Neurosensory effects of chronic exposure to arsenic via drinking water in Inner Mongolia: II. Vibrotactile and visual function

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ABSTRACT

This study was designed to assess the effects of exposure to arsenic in drinking water on visual and vibrotactile function in residents of the Bamen region of Inner Mongolia, China. Arsenic was measured by hydride generation atomic fluorescence. 321 participants were divided into three exposure groups– low (non-detectable-20), medium (100-300) and high (400-700 μg /l) arsenic in drinking water (AsW). Three visual tests were administered: acuity, contrast sensitivity and color discrimination (Lanthony's Desaturated 15 Hue Test). Vibration thresholds were measured with a vibrothesiometer. Vibration thresholds were significantly elevated in the high exposure group compared to other groups. Further analysis using a spline regression model suggested that the threshold for vibratory effects is between 150-170 μg /l AsW. These findings provide the first evidence that chronic exposure to arsenic in drinking water impairs vibrotactile thresholds. The results also indicate that arsenic affects neurological function well below the 1000 μg /l concentration reported by NRC (1999). No evidence of arsenic-related effects on visual function was found.

Key words | arsenic, drinking water, vibration threshold, vision

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INTRODUCTION

Peripheral neuropathy is a well-known consequence of acute arsenic poisoning (reviewed by Feldman 1999). Nerve conduction velocity (NCV) is the traditional measure of choice used to evaluate peripheral neuropathy. However Kreiss *et al.* (1983) failed to find any arsenic-related slowing of NCV in Alaskan residents exposed to levels as high as 15,000 μg/l in drinking water. These authors concluded that NCV may be an insensitive measure of arsenic toxicity, particularly if the effects are subtle and subclinical in nature. Gerr *et al.* (2000) also found no NCV effects in a population exposed to arsenic in dust and soil from a pesticide packing plant, although significant associations of arsenic exposure were found with measures of postural sway, tremor and vibrotactile sensitivity.

Alterations in current perception threshold (CPT) have also been reported in Taiwanese villagers (Tseng 2003) living in endemic areas of black foot disease resulting from arsenic in well water. Higher thresholds were observed in longer (peroneal and median) than shorter (trigeminal) nerves and at lower (5 and 250 Hz) than higher (2000 Hz) frequencies. Previous studies (Katims *et al.* 1986) suggest that these frequencies selectively activate different types of nerves,

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that is, small unmyelinated C fibers (5 Hz), small myelinated Aδ fibers (250 Hz) and large myelinated Aβ fibers (2000 Hz).

Ma *et al.* (1995) reported optic nerve atrophy and narrowing of visual field in a preliminary study of Bamen residents exposed to arsenic in drinking water. Although visual effects of exposure to arsenic in drinking water have been observed rarely (Feldman 1999), three tests of visual function–acuity, contrast sensitivity and color discrimination–were employed in this study in an effort to extend the previous findings of Ma *et al*. These tests, particularly contrast sensitivity and color discrimination, have been shown to be sensitive to glaucoma, optic neuritis, and inherited conditions that result in optic neuropathy and optic nerve atrophy (Kupersmith *et al.* 1984; Regan 1993; Hrynchak & Spafford 1994; Sadun *et al.* 1994; Votruba 2003; Castelo-Branco *et al.* 2004).

We have shown (Li *et al.* 2006 (this issue)) that arsenic elevates pinprick thresholds which reflect perceived pain. The present study was undertaken to evaluate the effects of arsenic exposure on visual and tactile function. The results demonstrate for the first time that arsenic in drinking water is associated with elevated vibrotactile thresholds.

METHODS

Study region

This study was carried out in the Bamen farming region of Inner Mongolia. The area is situated between a ridge of ancient mountains and the Yellow River. Arsenic concentrations found in soil between the mountains and river were known from previous studies to range from 50-1800 μg/l (Ma *et al.* 1999).

Subjects

Three exposure groups were defined *a priori* as low (nondetectable-20), medium (100-300) and high (400-700 μg /l) arsenic in drinking water. Arsenic levels from 363 wells in the Bamen region were determined prior to neurosensory testing. 321 Bamen residents aged 9-64 years (mean: 35.1) who obtained drinking water from these wells were selected to participate in the study. See Li *et al.* 2006 (this issue) for further details on subject selection. The sample included 166 males and 143 females. 12 subjects were not used due to missing data. Subjects were not informed of well-water arsenic levels prior to neurosensory testing. The educational level of participants was categorized as none (n = 54), primary (grades 1-6: n = 132), middle (grades 7-9: n = 97) and high (grades 10-12: n = 17). None had attended college.

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. The protocol was also reviewed and approved by the U.S. Environmental Protection Agency. Potential risks of sensory testing were explained to subjects prior to testing.

Exposure assessment

Total arsenic in drinking water (AsW) in samples obtained from the wells of individual families or community water sources was assessed by liquid chromatography with hydride generation atomic fluorescence as described by Le and Ma (1998).

Questionnaire

A questionnaire (Li *et al.* 2006 (this issue)) was administered to obtain demographic, health and exposure information from participants. If subjects were unable to read, questions were administered by interview. Questions included age, gender, education, smoking and drinking history, exposure to pesticides, ratings of sensory function and history of central or peripheral nervous system disorders. The primary use of this questionnaire was to identify possible confounders. Items which correlated with vibrotactile and visual measures were included as control variables in statistical analyses where appropriate (see below).

Sensory assessment training

Standard Operating Procedures including detailed instructions for the administration of each test were written and

translated into Chinese. Chinese staff were trained on-site to administer tests prior to beginning the study. Each investigator was required to run 10 pilot subjects under supervision to learn procedures. Vibrotactile testing, the most difficult procedure to learn, was administered by a single investigator (YL) to minimize inter-testor variability.

Assessment of vibration threshold

Vibration thresholds were measured with a vibrothesiometer (R. Fortier Ceramics Registered, Montreal, Canada) similar to the equipment described by Frenette *et al.* (1990).

In order to obtain a reliable measure of vibration threshold, the pressure applied to the limb must be constant. A counterweight mechanism in the vibrothesiometer yields a constant value of 50 gm. Amplitude thresholds were determined for detecting a 120 Hz, sinusoidal displacement in the vertical plane of a 13 mm diameter shaft. Vibration amplitude was measured by an accelerometer mounted on the shaft. The accelerometer output was amplified and displayed in RMS voltage on a digital voltmeter. Amplification was calibrated optically so that one RMS volt equaled 0.5 microns of amplitude displacement. Lower thresholds reflect better vibration sensitivity. A detailed description of vibrothesiometer technology and methodology is available at *www.bioforgo.com*.

Prior to testing, each participant was trained so that vibratory sensation and test procedures were familiar. Training consisted of a suprathreshold, 1 second pulse and a series of near threshold pulses administered to the dorsal surface of the middle phalanx of the third digit on the dominant hand. Participants were asked to say 'now' as soon as a pulse was detected.. Training continued until the concept of 'threshold' was clearly established. Formal testing involved threshold determinations obtained using an ascending method of limits. Amplitude was gradually increased from a sub-threshold level until the subject reported detection. The initial amplitude level and rate of increase were varied between trials to avoid providing temporal cues. Nine trials were administered to each digit tested. The highest and lowest scores in each set of nine trials were discarded and the remaining seven trials in the group were averaged to obtain a measure of vibration amplitude threshold for each digit.

Vibration thresholds were measured on the dorsal surface of the middle phalanx of digit 2, and on the ventral surface of the first phalanx of digit 5, first on the dominant hand and then on the non-dominant hand. As vibration thresholds were not normally distributed, mean thresholds for individual subjects were log (base 10) transformed.

Assessment of visual function

Three measures of visual function were obtained: visual acuity, contrast sensitivity and color discrimination. Detailed descriptions of methods are provided in Hudnell *et al.* (1996). Persons who normally used glasses were instructed to wear them during vision testing. Tests were administered monocularly. A 'daylight' illuminator (florescent source with a color temperature of approximately 6500°K, color rendering index >90, intensity $= 1150$ lux) provided a luminance of approximately 70 foot-lamberts. A holder placed below the cheek bones was used to position test cards at a constant distance from the eyes for acuity (36 cm) and contrast sensitivity (46 cm) testing.

Near visual acuity (Rosenbaum Pocket Vision Screener; Grass Instrument Co., Quincy, MA).

Visual acuity was measured to determine if subjects could adequately see stimuli used in other tests. The card contains rows of symbols (numbers, E = s facing in different directions, and XO) which progress from larger at the top to smaller at the bottom. Examinees were asked to read the symbols in each row, progressing from top to bottom. The Snellen distance equivalent of the row with the smallest numbers correctly identified was recorded as the visual acuity score.

Contrast sensitivity (Sine Wave Contrast Test; Stereo Optical Co., Chicago, IL).

The contrast sensitivity test card contains a matrix (5×9) of circles filled with sinusoidal gratings. Spatial frequency (1.5, 3, 6, 12 and 18 cycles/deg) increases from top to bottom, and contrast decreases from left to right in steps of approximately 0.15 log units. The grating bars are oriented either vertically, or tilted 15 deg to the left or right. The card was placed in the holder at a distance of 18 inches (46 cm) for administration. A light meter was used to insure

appropriate luminance. As the investigator called out each circle from left to right, row by row, subjects responded by saying either vertical, left, right or blank. Children were asked to point in the direction which the top of the grating was tilted, as well as to verbalize the orientation. Subjects were encouraged to guess the orientation if they thought they could see the bars. If the orientation was misjudged, the participant was instructed to view each grating to the left until a correct response was again obtained. Testing then proceeded to the right and the last grating correctly identified was taken as the score for that spatial frequency. This procedure was repeated for each row in descending order. Higher scores reflect better contrast sensitivity.

The last correctly identified patch score for each row was converted to a contrast sensitivity value using contrast values provided by the test manufacturer. Contrast sensitivity data were analyzed using a repeated measures analysis of variance, with spatial frequency as the repeated measure (SAS, Proc GLM). Differences between exposure groups were also tested at individual spatial frequencies to examine whether there were selective losses at low or middle spatial frequencies, as seen in some forms of optic neuropathy and optic nerve atrophy (Hyvärinen *et al.* 1983; Regan 1993; Wilensky & Hawkins 2001; Ansari *et al.* 2002).

Color discrimination (Lanthony's Desaturated 15 Hue Test according to Farnsworth – Munsell (D-15d); Luneau Ophthalmology, Paris, France).

Participants were shown a rectangular box containing 16 color chips arranged in chromatic order. The investigator then removed 15 chips, leaving the first as a standard, and randomized them outside the box. Participants were then instructed to identify the chip which most closely matched the standard in hue, place it in the box next to the standard, and continue the process until all chips were in the box. Subjects were allowed to rearrange chips in the box at any time, and to take as long as needed to complete the test. The order of chip placement was recorded. Bowman's (1982) method was used to quantify color discrimination errors using the color distance values appropriate to the D-15 test (Geller 2001). This method of scoring yields two equivalent measures – a color confusion index (CCI) and a total color distance score (TCDS). Lower scores reflect better color discrimination.

Statistical analysis

Pearson correlation coefficients were calculated to explore the association of dependent and independent variables. Group differences were tested using the SAS (v.8) General Linear Model (glm) procedure. Vibration thresholds were $\log_{10}$ transformed for regression models because the raw measures were highly skewed and non-normally distributed. Using the log transformation created an approximate normal distribution of the vibration threshold measures. Linear regression analysis was performed with the $\log_{10}$ vibration threshold as the dependent variable, and arsenic exposure as the primary independent variable of interest. Age, gender, education, smoking and drinking history, and pesticide exposure were controlled in statistical models for measures where significant correlations were found. To explore the possibility of a threshold and non-linear effects, vibration threshold and arsenic concentration were plotted and smoothed using cubic median splines. The resulting curves were visually examined for changes in slope or possible thresholds at low arsenic values. Iterative regression models were run to identify points where an abrupt change in slope occurred. When a potential threshold value was identified, a linear spline-regression model using a category indicator for arsenic concentration was created, where the indicator variable was defined as follows: 0 if less than threshold value; or arsenic concentration-threshold value if above threshold value (Rothman & Greenland 1998).

RESULTS

Vibration thresholds

Table 1a shows the mean and standard deviations of vibration thresholds in the three exposure groups. Significant differences among exposure groups were observed in the fifth digit of the dominant hand and both the second and fifth digits of the non-dominant hand. Step-down tests indicated significant differences between the low and high, medium and high, but not low and medium exposure groups (Table 1b). Group differences are illustrated in Figure 1.

Significant linear associations with arsenic concentrations were also found for vibration threshold measures

Table 1a | Mean (SD) Vibration Threshold Scores for low, medium and high arsenic exposure groups, controlling for age, education and packyears (N = 283) *

Vibration Measure	Low	Medium	High	F-value	p-value
Dominant Hand, Digit 2	1.49 (0.22)	1.49 (0.36)	1.55 (0.34)	2.11	0.1238
Dominant Hand, Digit 5	1.47 (0.26)	1.43 (0.34)	1.55 (0.33)	5.54	0.0044
Non-dominant Hand, Digit 2	1.45 (0.23)	1.44 (0.32)	1.57 (0.37)	7.72	0.0005
Non-dominant Hand, Digit 5	1.47 (0.27)	1.43 (0.32)	1.54 (0.29)	3.97	0.0031

Table 1b | Contrasts of exposure groups for vibration thresholds, controlling for age and gender. F-value (p-value)*

Vibration Threshold Measure	Low vs Med.	Low vs High	Med. vs High
Dominant Hand, Digit 2	0.07 (ns)	2.25 (ns)	1.64 (ns)
Dominant Hand, Digit 5	0.73 (ns)	4.57 (.03)	9.38 (.002)
Non-dominant Hand, Digit 2	0.05 (ns)	8.62 (.004)	10.55 (.001)
Non-dominant Hand, Digit 5	0.59 (ns)	3.67 (.06)	7.57 (.006)

*Vibration threshold scores were $\log_{10}$-transformed to normalize distributions. Subjects with scores > 999 were excluded (N = 2)

except for the second digit of the dominant hand (Table 2). Trends were not significant, however, when analysis was restricted to the low arsenic category, consistent with results in Table 1b, indicating the possibility of an exposure effect threshold. Approximate threshold values where the trend became positive ranged from 150 to 170 μg/l. Above these values, a 100 μg/l increase in arsenic was associated with approximately a 1.1 unit increase in vibration threshold. The predicted values from the regression spline and the observed log vibration threshold measures are shown in Figure 2 for the index finger of the non-dominant hand.

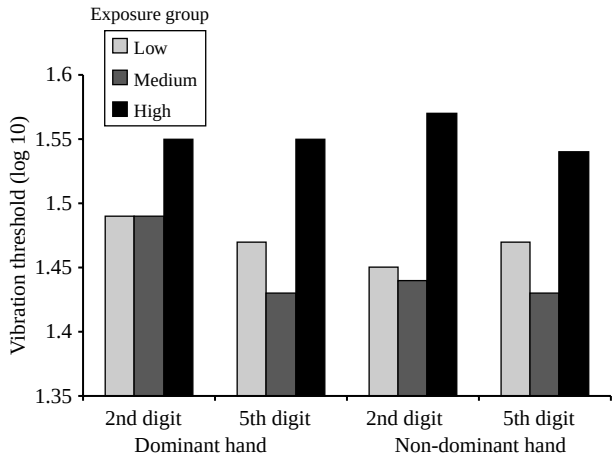

Figure 1 | Mean vibration threshold scores for exposure groups in the four fingers tested. Vibration thresholds are expressed in microns of amplitude displacement. Y-axis threshold values were log-transformed to normalize the distribution.

Visual assessment

Comparison of left and right eye scores indicated no significant differences for acuity, contrast sensitivity or color discrimination measures. Therefore scores for the two eyes were averaged and ANOVA group comparisons were performed for all visual measures with eyes combined. Group means and standard deviations for visual measures with the two eyes combined are shown in Table 3. None of the group comparisons of visual measures was significantly associated with arsenic well water concentration. There was no effect of arsenic exposure on overall contrast sensitivity or at any of the individual spatial frequencies tested as shown in Figure 3. Contrast sensitivity decreased significantly with increasing age ($p < 0.0001$). The group difference for color discrimination was also marginally significant ($p = .0805$) with stepdown

Table 2 | Linear regression analysis of vibration thresholds

	Non-dominant Hand, Digit 5	Non-dominant Hand, Digit 2	Dominant Hand, Digit 5	Dominant Hand, Digit 2
	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)
Arsenic (below threshold)	−0.51 (p = 0.078)	−0.31 (p = 0.37)	−0.55 (p = 0.07)	−0.25 (p = 0.38)
Arsenic (above threshold)	0.40 (p < 0.0005)	0.36 (p = 0.002)	0.40 (p = 0.001)	0.20 (p = 0.07)
Age	0.0068 (p < 0.0005)	0.007 (p < 0.0005)	0.007 (p < 0.0005)	0.008 (p < 0.0005)
Gender	0.034 (p = 0.39)	0.034 (p = 0.41)	−0.008 (p = 0.84)	−0.009 (p = 0.81)
Education*	0.02 (p = 0.29)	−0.013 (p = 0.55)	−0.027 (p = 0.237)	−0.01 (p = 0.63)
Pesticide Exposure	0.018 (p = 0.68)	−0.058 (p = 0.20)	−0.036 (p = 0.43)	−0.0996 (p = 0.02)
Approximate threshold value	170 μg/l	150 μg/l	170 μg/l	170 μg/l

Variable	df	Parameter Est.	SE	t	p
Intercept	1	1.266	0.089	14.22	<.0001
Arsenic	1	0.224	0.075	2.98	.003
Age	1	0.007	0.002	4.41	<.0001
Gender	1	0.024	0.042	0.59	ns
Education	1	−0.013	0.023	−.057	ns
Pesticide Exposure	1	−01226	0.083	−1.49	ns

*coded 1-5, 1 = None; 2 = primary school; 3 = middle school; 4 = high school

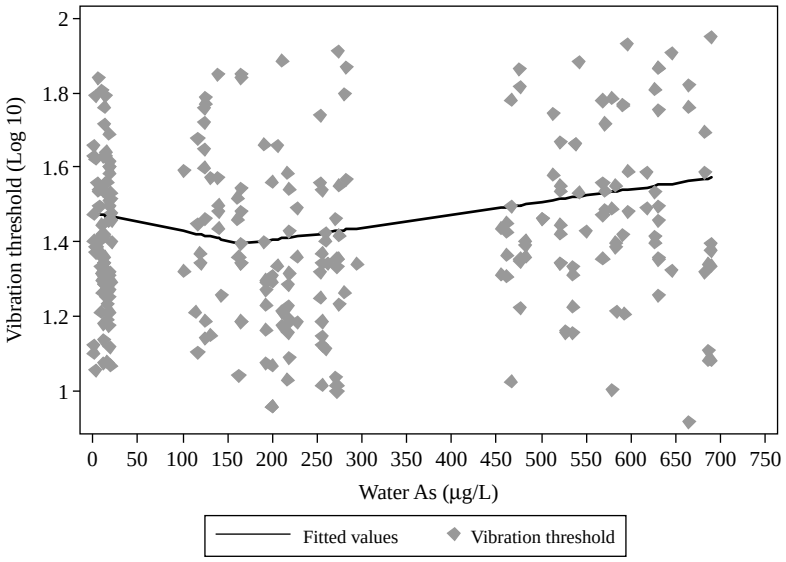

Figure 2 | Distribution of log-transformed vibration thresholds with linear function derived from spline regression model for index finger of non-dominant hand.

tests indicating that the difference between low and medium exposure groups was p = .0249 for the total color distance and color confusion index scores. However, this finding is contrary to prediction as the highest score, that is the poorest color discrimination, was found in the low exposure group.

DISCUSSION

Results of the present study indicate that effects on vibration threshold of chronic exposure to arsenic in drinking water occur well below the 1000 μg/l threshold for neurological impairment specified by the NRC (1999). Group comparisons revealed significant effects on vibration thresholds in the high exposure group (400-700 μg/l) and linear regression analysis suggests an apparent threshold between 150 and 170 μg/l.. This result closely parallels pinprick data reported elsewhere (Li *et al.* 2006 (this issue)). A 50% reduction in pinprick score was associated with a predicted 70-160 μg/l increase in arsenic concentration.

Gerr *et al.* (2000) have also reported reduced vibrotactile sensitivity in a population chronically exposed to arsenic dust

Table 3 | Mean (SD) Visual Contrast Sensitivity (VCS) and color discrimination scores for low, medium and high exposure groups, controlling for age and gender*

Visual Measure	Low	Medium	High	F/p-value
VCS (1.5 cpd)	60.4 (20.0)	61.4 (23.2)	57.0 (19.8)	1.46/p = .2336
VCS (3 cpd)	97.6 (27.2)	95.5 (32.6)	98.9 (29.3)	0.74/p = .4766
VCS (6 cpd)	112.1 (35.7)	106.9 (36.3)	110.2 (37.1)	1.47/p = .2317
VCS (12 cpd)	59.8 (27.3)	59.1 (28.1)	58.8 (28.3)	0.49/p = .6107
VCS (18 cpd)	26.2 (17.1)	27.8 (15.9)	23.0 (14.3)	2.56/p = .0795
Color Confusion Index	1.54 (0.39)	1.40 (0.40)	1.47 (0.46)	2.54/p = .0805

*VCS = mean visual contrast sensitivity for both eyes averaged for L and R eyes
CCI = Color Confusion Index averaged for L and R eyes
Subjects excluded if acuity <20/70 for either eye

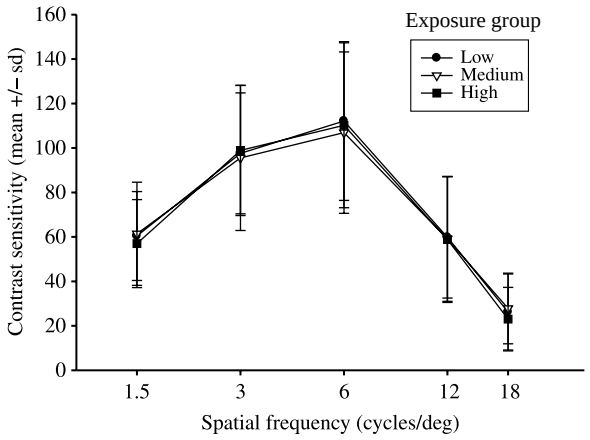

Figure 3 | Mean contrast sensitivity scores, averaged for both eyes, in low, medium and high exposure groups at the five spatial frequencies tested.

from a pesticide packaging plant. Direct comparison of results is not possible as the exposure medium (soil vs. water) is different. Gerr *et al.* also found increased tremor and postural sway in the exposed vs. control group, but no difference in nerve conduction velocity measures. Alteration in postural sway attributed to arsenic exposure (in air) has also been observed by Kilburn (1997) in residents living near a chemical plant that manufactured arsenic trioxide used as an agricultural defoliant and arsenic acid used to treat wood. Interpretation of the latter report is complicated by several factors including: (1) many other toxic chemicals were manufactured by the plant; (2) no body burden measures were obtained; and (3) all participants were plaintiffs in a lawsuit against the plant.

Effects on somatosensory function were also indicated by elevations in current perception thresholds (CPTs) reported by Tseng (2003) in Taiwanese villagers chronically exposed to arsenic in drinking water. Three nerves were tested: trigeminal, median and peroneal. Higher CPT thresholds were found in arsenic-exposed villagers than controls. The probability of abnormal values was higher in nerves which mediate pain (small, unmyelinated C fibers) and vibrotactile sensitivity (small myelinated Aδ fibers) than in large myelinated fibers which mediate touch and pressure.

Comparison of somesthetic measures

Somesthetic sensitivity was measured by two methods in the present study: vibrothesiometer and pin-prick (see Li *et al.* (this issue)). Significant group differences were observed in both measures, that is, pinprick (pain) and vibration thresholds were increased in the high exposure group relative to the low and middle groups, but no difference was found between low and middle groups for either method. Comparison of results obtained with the two measures raises a number of questions. Is one method more sensitive to arsenic exposure than the other? Do the two methods measure the same phenomena, in other words, are different receptors and/or fiber pathways involved in the two types of somesthetic sensation?

Sensitivity of measures

The vibrothesiometer yields a continuous, quantitative measure of tactile sensitivity derived by the ascending method of limits, a well-established psychophysical procedure. The pin-prick method is simpler, but less precise and more subjective than the vibrothesiometer. The pin-prick 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 pin-prick sensitivity, for instance, normal, end of finger, whole finger, below wrist or below elbow. A distinct advantage of the continuous (vibrotactile) vs. categorical (pin-prick) measure is the ability to perform linear regression analyses. In particular, the spline-regression model indicated an apparent vibration effect threshold between 150 and 170 μg/l.

Neuronal mechanisms

The sensory receptor considered to mediate vibratory perception (250-300 Hz) is the Pacinian corpuscle, while pin-prick sensation is associated with other receptor cells including Meissner corpuscles (touch) and free nerve endings (pain) (Sinclair 1981; Shepherd 1994). Free terminals are located in the superficial epidermis, Meissner corpuscles in the dermal papillae, and Pacinian corpuscles are located in the dermis or subcutaneous tissue. The size and myelin density of fibers connected to the different types of receptors also vary considerably: least with fibers leading to free endings (pain perception) and most with fibers leading to Pacinian corpuscles (vibrotactile perception). In some cases, small diameter fibers are more susceptible

than large diameter fibers to damage from exposure to toxic chemicals (Feldman 1999).

Lack of visual effects

Ma *et al.* (1995) reported optic nerve atrophy and narrowing of visual field in a preliminary study of Bamen residents exposed to arsenic in drinking water. Three tests of visual function, acuity, contrast sensitivity and color discrimination, were employed in this study to assess the visual effects of arsenic exposure. In the present study, there were no consistent arsenic-related effects on measures of visual function. Further evaluation of optic nerve function and visual fields may have shown effects. However the lack of effect on contrast sensitivity suggests that there is no effect on visual fields, since visual field loss is associated with reduced contrast sensitivity in patients with optic nerve damage (Wilensky & Hawkins 2001).

Test subjects made many errors on the Lanthony D-15 test of color discrimination. Color confusion index (CCI) scores were high, indicating poor performance in all three exposure groups (Table 3). For example, the mean CCI (1.54) in the low exposure group was in the 90th percentile of non-exposed subjects reported by Iregren *et al.* (2002). It is not clear whether this poor performance was due to effects of other environmental variables, color vision deficits present in the population at large, problems with the administration of the test or participants' understanding of instructions.

Visual tests have been employed only rarely in clinical or field studies of arsenic exposure. Visual symptoms such as the loss of blink reflex have been reported occasionally in cases of arsenic poisoning (Feldman 1999). Not surprisingly, Fincher and Koerker (1987) reported the absence of visual evoked potentials in a comatose patient following acute arsenic poisoning. Visual function has been assessed systematically in only one other arsenic field study (Kilburn 1997). Lanthony D-15 color discrimination and blink reflex tests were used in a population exposed to arsenic in the air (vide supra). Slower blink reflex latency was found in arsenic-exposed subjects, but no effect on color discrimination was reported. The present results are consistent with the finding of Kilburn, suggesting that arsenic exposure does not impair higher-order visual function.

CONCLUSIONS

(1) Results of this study provide the first evidence that chronic exposure to arsenic in drinking water is associated with elevated vibration thresholds.
(2) Group comparisons indicate that arsenic alters vibration thresholds at concentrations well under the threshold for neurological impairment specified by NRC (1999). Specifically, the spline-regression model suggests a threshold for vibration effects between 150 and 170 μg/l.
(3) (3) Finally, no evidence of arsenic-related effects on visual function was found.

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