Scand J Work Environ Health 1985;11(4):265-269

<https://doi.org/10.5271/sjweh.2227>

Issue date: Aug 1985

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This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/2997912

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Arsenic exposure to smelter workers

Clinical and neurophysiological studies

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BLOM S, LAGERKVIST B, LINDERHOLM H. Arsenic exposure to smelter workers: Clinical and neurophysiological studies. *Scand J Work Environ Health* 11 (1985) 265–269. Forty-seven copper smelter workers, exposed to airborne arsenic for 8–40 years, were examined clinically with electromyography, and the motor and sensory conduction velocities in their arms and legs were determined. Fifty age-matched industrial workers not exposed to arsenic formed a reference group. The level of arsenic in the air at the smelter was estimated to be below 500 $\mu\text{g}/\text{m}^3$ before 1975 and approximately 50 $\mu\text{g}/\text{m}^3$ thereafter. Urine analyses of arsenic showed a mean value of 71 $\mu\text{g}/\text{l}$ (1 $\mu\text{mol}/\text{l}$) in the exposed group; this value is lower than that found in earlier studies reporting clinically detectable neuropathy. Only minor neurological and electromyographic abnormalities were found. A slightly reduced nerve conduction velocity in two or more peripheral nerves was more common among the arsenic workers than the referents, and a statistically significant correlation between cumulative exposure to arsenic and reduced nerve conduction velocity in three peripheral motor nerves was found. This occurrence was interpreted as a sign of slight subclinical neuropathy. In conclusion the risk of clinically significant neuropathy is small when exposure is kept below 50 $\mu\text{g}/\text{m}^3$ in workroom air. The subclinical findings may be of interest in relation to the prevention of early adverse health effects from arsenic exposure.

Key terms: arsenic, electromyopathy, nerve conduction velocities, occupational exposure, subclinical neuropathy.

Inorganic arsenic (As) is known to have adverse effects on the human nervous system after both short-term and long-term exposure. There are many reports on peripheral nervous disturbances caused by arsenic intoxication. [See the reviews of Landrigan (8), Nordberg et al (12), Pershagen & Vahter (14), and the World Health Organization (23).] But there are fewer studies dealing with effects after long-term occupational exposure to inorganic arsenic (3, 4). According to Landrigan (8), approximately 1.5 million workers in the United States are exposed to arsenic, primarily by inhalation of the trivalent (III) form.

Studies of dose-response relationships between inorganic arsenic and peripheral neurological damage are scarce. Feldman et al (3) found a high prevalence of clinical and subclinical neuropathy in men with high urinary levels of arsenic (250 $\mu\text{g}/\text{l}$ or 3 $\mu\text{mol}/\text{l}$). The damage to the peripheral neuron was mainly intracellular, causing a distal axonopathy. A segmental demyelination may occur as a secondary phenomenon (1, 4). Sensory nerves were affected before motor nerves, and neurons with long axons before those with short axons. Therefore, clinical

symptoms were usually first seen in distal parts of the extremities. This type of neuropathy is also seen in other genetic and acquired neuropathies, ie, in connection with exposure to lead, vibration, and alcohol (16, 17). A slow recovery has been seen after the cessation of arsenic exposure (4, 5, 9, 11).

The aim of the present study, which is part of a larger one (6), was to examine peripheral nervous function in workers from a copper and lead smelter in northern Sweden. The workers had a long exposure to arsenic dust, mainly arsenic(III) oxide.

Subjects

At the time of the study (1982), 62 men at the copper smelter, Rönnskärverken, had been exposed to arsenic in the air for 8–40 (mean 23) years. Nine declined to take part in the investigation, and six were excluded because of chronic illness unrelated to arsenic, partly involving the nervous or vascular systems (two had diabetes, one arthritis, one chronic kidney disease, one familial polyneuropathy, and one a high intake of alcohol). The remaining 47 individuals (mean age 53.6 years) formed the group exposed to arsenic, referred to as arsenic workers. They had also been exposed to sulfur dioxide and heavy metals such as a gold, silver, copper, and lead. This exposure was small, except for three men who had a long-term exposure to lead. Lead exposure was checked through an examination of the blood lead levels available from the medical records of the fac-

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Table 1. Age distribution of the arsenic workers and referents.

Age (years)	Arsenic workers (N = 47)	Referents (N = 50)
36—39	3	2
40—44	3	6
45—49	6	11
50—54	9	8
55—59	15	14
60—64	11	7
65	—	2

tory. They were low (mean 160 $\mu\text{g/l}$ or 0.8 $\mu\text{mol/l}$) except for the three men with known exposure to lead. The arsenic content of the air to which they had been exposed had been around and below the accepted Swedish occupational standard, which from the late 1940s to 1975 was 500 $\mu\text{g/m}^3$ and thereafter 50 $\mu\text{g/m}^3$.

To get an unexposed reference group, we sent a questionnaire to all the men in the age range 41—65 years at a mechanical industrial enterprise in the same county. One hundred and ninety-eight of the 262 men (76 %) responded. The 50 referents were selected from among these. They were the best matches to the arsenic workers with respect to age and use of tobacco and vibrating handtools. Subjects with diabetes were rejected. The referents' mean age was 52.2 years. (For the age distribution, see table 1.)

The "nonparticipant group," 64 men not having answered the questionnaire, had a mean age of 52.8 years. Their declarations of health and medical records at the company were studied, and the only difference found was that one-third of these workers had suffered from acute back pain.

Methods

The questionnaire identified the following factors impairing peripheral circulation or nerve function: trauma, diabetes, peripheral vascular disease, drug use, and environmental factors such as vibrating handtools and exposure to heavy metals or solvents.

All subjects taking part in the whole investigation had a physical examination, carried out by the same physician (BL). Finger systolic pressures during cold provocation were measured and have been described elsewhere (7). Urine samples were collected for the analysis of arsenic. With few exceptions, the neurological examinations were carried out by the same neurologist (SB). Gross motor strength in the extremities, tendon reflexes, and sensitivity to touch, pinprick and vibration (tuning fork, 128 Hz) were tested.

Electromyography (EMG) was performed bilaterally in the calves and feet of all the individuals with concentric needle electrodes and a Medelec MS 92 electromyograph. The results were graded according to principles used in routine clinical work (10).

Conduction velocity measurements were made on a Disa 1500 electromyograph. The room temperature was kept at 22—25°C, and the measurements were made at a skin temperature of approximately 32°C, the skin being warmed in water if necessary. Motor conduction velocities were measured in distal segments with surface electrodes both for stimulation and recording (ulnar nerve bilaterally elbow-wrist, peroneal and tibial nerves bilaterally knee-ankle). Sensory conduction velocities were measured in distal segments (ulnar nerve bilaterally wrist-finger, sural nerve bilaterally calf-foot), action potentials being averaged 24—32 times.

The determinations of inorganic arsenic and its methylated metabolites in urine were made with atomic absorption spectrometry after hydride generation. A crude estimation of the cumulative arsenic exposure was made on the assumption of a mean absorption of 25 mg per year from 1975 on and 250 mg per year before that (7).

Nerve conduction velocities were calculated for each individual as the mean value of the right and left extremity. The differences between the means were tested with a two-tailed Student's *t*-test. When the number of values was less than five, Fisher's exact probability test was used. Simple regression coefficients between the variables were calculated with the method of least squares (2, 18). Multivariate data analysis (MVDA) was performed with the partial least squares method recently developed by Wold (22). The response variables (*Y*) tested were nerve conduction velocity in five peripheral nerves, decrease of finger systolic pressure during cold provocation, and Raynaud's phenomenon. The predictor variables (*X*) were smoking habits, use of vibrating handtools, age, arsenic in urine, and arsenic exposure. We use the terms response and predictor variables in accordance with the custom of MVDA to emphasize the difference in philosophy to traditional multiple regression. The predictor variables need not be independent in MVDA, as they must in multiple regression.

Results

Clinical examination

Ten arsenic workers were found to have a perforation of the nasal septum, acquired long ago. Forty of them reported occasional arsenic dermatitis of the face. Pigment changes and hyperkeratosis of the skin, considered to be major manifestations of chronic arsenic poisoning (21), were found to the same extent on both the arsenic workers and the referents. One arsenic worker had a malignant skin tumor. Alcohol consumption was similar in both groups.

Raynaud's phenomenon and low blood pressure in the fingers during cold provocation were found more often in the arsenic workers than in the referents (7).

The neurological history and clinical examination did not reveal any significant differences between the arsenic workers and the referents. It should be noted that 16 arsenic workers and 24 referents reported that they had suffered from lumbago and/or sciatica. One arsenic worker complained of burning paresthesia around the wrists.

Absorption of arsenic

From the exposure level in workroom air and the concentration of arsenic in urine, the daily absorption of inorganic airborne arsenic was estimated to be below 300 µg (7). The mean urinary level was 71 µg/l (1 µmol/l) in the arsenic workers and 7 µg/l (0.1 µmol/l) in the referents. Determinations of total urinary arsenic were made at the copper smelter about five years before the study. The mean value at that time was 425 (range 40–2 000) µg/l or 6 µmol/l. A correlation was found between the earlier determinations in individual subjects and those made by us ($r = 0.7$, $p < 0.01$). No statistically significant correlation was found between arsenic concentration in urine and nerve conduction velocity in single nerves. Correction for osmolality of the urine did not alter the results.

Neurophysiological examination

Electromyography. The electromyographic examination showed signs of denervation in the calves in 15 arsenic workers and 14 referents (table 2). Four of these arsenic workers and six of these referents were above 60 years of age. Some of the denervated subjects had suffered from sciatica. One of the arsenic workers was known to have used alcohol in excess.

Nerve conduction velocities. The arsenic workers had lower mean conduction velocities than the referents in all the examined nerves, but the differences between the individual nerves of the two groups were not statistically significant (table 3). However statistically significant differences between the groups were obtained when all the examined nerves were included in the statistical evaluation performed as follows:

Lower limits of nerve conduction velocities were obtained from the reference group, by the calculation of mean values from all except four men with moderate denervation in the electromyographic examination. The lower limits (mean -2 SD) were 36–38 m/s in the different nerves of the legs and 41–47 m/s in the nerves of the arms.

Seven arsenic workers (15 %) and two referents (4 %) had nerve conduction velocities below the lower limits of the reference group in two or more nerves. They were classified as having subclinical neuropathy. Among the referents earlier sciatica may explain this finding. One of the arsenic workers had long-term exposure to lead and another high alcohol consumption which could explain the low conduction velocities. The difference between the arsenic workers and the referents was statistically significant and remained so when the four men with other possible causes were eliminated ($p = 0.03$).

Effects of arsenic exposure and other factors on the nerve conduction velocity

The partial least squares analysis of the combined group of arsenic workers and referents revealed a statistically significant correlation between reduced nerve conduction velocity in the ulnar motor ($p < 0.05$), tibial ($p < 0.05$), and peroneal nerves ($p < 0.001$), as well as a decrease in finger systolic pressure during cold provocation ($p < 0.05$) [response variables (Y)] and exposure to arsenic [predictor variable (X)]. Age also entered the correlation but less so than the exposure to arsenic (loadings 0.49 versus 0.58). Smoking habits, or use of vibrating handtools had negligible loadings in the correlation.

Table 2. Electromyographic findings in the arsenic workers and referents.

Finding	Arsenic workers ^a (N = 47)	Referents ^a (N = 50)
Normal	32	36
Slight denervation	11 (7)	10 (6)
Moderate denervation	4 (2)	4 (2)

^a Figures in parentheses indicate the number of individuals suffering from lumbago or sciatica.

Table 3. Nerve conduction velocities in peripheral nerves of the arsenic workers and referents.

Nerve, type of nerve	Arsenic workers			Referents			Difference ^a
	Number	Conduction velocities (m/s)		Number	Conduction velocities (m/s)		
		Mean	SD		Mean	SD	
Ulnar, motor	47	54.26	4.81	50	55.30	4.21	-1.04
Ulnar, sensory	47	47.48	3.99	50	48.12	3.91	-0.64
Peroneal, motor	47	44.28	5.32	50	45.65	4.13	-1.37
Tibial, motor	46	42.38	5.13	40	44.31	4.57	-1.93
Sural, sensory	45	43.68	5.62	48	44.57	4.70	-0.89

^a Difference = mean conduction velocity of the arsenic workers minus that of the referents.

As the referents had no exposure to arsenic, the correlation found between reduced nerve conduction velocity and exposure to arsenic sustained the result of a statistically significant difference between the arsenic workers and the referents.

Discussion

In this study a group of smelter workers with long-term exposure to inorganic airborne arsenic was found to have lower mean conduction velocities in five peripheral nerves than age-matched referents. When these five variables were included as response variables in the multivariate data analysis, the correlation to cumulative arsenic exposure was statistically significant. Fifteen percent of the arsenic workers and 4 % of the referents had velocities below the lower limits of the reference group in two or more peripheral nerves. This difference was statistically significant and remained so even when subjects with other possible causes of neuropathy were eliminated.

In other studies (1, 4) sensory nerves have been reported to be more sensitive to arsenic than motor nerves. In the present study this was not the case, and the reason is unclear. The prevalence of neurological symptoms, clinically detectable neuropathies, and electromyographic abnormalities were the same in both groups. A relatively high proportion of the arsenic workers and the referents showed slight to moderate, mostly unilateral signs of denervation in the electromyographic examination (table 2). A possible explanation for this finding is sciatica, often affecting individuals in heavy industrial work. Slight signs of denervation above the age of 60 years may, furthermore, be explained by a "physiological" loss of motor neurons during normal ageing.

The arsenic workers had a limited exposure to other metals, such as copper, selenium, antimony and lead, and to sulfur dioxide. The referents did not have a similar exposure except for a low exposure to lead and solvents. There is no evidence that the metals mentioned, except lead, cause peripheral neuropathy. As the lead exposure of the arsenic workers was low and as the alcohol consumption was similar in both groups, these factors were probably not responsible for the difference found. In a previous study on 58 lead workers and referents from the same smeltery, no difference in nerve conduction velocities was found between the groups (13). In a recent study of smelter workers with a concomitant exposure to lead and arsenic, no overt peripheral neuropathy was found. Nerve conduction velocity measurements detected slight changes in sensory and, after long-term exposure, motor nerve conduction velocity (19). These findings do not contradict ours.

In this study we found fewer neurological abnormalities in connection with arsenic exposure than reported in other studies (3, 4). Feldman et al (3) reported a statistically significant relationship between

arsenic load and clinical or subclinical evidence of polyneuropathy. Workers at a site with a high arsenic level had the highest urinary arsenic values (250 $\mu\text{g/l}$ or 3.3 $\mu\text{mol/l}$) and an increased prevalence of neurological abnormalities. Atomic absorption spectrometry was used, probably without hydride generation, and thus inorganic arsenic only was determined and not its methylated metabolites. In the study by Heyman et al (4), 41 cases of peripheral neuropathy caused by arsenic intoxication were described. The majority of the patients with clinical evidence of arsenic intoxication were said to have urinary values of total arsenic greater than 100 μg (1.3 μmol)/24 h of urinary excretion. Our referents were better matched to the arsenic workers with regard to age than in the other studies discussed.

Inhaled inorganic arsenic is mainly metabolized to methylated species (20). We have determined inorganic arsenic and its methylated compounds. Such values are lower than total urinary arsenic, which includes dietary arsenic. Atomic absorption spectrometry of inorganic arsenic without hydride generation gives the lowest values. Therefore, comparisons between different studies are difficult. Other authors have, however, reported a significant correlation between arsenic levels in urine and the concentration of inorganic arsenic in the air (15, 20).

If arsenic levels in urine are taken as an indicator of current exposure, our workers appear to have had a lower exposure than those in previous studies, although the methods of analysis were not directly comparable. In our study the daily absorption of arsenic was estimated to be less than 300 μg . This estimate was confirmed by the urinary analysis (7). The arsenic workers had been exposed to arsenic for a long time (mean 23 years). Before 1975, when the occupational exposure limit was 10 times higher, urinary arsenic must have been higher, probably of the same magnitude as that which caused neuropathy in the Feldman et al study (3). The urinary levels of arsenic measured earlier at the factory confirm this assumption. It appears that the present air level of arsenic (50 $\mu\text{g/m}^3$) is low enough not to cause clinical neuropathies. The subclinical neurological disturbances (low conduction velocities) found could be due to the previous higher exposure to arsenic. Clinical experience suggests that arsenic neuropathy is, at least partly, reversible (1, 4). It is not known if this is the case in long-term continuous exposure.

In conclusion, we found a slightly increased prevalence of subclinical neuropathy manifested as low conduction velocities in peripheral nerves in workers with long-term exposure to airborne arsenic. The prevalence of clinical symptoms and signs and electromyographic abnormalities was, however, approximately the same in both the arsenic workers and their age-matched referents. The exposure levels were lower than in earlier studies reporting both clinical and subclinical neuropathy.

Acknowledgments

Valuable advice and assistance was given by Prof G Nordberg, Department of Environmental Medicine, University of Umeå, and Dr P Thorulf and analyst U Westerlund, MSc, at Rönnskärswerken, Skelleftehamn. Technical assistance was provided by Mr A Bohlin and Ms R-M Persson. Statistical assistance was given by Mr S Wold, Department of Organic Chemistry, University of Umeå.

Economic support was provided by the University of Umeå and the Swedish Coal Health Environment Project.

The study was approved by the research-ethical committee, Umeå University.

References

1. Chhuttani PN, Chopra JS. Arsenic poisoning. In: Vinken PJ, Bruyn GW, ed. *Handbook of clinical neurology*. Volume 36: 1. North Holland Publishing Co, Amsterdam 1979, pp 199–216.
2. Colton T. *Statistics in medicine*. Little, Brown and Company, Boston, MA 1974.
3. Feldman RG, Niles CA, Kelly-Hayes M, Sax DS, Dixon WJ, Thompson DJ, Landau E. Peripheral neuropathy in arsenic smelter workers. *Neurology* 29 (1979) 939–944.
4. Heyman A, Pfeiffer JB, Willett RW, Taylor HM. Peripheral neuropathy caused by arsenical intoxication: A study of 41 cases with observations on the effects of BAL (2,3 dimercapto-propanol). *New Engl J Med* 254 (1956) 401–409.
5. Jenkins RB. Inorganic arsenic and the nervous system. *Brain* 89 (1966) 479–498.
6. Lagerkvist B, Linderholm H, Blom S, Thorulf P, Nordberg G. Systemeffekter av arsenik (1983). The Coal Health Environment Project, The Swedish State Power Board. Vällingby, Sweden 1983. (Teknisk rapport nr 78). (Summary in English).
7. Lagerkvist B, Linderholm H, Nordberg GF. Vasospastic tendency and Raynaud's phenomenon in smelter workers exposed to arsenic. *Environ Res* (in press).
8. Landrigan PJ. Arsenic — State of the art. *Am J Ind Med* 2 (1981) 5–14.
9. LeQuesne PM, McLeod JG. Peripheral neuropathy following a single exposure to arsenic. *J Neurol Sci* 32 (1977) 437–451.
10. Mayo Clinic and Mayo Foundation. *Clinical examinations in neurology*. Saunders W, Philadelphia, PA 1971.
11. Murphy MJ, Lyon IW, Taylor JW. Subacute arsenic neuropathy: Clinical and electrophysiological observations. *J Neurol Neurosurg Psychiatry* 44 (1981) 896–900.
12. Nordberg G, Pershagen G, Lauwerys R. Inorganic arsenic — Toxicological and epidemiological aspects: Report to the Commission of European Communities. Department of Community Health and Environmental Medicine, Odense University, Odense 1979.
13. Persson HE, Knave B, Goldberg JM, Johansson B, Holmqvist J. Långvarig exposition för bly: III En neurologisk och neurofysiologisk undersökning av personal vid Rönnskärswerken, Boliden AB. Arbetskyddsverket, Stockholm 1979 (Arbete och hälsa 1). (Summary in English).
14. Pershagen G, Vahter M. Arsenic, a toxicological and epidemiological appraisal. The National (Swedish) Environment Protection Board, Stockholm 1979.
15. Pinto SS, Enterline PE, Hendersen V, Varner MO. Mortality experience in relation to a measured arsenic trioxide exposure. *Environ Health Perspect* 19 (1977) 127–130.
16. Schaumburg HH, Spencer PS. Toxic neuropathies. *Neurology* 29 (1979) 429–431.
17. Seppäläinen AM. Applications of neurophysiological methods in occupational medicine: A review. *Scand J Work Environ Health* 1 (1975) 1–14.
18. Siegel S. *Nonparametric statistics*. McGraw-Hill Book Co Inc, New York, NY 1956.
19. Singer R. Nerve conduction velocity assessment of copper smelter employees. In: *Health hazards among copper smelter workers: A report to the National Institute of Environmental Health Sciences*. National Institute of Environmental Health Sciences, North Carolina 1982, pp 127–142.
20. Smith TJ, Crecelius EA, Reading JC. Airborne arsenic exposure and excretion of methylated arsenic compounds. *Environ Health Perspect* 19 (1977) 89–93.
21. Tseng WP, Chu HM, How SW, Fong JM, Lin CS, Yeh S. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J Natl Cancer Inst* 40 (1968) 453–463.
22. Wold H. Soft modeling: The basic design and some exclusions. In: Jöreskog KG, Wold H, ed. *Systems under indirect observation*. North-Holland, Amsterdam 1982, pp 1–54 (Part II).
23. World Health Organization. *Arsenic*. Geneva 1981. (Environmental health criteria 18).

Received for publication: 12 October 1984