Neurosensory effects of chronic exposure to arsenic via drinking water in Inner Mongolia: I. signs, symptoms and pinprick testing

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ABSTRACT

This study was designed to assess the effects of exposure to arsenic in drinking water on neurosensory function. A questionnaire including neurological signs and symptoms and a brief neurological exam consisting of pinprick testing of the arms and legs and knee-jerk test were administered to 321 residents of the Bamen region of Inner Mongolia, China. Arsenic in water was measured by hydride generation atomic fluorescence. Participants were divided into three exposure groups—low (non-detectible-20), medium (100–300) and high (400–700 μg/l) arsenic. Significant group differences were observed in pinprick scores for all four limbs. Results indicate that arsenic alters pinprick (pain) thresholds at well-water concentrations as low as 400 μg/l, well below the 1000 μg/l threshold for neurological effect specified by NRC (1999). Regression models suggest that a 50% increase in pinprick score is associated with a 71–159 ppb increase in arsenic concentration.

Key words | arsenic, drinking water, pain, pinprick, symptoms

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INTRODUCTION

Arsenic occurs naturally in soil and ground water in many parts of the world from the weathering of bedrock or other materials in the crust of the earth (Thornton & Farago 1997). Alluvial and organic soils contain more arsenic than sandy soils (Kabata-Pendias & Pendias 1984). The present study was carried out in the Bayingnormen (Bamen) region of Inner Mongolia. Bamen is a major agricultural area–the melon and sunflower capital of China–located between ancient mountain ranges (Langsan and Da Qingsan) to the north and the Yellow River to the south. Arsenic has accumulated in the soil of the Bamen region over the millennia from erosion of the mountains and periodic flooding of the Yellow River. Arsenic concentrations found in the underground lake basin, between the mountains and river, range from nondetectable to1,800 μg/l (Ma *et al.* 1999). Arcenicism has been known to occur in this area since 1990.

Sensory axonal peripheral neuropathy is a common sequela of acute arsenic poisoning, reported to occur at doses as low as 40–50 μg/kg (ATSDR 1998; NRC 1999). However, there is considerable uncertainty about the threshold for neurological effects of chronic arsenic exposure in drinking water. Based on a review of data from Taiwan, Agentina and Chile by Hotta (1989) and other available findings, the National Research Council (1999) concluded that there is

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no consistent evidence of peripheral neuropathy in humans exposed to arsenic in drinking water at levels below 1000 μg/l. Similarly, Kreiss *et al.* (1983) failed to find any evidence of arsenic-induced neuropathy in 147 residents of Ester Dome, Alaska who were drinking well water with arsenic levels up to 15,000 μg/l. Clinical neurological examinations and nerve-conduction velocity (NCV) tests were administered under blinded conditions in this careful study. However, the authors concluded that NCV was an insensitive screening measure for subclinical arsenic neuropathy.

Adverse neurological effects have been reported in other studies at arsenic levels below 1000 μg/l. Hindmarsh *et al.* (1977) found abnormal electromyograms in 32 of 110 Canadians with well water concentrations of 60–1400 μg/l. Basu *et al.* (1996) observed sensory polyneuropathy in 8 West Bengali patients chronically exposed to drinking water arsenic levels of 200–2000 μg/l. A variety of neurotoxic effects have also been reported in a study (Ma *et al.* 1995) of Inner Mongolian farmers whose drinking water was contaminated by arsenic with concentrations ranging from nondetectable −1,800 μg/l. These effects included hearing loss, atrophy of the optic nerve, narrowing of the visual field and peripheral neuropathy.

A variety of health problems including skin cancer, peripheral neuropathy, gastroenteritis and cardiovascular disease have been associated with arsenic exposure in Bamen residents (Ma *et al.* 1995). The present study was undertaken to evaluate the effects of exposure to arsenic in drinking water on sensory signs and symptoms assessed by questionnaire and on pain sensation measured by pinprick testing. Tests of visual and tactile function were also administered and are reported elsewhere in this volume (Otto *et al.* 2006 (this issue)).

METHODS

Subjects

321 residents from the Bamen region of Inner Mongolia participated in this study. Three exposure groups were defined *a priori* as low (0–20), medium (100–300) and high (400–700 μg /l) arsenic in drinking water. A database containing arsenic concentrations for more than 10,000 wells in areas of chronic arsenicism was available from local anti-epidemic stations. This database was used to identify areas which would yield a wide range of exposure (0–800 ug/l). Water samples were then obtained from 363 households. Participants were recruited from this sample to obtain the three exposure groups. Participants were not informed of water arsenic levels prior to neurosensory testing.

Demographic characteristics of these groups are shown in Table 1. Few of the participants had a high school education and none had been to college. The mean age of participants was 34.7 years. 12 subjects were eliminated from statistical analyses due to missing well water data.

Protection of human subjects

This study was conducted according to the Declaration of Helsinki recommendations for the protection of human subjects (World Medical Association 1989). Informed consent was obtained from all subjects to participate in the study. Test procedures and potential risks were described to subjects in the consent form. The protocol was reviewed and approved by the U.S. Environmental Protection Agency.

Assessment of arsenic

Total arsenic in water samples obtained from the wells of individual families or community water sources was assessed by hydride generation atomic fluorescence (Le & Ma 1998). Distribution of arsenic concentrations in the three groups is shown in Figure 1.

Questionnaire

A questionnaire, designed for this study, was administered to obtain demographic information, health and exposure history of participants, and self-reported neurosensory signs and symptoms. Questions included age, gender, education, smoking and drinking history, pesticide exposure, ratings of neurological function and history of central or peripheral nervous system disorders. Neurological symptom items are shown in Table 2. Education level was classified as none, primary, middle school or high school. Drinking

Table 1 | Distribution of Demographic Data by Arsenic Exposure Group

	Exposure group (arsenic in drinking water)		
	Low Mean(SD)	**Medium Mean(SD)**	**High Mean(SD)**
Mean As (μg/l)	12.4 (5.7)	200.9 (55.6)	567.3 (70.7)
Mean age	35.8 (12.8)	35.7 (14.0)	33.7 (13.9)
	N	N	N
Sample size	97	109	103
	N (%)	N (%)	N (%)
Gender (Male)	49 (51%)	59 (54%)	58 (56%)
Education			
None	14 (15%)	21 (20%)	19 (19%)
Primary	38 (41%)	51 (48%)	43 (42%)
Middle	35 (38%)	26 (25%)	36 (35%)
High	5 (5%)	8 (8%)	4 (4%)
Smoke			
Yes	25 (25%)	40 (41%)	32 (33%)
Drink Alcohol			
Yes	20 (25%)	18 (17%)	9 (12%)
Exposure to pesticides more than 5 years ago			
Yes	50 (56%)	56 (53%)	41(42%)
Exposure to pesticides within past 5 years			
Yes	55 (62%)	57 (54%)	48 (49%)

history was measured simply as 'Do you drink alcohol more than twice a week (Y/N)?' Information was obtained on the type and amount of tobacco used and age when smoking commenced. Pack years were calculated as (years smoked) × (# cigarettes per day)/20 × 365. Participants were also questioned whether they had been exposed to pesticides during the past five years (Y/N) or prior to that time (Y/N). If subjects were unable to read, questions were administered by interview. The primary purpose of this questionnaire was to identify possible confounders.

Brief neurological examination

A brief neurological examination consisting of pinprick testing of the left and right upper and lower extremities and the knee-jerk reflex was conducted by physicians with extensive clinical experience. The pinprick test was administered from distal-to-proximal positions of the hands and feet in order to determine the extent of pain detection (ability to feel sensation from a blunt needle). Participants were instructed to close both eyes and to extend the right hand (or foot) for examination. Testing began at the end of the finger (or toe) and continued toward the elbow (or knee) until the subject said (s)he could feel pain. The procedure was then repeated with the left hand and foot.

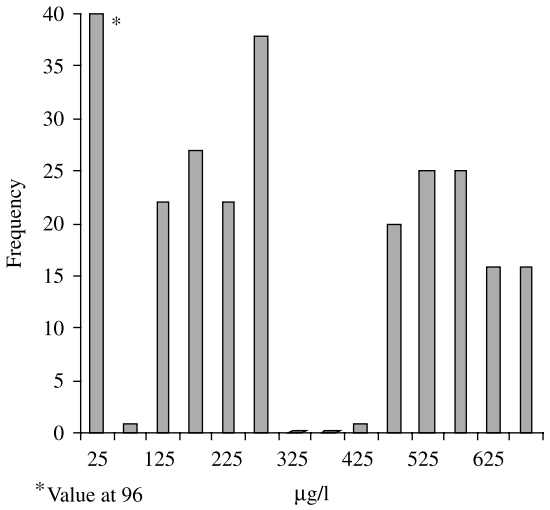

Figure 1 | Distribution of arsenic concentrations in well water of participants. Bin width on x-axis is 50 μg/l; values below x-axis correspond to midpoint of bin. The distribution reflects gaps between low, medium and high exposure groups.

Table 2 | Number and percent of self-reported neurological signs and symptoms

	Exposure group (arsenic in drinking water)		
	Low	**Medium**	**High**
Amnesia	N(%)	N(%)	N(%)
Yes	16 (18%)	24 (23%)	28 (29%)
Impaired autonomic nervous system			
Yes	16 (18%)*	8 (8%)*†	28 (29%)†
Headache			
Yes	24 (27%)	34 (33%)	27 (28%)
Hearing loss			
Yes	14 (16%)	5 (5%)	8 (8%)
Impaired heat/cold sensation			
Yes	18 (20%)*	4 (4%)*†	22 (22%)*†
Numbness			
Yes	22 (25%)*	14 (14%)*†	29 (30%)*†
Pain			
Yes	7 (8%)‡	3 (3%)†	33 (34%)‡†
Impaired sense of smell			
Yes	9 (10%)*	2 (2%)*†	12 (12%)*†
Impaired vibration sensation			
Yes	23 (26%)‡	17 (16%)†	42 (43%)‡†

*$p < 0.05$, low vs. medium, (χ2-test, 1 degree of freedom)
†$p < 0.05$, medium vs. high, (χ2-test, 1 degree of freedom)
‡$p < 0.05$, low vs. high, (χ2-test, 1 degree of freedom)

Neither the subject nor the examiner was aware of the well-water arsenic level or exposure group at the time of testing, in other words, the test was administered double-blind. Testing with eyes closed also prevented participants from knowing the location of the needle during examination.

Clinical tests were scored as follows: absence of pinprick sensation in upper extremities (1 = none, 2 = end of finger only, 3 = whole finger, 4 = below wrist, 5 = below elbow); absence of pinprick sensation in lower extremities (1 = none, 2 = end of toe, 3 = whole toe, 4 = below ankle, 5 = below knee); and knee jerk reflex (1 = normal, 2 = low, 3 = high). Testing was conducted in medical facilities located in the villages where participants lived.

Statistical analyses

Statistical analyses were conducted in SAS v. 8.0 (2001, SAS Institute, Inc.) and Stata v. 8.2 (2004, Stata Corporation). Chi square tests were used to explore the association of categorical dependent and independent variables. Mean group differences were tested using analysis of variance (ANOVA). Because the outcome measure was an ordered categorical variable, multivariate models were also performed with ordered logistic regression (McCullagh 1980). Dummy variables were used for categories of arsenic exposure with low exposure as the referent group and modeling arsenic level as a continuous variable. Variables which were significantly related to arsenic exposure or neurological test results were included in the multivariate analysis. P-values < 0.05 (two-sided) were considered to be statistically significant; and p-values <0.1 (two-sided) to be of borderline statistical significance.

RESULTS

Demographic data broken down by exposure group are shown in Table 1. No demographic variables were significantly ($p < 0.05$) associated with exposure category by χ^2 tests for association, although there was a tendency for alcohol consumption ($p = 0.12$) and pesticide exposure ($p = 0.11$) to be related to arsenic exposure. Table 2 shows the number and percent of respondents by exposure category for neurological signs and symptoms. Self-reported autonomic nervous system dysfunction, heat sensitivity, numbness, pain, impaired smell, and reduced sensitivity to vibration were significantly associated with arsenic exposure category. Although the highest arsenic category generally had the highest proportion reporting the condition, the medium arsenic category, and not the low arsenic category, generally had the lowest proportion reporting the condition.

Less than 20% of participants had reduced sensitivity on any of the pinprick or knee-jerk measures. Since the distributions of pinprick and knee-jerk ratings were highly skewed, ratings were scored as either normal ($= 1$) or abnormal (>1). The χ^2-test was then used to assess the percentage of participants with abnormal pinprick or knee-jerk ratings for each survey or demographic question. Table 3 depicts the association of pinprick score (score > 1) and questionnaire responses. Symptoms associated with the highest percentage of abnormal pinprick response ($p < .005$) were numbness, pain and vibration sensation. Other items (amnesia and autonomic nervous system dysfunction) were also significantly associated with

Table 3 | Percent with higher scores (>1) in pinprick and knee-jerk tests by demographic characteristics and self-reported neurological signs and symptoms[a]

			Pinprick test				
		N	L. Arm	R. Arm	L. Leg	R. Leg	Kneejerk
Gender-	Male	163	16%	16%	8%	6%*	1%
	Female	143	19%	19%	11%	11%	4%
Drink alcohol-	Yes	46	15%	15%	9%	7%	2%
	No	213	17%	17%	10%	9%	2%
Education (middle school- or above)	Yes	112	15%	14%	5%*	4%†	2%
	No	176	20%	20%	12%	11%	3%
Smoke cigarettes-	Yes	93	14%	14%	7%	4%*	4%
	No	197	20%	20%	11%	11%	2%
Amnesia-	Yes	68	31%‡	31%‡	16%†	16%†	2%
	No	221	14%	14%	8%	8%	3%
Autonomic Nervous	Yes	52	29%†	33%‡	23%‡	17%†	2%
System impairment	No	237	16%	15%	7%	7%	3%
Headache-	Yes	85	20%	21%	12%	12%	4%
	No	204	18%	17%	9%	7%	2%
Hearing impairment-	Yes	27	26%	22%	19%	15%	0%
	No	262	18%	18%	9%	8%	3%
Numbness-	Yes	65	35%¶	37%¶	20%¶	19%¶	2%
	No	222	14%	13%	7%	6%	3%
Pain-	Yes	43	93%¶	88%¶	49%¶	42%¶	5%
	No	245	5%	6%	3%	3%	2%
Pesticide exposure more than 5 years ago-	Yes	145	17%	17%	11%	8%	4%*
	No	145	19%	20%	8%	9%	1%
Pesticide exposure within 5 years-	Yes	158	17%	16%	11%	8%	4%*
	No	132	20%	20%	8%	9%	1%
Impaired sense of smell	Yes	22	32%*	27%	23%†	14%	0%
	No	267	17%	18%	9%	8%	3%
Vibration sensation	Yes	80	34%¶	35%¶	23%¶	19%¶	1%
	No	209	12%	12%	5%	5%	3%

*$p < 0.1$, †$p < 0.05$, ‡$p < 0.01$, ¶$p < 0.005$ (χ2-test, 1 degree of freedom)
[a]numbers do not add to 309 due to missing responses

pinprick ratings ($p < .01$ or .05). Several demographic variables (smoking, education level and gender) were weakly associated with a few pinprick measures.

Figure 2 illustrates pinprick scores by exposure group for each limb. ANOVA tests indicated significant differences in pinprick scores of both arms and legs, but not in knee-jerk reflex ratings. Pinprick tests of all four limbs indicate a trend for the absence of pinprick sensation to increase in a proximal direction with increasing arsenic concentrations in drinking water. Significant group differences in pinprick scores were observed between low and high, medium and high, but not between low and medium exposure groups. The largest differences in pinprick score were found between low and high exposure groups.

In view of the categorical nature of the dependent variables, categorical multivariate regression analyses were also performed on pinprick scores. Results are shown in Table 4. Knee-jerk response was unrelated to arsenic and was not included in the regression analyses. Significant increases in pinprick score were found for all pinprick measures

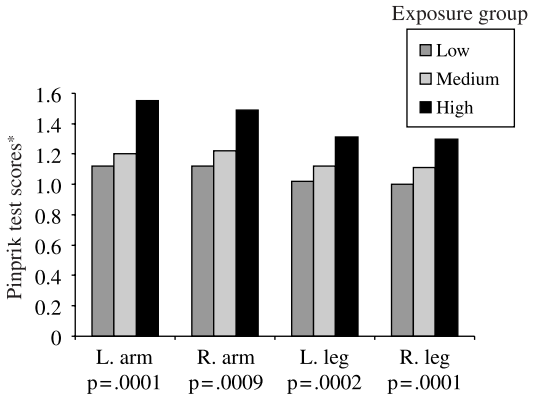

Figure 2 | Comparison of mean pinprick test scores for low, medium and high exposure groups in four limbs tested.

comparing high to low arsenic categories, controlling for age, gender, education, smoking and drinking. Increases in pinprick scores were also noted comparing medium to low categories, but none of the tests were statistically significant. Participants in high arsenic groups had predicted probabilities of reduced response ranging from 0.22–0.33. Although more respondents reported increased pinprick score in the hands, regression coefficients were stronger for leg measures. Coefficients are interpreted as the increase in log odds of a one-unit increase in pinprick score for a change from low-to-medium or low-to-high arsenic categories. Exponentiating the coefficients (Selvin 1996) provides an estimate of the relative risk of a one unit increase in pinprick score associated with an increase in arsenic category. For example, those in the high arsenic group were more than five times as likely (exp[1.70] = 5.47) to have a left arm pinprick score one unit higher than those in the lowest category. Those in the high arsenic category were almost 20 times more likely to have a left leg pinprick score one unit higher than the lowest arsenic exposure category.

Finally, a multivariate regression model was run to determine the quantity of arsenic in drinking water required to increase pinprick score by 50% or 100%. Results from modeling arsenic as a continuous variable are shown in Table 5. A 50% reduction would be equivalent to an increase in pinprick score from 2.0 to 3.0; a 100% increase in score would be equivalent to an increase from 1 to 2 or 2 to 4. Regression coefficients were again stronger in leg compared to arm measures. A 50% increase in pinprick score was associated with a 71–159 ppb increase in arsenic concentration and a 100% increase was associated with a 121–171 ppb increase.

DISCUSSION

The pinprick test is widely used in clinical neurology to assess the integrity of pain and/or touch sensation in

Table 4 | Categorical multivariate analysis[a]: mean predicted probability of elevated pinprick score (>1) and regression coefficients[b]

		Arsenic exposure category		
Extremity	**Measure**	**Low**	**Medium**	**High**
Left Arm	Coefficient (se)	Referent	0.35 (0.5)	1.70 (0.47)**
	Predicted Probability of Elevated Pinprick Score	0.09	0.12	0.33
Right Arm	Coefficient (se)	Referent	0.62 (0.48)	1.51 (0.47)**
	Predicted Probability of Elevated Pinprick Score	0.09	0.14	0.29
Left Leg	Coefficient (se)	Referent	1.41 (0.85)*	2.96 (0.82)**
	Predicted Probability of Elevated Pinprick Score	0.02	0.07	0.24
Right Leg[c]	Coefficient (se)	Referent	NA[c]	2.16 (0.51)**
	Predicted Probability of Elevated Pinprick Score		0.04[d]	0.22

[a]Ordered logistic regression, outcome is pinprick score coded 1 through five, controlling for age, gender, smoking, drinking and education. Dummy variables were used for arsenic exposure category, with low exposure as the referent group

[b]Coefficients are interpreted as the increase in log odds of a one-unit increase in pinprick score for a change from low to medium or low to high arsenic categories

[c]No reduced pinprick response events in low arsenic category, low and medium were combined

[d]Estimate for combined low and medium arsenic exposure categories

*$p < 0.1$, **$p < 0.005$

Table 5 | Multivariate Regression Model[a]: coefficients for continuous arsenic variables and estimates of increase in arsenic required to increase pinprick score by 50% or 100%

Pinprick measure	Regression coefficient[b]	Standard error	Predicted increase in arsenic needed to increase pinprick score	
			50%	100%
Left arm	0.00328*	.0008	123 ppb	211 ppb
Right arm	0.00255*	.0008	159 ppb	271 ppb
Left leg	0.00528*	.0011	77 ppb	131 ppb
Right leg	0.0057*	.0012	71 ppb	121 ppb

[a]Ordered logistic regression; continuous As measure; pinprick sensitivity scored 1-5
[b]Coefficients interpreted as the increase in log odds of a one unit increase in pinprick rating
[c]50% reduction would be equivalent to an increase in pinprick scores of 2 to a 3, or a 1 to a 1.5. Similarly, a 100% reduction is equivalent to an increase in pinprick scores of 1 to 2, or 2 to 4
*$p < 0.005$

somatosensory pathways (Greenberg *et al.* 2002). Peripheral-to-central and side-to-side comparisons provide rapid indications of lesions in contralateral sensory pathways or peripheral neuropathy. The pinprick test was used in the present study since peripheral neuropathy is a well-known concomitant of acute arsenic poisoning.

The results indicate subtle, but significant impairment in the perception of pain in the hands and feet associated with arsenic exposure, consistent with case reports of peripheral neuropathy (Feldman 1999). Furthermore the results demonstrate that sensory effects of chronic exposure to arsenic in drinking water occur well below the 1000 μg/l level specified by NRC (1999) as the threshold for neurological impairment. Reduced pain sensation assessed by the pinprick test was observed at levels as low as 400 μg/l based on group comparisons. Regression analyses suggest effects at even lower concentrations. In particular, logistic regression modeling suggests that a 70–160 μg/l increase in drinking water arsenic results in a 50% increase in pinprick scores. The possibility of a threshold effect was not explored due to the limitations associated with a categorical response variable. Further study is needed to clarify the threshold for arsenic-related impairment of pain sensation.

Self-reported symptoms (numbness, pain, and reduced vibration sensation) were significantly associated with increased pinprick scores, providing face validity for pinprick test results. On the other hand, questionnaire responses were somewhat less consistent than pinprick measures in relation to arsenic exposure category. That is, the highest proportion of respondents reporting neurological abnormalities occurred in the highest arsenic category, but a surprisingly high proportion of respondents in the lowest category also reported these signs or symptoms.

Similar findings were obtained in measures of vibrotactile sensation (Otto *et al.* 2006 (this issue)). Vibration thresholds were measured in two fingers (2nd and 5th) of both hands. The pattern of effects was the same for pain and vibration tests, that is, significant group differences were found between high and medium, high and low, but not medium and low exposure groups. Spline regression modeling of vibration measures suggests an effect threshold of 150–170 μg/l arsenic in drinking water.

These findings are consistent with a recent study of current perception thresholds (CPT) in asymptomatic Taiwanese living in villages where blackfoot disease (BFD) is endemic (Tseng 2003). BFD results from chronic exposure to arsenic in drinking water. Three nerves, trigeminal, median and peroneal, were assessed using standard CPT test frequencies: 5, 250 and 2000 Hz (Katims *et al.* 1986). Higher thresholds were found at all three frequencies in arsenic-exposed villagers compared to controls. However, the probability of abnormal values was higher in longer (peroneal and median) than shorter (trigeminal) nerves and at lower (5 and 250 Hz) than higher (2000 Hz) frequencies. It should

be noted that Tseng did not assess pain or vibration directly and that no environmental or body burden measures of arsenic were obtained in this study.

Few other epidemiological studies of peripheral neuropathy in arsenic-exposed populations have been undertaken. Kreiss *et al.* (1983) measured nerve conduction velocity (NCV) in Alaskan residents exposed to arsenic in well water at levels up to 15,000 μg/l. No significant association of arsenic concentration and NCV was found in that study. Gerr *et al.* (2000) also failed to find any relationship of arsenic exposure (from dust and soil) and NCV in residents living in the vicinity of a pesticide packaging plant, although strong associations were found with measures of postural balance, vibrotactile thresholds and hand tremor. Results of the latter study suggest that NCV is not as sensitive as other measures in assessing the neurological consequences of arsenic exposure, a possible explanation of the negative result in the Alaskan study.

The pinprick method is simple, but imprecise and subjective. The pinprick test is not calibrated and the method is not standardized, although it is widely used in clinical neurology. Fairly crude categories were used in assessing pinprick score, for instance, normal, end of finger, whole finger, below wrist or below elbow. Related measures such as the vibrothesiometer (Otto *et al.* 2006) (this issue) provide a more quantitative measure of sensory (vibration) threshold. The vibrothesiometer yields a continuous measure derived by the ascending method of limits, a well-established psychophysical procedure. However, both methods of assessing sensory thresholds ultimately reduce to subjective judgments. Despite these limitations, both methods provide evidence that arsenic exposure impairs somatosensory function in humans at levels not previously appreciated.

CONCLUSIONS

NRC (1999) concluded that arsenic in drinking water does not impair neurological function at concentrations below 1,000 μg/l. This study demonstrates that arsenic alters pain thresholds at well-water concentrations at least as low as 400 μg/l. Furthermore the results show that a small increase in drinking water arsenic (70–160 μg/l) is associated with a 50% increase in pinprick score. Although further research is needed to clarify the precise threshold for neurological effects, neurosensory measures appear to be a useful non-cancer endpoint for assessing the health effects of arsenic in drinking water. Finally, this study provides the first evidence that chronic exposure to arsenic in drinking water is associated with elevated pain thresholds.

DISCLAIMER

Although this document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication, approval does not signify that the contents reflect the views or policies of the agency.

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