beyond the outermost monitoring locations. Kriging of the data generated an "exposure" map consisting of four classifications of H_2S exposure. Neighborhoods of Dakota City were geographically classified as the target area ($\geqslant 90$ ppb exposure) and the comparison area (< 50 ppb exposure). We observed that the designated exposed and unexposed neighborhoods were consistent with the history of odor complaints in Dakota City.

2.2. Identification and selection of participants

A study census of target and comparison neighborhoods was completed in March 2000. The census enumerated all adult members of each household in the target area and approximately every other household's adult members in the comparison area. The two eligibility criteria were $\geqslant 16$ years of age as of March 1, 2000, and a 2-year residency beginning March 1, 1998. Partial-year residents were ineligible to participate. After the sampling frame was created, names were selected by simple random sampling, stratified by exposure status (target versus comparison area).

2.3. Neurobehavioral tests

Fourteen standardized tests using preset test parameters (i.e., instructions and tests) were used to assess neurobehavioral performance for four neurological functions: cognitive, motor response, sensory, and mood/affect (Table 1). Tests were selected to measure possible neurobehavioral effects that were hypothesized to be related to exposure to H_2S (ATSDR, 1999). Most of these tests were administered in a computer-assisted manner and with English or Spanish instructions. The test battery consisted of eight tests of the ATSDR Adult Environmental Neurobehavioral Test Battery (ATSDR, 1995) and six tests of the Oregon Health and Sciences University's Behavioral Assessment and Research System (BARS). A 36-item questionnaire was used to assess possible psychological or medical problems (Storzbach et al., 2000). The Spanish version protocol was pilot tested at the Oregon Health and Sciences University's CROET laboratory (Portland, OR). Computer-assisted testing was conducted using a Mac PowerBook computer and a nine-button response input device placed over the keyboard. BARS tests were written as external C^{++} routines to allow millisecond timing between screen stimuli and responses. We assessed for cutaneous

Table 1
Neurobehavioral test battery for Dakota and South Sioux cities, Nebraska, May 2000

Name of test	Function	Domain	Reason for selection
OPTEC/visual acuity	Vision acuity	Sensory	Ensure person can see tests
OPTEC/contrast sensitivity	Visual acuity under Varying contrast	Sensory	Correlates with performance
Vibrotactile Threshold	Sensation of vibration	Sensory	Resident symptoms
Dynamometer (Jamar)	Grip strength, fatigue	Sensory	Resident symptoms
WRAT 3 Reading or bateria-R listening comprehension	Educational attainment, equating performance	Other	Covariables of interest
SF-36 Questionnaire	Perception of health	Affect	Resident symptoms
Health Screening system, SF-36 questionnaire	Physical functioning	Affect	Resident symptoms
Symbol digit	Complex function/coding	Cognitive	Universally sensitive
Match to sample	Memory 1-delay	Cognitive	Test of memory
Match to sample	Memory 8-delay	Cognitive	Test of memory
Match to sample	Memory 16-delay	Cognitive	Test of memory
Tapping	Response speed, coordination	Motor	Negative control
Digit span	Attention, memory	Cognitive	Resident symptoms
Serial digit learning	Learning/coding	Cognitive	Universally sensitive
Simple reaction time	Response speed	Motor	Negative control

Total of 28 test trials, i.e., outcomes. The tests are listed by their sequence of administration.

vibrotactile sensitivity using the participant's non-dominant hand's index and small fingers (Vibraton II). Strength and fatigue were assessed using the participant's dominant hand with a hand-held dynamometer (Jamar). Vision tests were administered using the OPTEC 1000 CS.

To assess the verbal reading/intellectual ability of participants for group comparability purposes, the Wide Range Achievement Test 3-Reading (WRAT 3) was administered to participants tested in English, and, the Woodcock–Johnson-Revised Achievement Standard Battery and Bateria-R Listening Comprehension tests were used for individuals testing in Spanish. Standardized forms were used for scoring.

In May 2000, neurobehavioral testing was conducted in nearby downtown Sioux City, Iowa. Testing was carried out in temperature-controlled, private rooms to promote data quality. Professional examiners were blinded to participants' exposure status, although participants occasionally made statements that suggested their group exposure assignment. Spanish language testing was administered by the same Spanish-speaking examiner, whereas English language testing was administered by any one of five examiners.

2.4. Data analyses

Statistical analysis was conducted using SAS (Release 8e, SAS Institute, Cary, NC). A descriptive analysis was performed to summarize important variables. Multivariate analyses were performed to assess the magnitude and nature of the association between neurobehavioral outcomes and key factors. Neurobehavioral outcomes and their log-transformed values were not normally distributed, and multivariate linear regression diagnostics indicated that some linear regression assumptions were not met. Therefore, a generalized multivariate logistic regression approach was used to investigate associations between covariates and neurobehavioral outcomes. Neurobehavioral scores were converted to ordered categorical variables with four levels, each corresponding to a quartile of the outcome variable's distribution. A proportional odds cumulative logit model was then used to examine the association between neurobehavioral outcomes and the following 11 variables: exposure status (geographic area); educational attainment, age, sex, language for testing, body mass index, prior caffeine consumption, prior alcohol consumption; prior drug use (prescription, nonprescription, and street drugs), treatment for drug or alcohol use, and job-related exposure to hazardous materials, chemicals, or gases. These variables were identified based on previous neurobehavioral research and those variables hypothesized as important for the Dakota City study (Slikker et al., 2000; Anger et al., 1997). The analysis was conducted using three different categories of the age variable. The three-category age variable was used in the final analysis and represents young adults, middle-aged adults, and older adults (i.e., persons aged 16–29 years, 30–59 years, and $\geqslant 60$ years, respectively). The geographic area-of-residence (target versus comparison area) was maintained as a variable in every model.

3. Results

3.1. Participation rates and baseline characteristics

Analyses were conducted on 335 people; of these, 171 were in the target group and 164 were in the comparison group. For individuals randomly selected from a listing of names, stratified by exposure status, and whom we

Table 2
Demographic and other characteristics for target and comparison study groups, Dakota and South Sioux cities, Nebraska, May 2000

Characteristic	Target group		Comparison group	
	Number	Percentage	Number	Percentage
Sex				
Male	72	41.1	86	50.5
Female	103	58.8	84	49.4
Age				
16–24	19	10.8	21	12.3
25–34	27	15.4	42	24.7
35–44	34	19.4	34	20.0
45–54	56	32.0	34	20.0
55–64	26	14.8	19	11.1
65–74	8	4.5	13	7.6
$\geqslant 75$	5	2.8	7	4.1
Ethnicity				
Not Hispanic	135	77.1	133	78.2
Hispanic	40	22.8	37	21.7
Race				
White	144	82.2	150	88.2
Black	0	0	3	1.7
Asian	4	2.2	1	0.5
American Indian	4	2.2	2	1.1
Other	23	13.1	14	8.2
Education				
Less than 11th grade	39	22.2	36	21.1
11th or 12th grade	60	34.2	84	49.4
Some college	35	20.0	35	20.5
$\geqslant 4$ years college	41	23.4	15	8.8
In the past 24 h, took medications or drugs?				
Yes	96	54.8	74	43.5
No	79	45.1	96	56.4
Alcohol use in past 24 h?				
Do not drink	118	67.4	101	59.4
Usual amount	39	22.2	47	27.6
Less than usual amount	15	8.5	20	11.7
More than usual amount	3	1.7	2	1.1
Sleep in the past 24 h?				
Usual amount	128	73.1	124	72.9
Less than usual amount	39	22.3	35	20.6
More than usual amount	8	4.6	11	6.5
Ever medically treated for chronic drug or alcohol use?				
Yes	1	<1	10	5.8
No	174	99.4	160	94.2

were able to contact, the study participation rates for the target and comparison groups were 73% and 64%, respectively. Ten people were excluded from the analyses: 4 from the target group and 6 from the comparison group. Reasons for exclusion include a severe medical condition (4 persons), blindness or loss of vision (2 persons), excessive difficulty with tests instructions (2 persons), and poor personal effort during testing, as judged by the examiner (2 persons).

The two groups had similar distributions of race and ethnicity. The target group was made up of a higher percentage of females and people aged 45 years and older (Table 2). The proportions of white participants in the target and comparison groups were 82% and 88%, respectively. The age range of participants was 16–88 years, with a mean age of 44 years for the target group and 42 years for the comparison group. Target group participants had completed more years of education (23% completed four or more years of college) than had the comparison group participants (9%). For the target group, a majority (74%) of participants reported $\geqslant 5$ years' length of residence, an indicator of long-term exposure to H_2S. For both target and comparison groups, a majority of participants reported that they did not smoke (76% and 75%, respectively) and did not drink alcohol (67% and 59%, respectively). For both groups, a majority of participants (73%) reported that they had had their usual amount of sleep during the 24 h before testing (i.e., a surrogate of personal alertness). The target group reported more frequent use of drugs or medications within the 24 h before testing (55% compared with 44%). Sixteen (9%) target group

Table 3
Generalized logistic regression analysis -odds ratios for better test performance for target group participants, Dakota and South Sioux cities, Nebraska, May 2000

Neurobehavioral test	Variables remaining in final model	Target group odds ratio (95% CI) for better performance on tests
Cognitive domain		
Match to sample score	Age, testing language	0.6 (0.4–1.0)
Match to sample, 1-delay	Age, testing language	1.3 (0.8–1.7)
Match to sample, 8-delay	None	0.8 (0.6–1.3)
Match to sample, 16-delay	Education	1.1 (0.8–1.7)
Digit span forward	Age, education	1.2 (0.8–1.9)
Digit span reverse	Age, testing language	1.2 (0.8–1.8)
Serial digit learning	Age, education	1.5 (1.0–2.3)
Symbol digit latency	Age, education, sex	1.1 (0.7–1.7)
Symbol digit error	Age, education	1.0 (0.7–1.7)
Sensory domain		
Contrast sensitivity le[a] set c	Age, sex, testing language	1.5 (1.0–2.3)
Contrast sensitivity le set d	Age	1.0 (0.7–1.5)
Contrast sensitivity re[b] set c	Age	1.4 (0.9–2.2)
Contrast sensitivity re set d	Age, sex	1.3 (0.9–2.0)
Vibrotactile threshold[c]	Age	1.7 (1.1–2.5)
Motor domain		
Simple reaction time latency	Age, testing language	0.8 (0.6–1.3)
Simple reaction time error	None	1.3 (0.5–1.3)
Tapping	Age, testing language	1.3 (0.8–2.0)
Dynamometer grip strength	Age, sex	0.7 (0.4–1.0)
Dynamometer fatigue	Age	1.1 (0.8–1.7)
Mood/affect domain		
SF-36 vitality scale	Testing language, medication use	0.9 (0.6–1.4)
SF-36 social function	Education, caffeine use	0.9 (0.6–1.3)
SF-36 physical scale	Age, body weight	1.0 (0.6–1.6)
SF-36 emotional scale	Body weight, medication use	1.1 (0.7–1.7)
SF-36 physical function	Age, body weight, medication use	1.3 (0.9–2.1)
SF-36 general health	Education, medication use	1.1 (0.7–1.6)
SF-36 mental health scale	Testing language	1.0 (0.7–1.6)
Other		
WRAT 3 Reading	Education	1.2 (0.5–2.8)
Bateria-R Listening Comprehension	None	0.6 (0.1–2.8)

The eleven variables included in all models were exposure status (target versus comparison group), educational attainment, age, sex, language of testing, body mass index, prior caffeine, prior alcohol use, prior drug use, treatment for substance abuse, and job-related exposure to hazardous materials. Body weight = body mass index >30.

[a] Left eye, set c, set d.

[b] Right eye, set c, set d.

[c] Vibration sensitivity of non-preferred hand, index finger, trial 2.

members and 10 (6%) comparison group members reported ever having had a concussion or loss of consciousness event. Testing in Spanish was almost equal for the groups (16% of target group and 15% of comparison group participants). About 17% of all participants reported current potential occupational exposure to hazardous materials, a surrogate for neurotoxic substances, and 11% of all participants reported ever having been employed as a meat packer or worked for IBP Inc. (data not shown).

3.2. Neurobehavioral testing results

The findings of the adjusted logistic regression analyses are presented in Table 3. For the 28 neurobehavioral outcomes, the target group showed better or equal performance on 21 (75%) of 28 tests, but the differences were not large and just one test achieved statistical significance (vibrotactile threshold).

Visual acuity was measured to assess participants' ability to see the tests. The distribution of visual acuity scores between the two groups was similar: 14% of both target and comparison subjects had 20/20 vision, followed by 20% and 17%, respectively, for 20/30 vision; 2% of target and 5% of comparison subjects had poor vision scores (20/200) (data not shown).

Eleven covariates were included in the analytic model. The variable age was most commonly associated with the outcome, appearing in 18 (64%) of the models.

Educational attainment (highest grade completed) and language used for testing were key covariates in 8 (29%) models, sex and medication use (affect function only) were key covariates in 4 (14%) models, and exposure group and body weight (body mass index) were key covariates in 3 models.

For sensory function, exposure to H_2S (residence in the target area) was a key covariable for the vibration sensitivity test result (reported as the reciprocal of the odds ratio, (OR) of 1.7; 95% confidence interval (CI), 1.1–2.5). For motor skills function, exposure to H_2S was a covariate for poorer performance for hand grip strength after controlling for age, sex, and body mass index (OR, 0.7; 95% CI, 0.4–1.0). The two groups had generally comparable test scores for WRAT 3 Reading and Bateria-R Listening Comprehension; performance on tests improved with more years of education. Additionally, we examined the impact of lifestyle (ingestion of substances) and work-related exposures but found no significant change in the results (data not shown).

In consideration of previous neurobehavioral research findings for H_2S toxicity, along with our preliminary hypothesis testing, all test results for cognitive function were reviewed for direction, consistency, magnitude, and statistical significance of findings. Most of the nine tests results, except for match to sample (Table 3), showed consistently favorable performance (direction) for the target group versus the comparison group. The differences were modest in magnitude, with an OR range of 0.6–1.5. Group differences were greatest for the serial-digit learning test (OR, 1.5; 95% CI, 1.0–2.3). Conversely, target group members scored poorer for a test of memory, match to sample score (OR, 0.6; 95% CI, 0.4–1.0), and the 8-s delay test trial of match to sample (OR, 0.8; 95% CI, 0.6–1.3). The covariable age, followed by educational level, was most commonly associated with cognitive test outcomes.

Overall, the results indicate that being younger, being male, having higher educational attainment, taking the test in English, and living in the target area (H_2S exposure) were independently associated with better performance on most of the tests. For mood/affect domain tests, being obese (body mass index $\geqslant 30$) was associated with lower performance on three of the tests.

4. Discussion

In the mid-1990s, peak levels of H_2S in Dakota City periodically registered up to 5000 ppb and repeatedly exceeded the state's time-averaged standard of 100 ppb. The uncertainty of the potential for neurotoxicity for these exposures was the impetus for this study. Standardized validated tests were used to assess for indicators of subtle (subacute) differences in neurobehavioral health for two demographically comparable populations in Dakota City. Of the 28 neurobehavioral tests results, 21 showed no adverse relationship with area of residence, the surrogate for H_2S exposure, after adjusting for potential confounders. This study found weak associations between area of residence and poorer performance of a test of memory (match to sample score) and measure of strength (grip strength). This study did not find an association between measurable fatigue, a symptom reported by local residents, and H_2S exposure.

Studies report neurobehavioral impairment (cognitive, balance, mood) for nonoccupational, moderate exposures to H_2S (Kilburn and Warshaw, 1995). Studies indicate an increased risk for neurological impairment with exposure to H_2S or total reduced sulfur compounds (Partti-Pellinen et al., 1996; Bates et al., 1998; Kilburn, 1997). Using neurophysiological and neuropsychological tests and predicted values of performances, Kilburn (1999) found neurobehavioral abnormalities (cognitive, motor, and somatosensory) among persons with H_2S exposure compared to unexposed referents. H_2S concentrations were higher in the Kilburn study (range of 10–30,000 ppb) than in Dakota City. In contrast to Kilburn (1999), for Dakota City one test of memory (match to sample) reflected slightly poorer performance compared to the nonexposed group, at the 8-s delay, but on other tests that rely on memory for effective performance (digit span, symbol digit, serial-digit learning) the residents exposed to H_2S had better performance scores. However, the administration of these tests may have differed for the two studies (e.g., instructions to participants and equipment used).

A study of Legator and colleagues (2001) found an elevated risk for self-reported symptoms of the central nervous system (e.g., fatigue, headache, and difficulty sleeping) for two communities with long-term exposure to H_2S. Arguably, estimated H_2S exposures (100–500 ppb) were comparable to those in Dakota City. In contrast to the Legator study, this study found that group responses for mood/affect function were similar. These two studies used different methods for participant selection, exposure determinations, and health outcomes, thereby making it difficult to compare results.

Studies have identified that personal (subject) variables can be important modifiers of neurobehavioral performance and that data analyses and data interpretation should carefully assess the impact of these subject variables (Slikker et al., 2000; Anger et al., 1997; White et al., 1996). Educational level has a substantial impact on neurobehavioral performance, especially on cognitive tests (Slikker et al., 2000; Anger et al., 1997). Consistent with other studies, this study found these same variables to be covariates of performance on neurobehavioral tests along with the language of testing. In this study, the participant's age, sex, and educational level were included in the final regression models to control for potential confounding by these variables.

Intense odor in Dakota City could be a trigger of stress, anxiety, and worry (measures of affect). These odor exposures may worsen preexisting diseases among the target population, thus indirectly affecting neurobehavioral measures of mood/affect. However, in this study an association between chronic exposure to H_2S and impairment of mood/affect was not found.

Limitations of this study include the possibility of measurement error for the classification of exposure. Assigning gradients of exposure and dichotomizing exposure status, namely target and comparison populations, may have introduced mis-classification bias. Although these H_2S gradients of exposure and their populations exist in relatively close geographic areas, the investigators used an acceptable methodology and EPA air modeling expertise to reduce nondifferential misclassification of exposure. Even though the investigators were careful in assigning exposure status, this misclassification could have precluded the finding of a significant difference in neurobehavioral performance between the two groups.

Regarding occupational exposures to neurotoxicants including H_2S, approximately 17% of all subjects reported potential exposures; of these, 67% of subjects indicated employment or possible exposures at meatpacking facilities. The comparison group had a slightly greater proportion of subjects with possible hazardous materials exposure; this may have precluded detection of an association of neurobehavioral effect. However, the investigators controlled for hazardous materials exposure in the multivariate analysis. This variable did not affect the association between H_2S exposure and neurobehavioral outcomes.

Standardized valid tests were used to reduce the possibility of measurement error for neurobehavioral outcomes. Selection bias was reduced with random sampling among target and comparison sampling frames. Interviewer bias was reduced by using a study protocol with standardized collection instruments and scripts and "blinded" test examiners.

The overall study participation rate, less than 75%, was a potential limiting factor for the generalizability of results; a greater number of persons from the comparison area declined participation. The Spanish-language testing subgroup was too small in number, thus lacking in statistical power, to measure effects by exposure status in this subgroup. However, 8 (29%) of 28 tests showed that testing language was an important variable in the adjusted analysis. To the extent that the two groups of Spanish test takers were not equivalent for baseline ability, any such effects were likely addressed by the inclusion of language of testing as a covariable.

5. Conclusions

In Dakota City, Nebraska, repeated and long-term exposure to moderate-to-low-level H_2S, which was based on the surrogate measure of area of residence, was not associated with poorer performance on neurobehavioral tests except for 2 of 28 tests, namely the match to sample score test of memory and the dynamometer grip strength test, but even these deficits were marginal. Although some areas of nervous system function were not examined, those functions known to be affected by high concentrations of H_2S were assessed with well-validated tests. The H_2S-exposed and comparison groups were similar in demographic and other baseline characteristics. Standard and well-accepted selection procedures were employed in this study, and known confounders were taken into account in analyzing the results, thus reducing the potential impact of many sources of bias. Additional research is needed to determine whether different effects on neurobehavioral function are observed either for longer periods of exposure or among certain population subgroups.

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