

Environmental Pollution and Nonmalignant Chronic Effects of Arsenic Exposure

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Abstract

A series of studies concerning exposure to arsenic and some novel chronic health effects namely diabetes mellitus and hypertension. The well-known skin manifestations of arsenic ingestion was also found to occur as a result of arsenic exposure through drinking water.

Two case-control studies on diabetes mellitus and exposure to arsenic included individuals employed at a copper smelting industry and in art glassworks in Sweden. Although the number of smelter workers involved was small, a significant exposure-response trend was obtained ($p = 0.03$). The assessment of arsenic exposure among 888 glass workers was less detailed, nonetheless it revealed an approximately doubled risk (MH-OR = 2.1; 95% confidence interval 1.2-3.7) for the workers with occupational titles that suggested exposure. Overall, the results of these studies provide evidence that occupational arsenic exposure may play a role in the development of diabetes mellitus. Four cross-sectional studies were carried out in Bangladesh, where a fairly large part of the population is exposed to inorganic arsenic in drinking water. In the first study, the prevalence of diabetes mellitus among subjects with keratosis ($n = 163$) was compared with unexposed subjects ($n = 854$); keratosis was considered to be a definite sign of exposure. A dose-response relationship was found between categories of time-weighted arsenic exposure and the prevalence of diabetes mellitus ($p < 0.001$), and the crude overall prevalence ratio amounted to 4.4. Despite the lack of detailed individual exposure data and information on potential confounders other than age, sex, and body mass index (BMI), the association seems strong enough to support a causal relationship, because the adjusted overall prevalence ratio was 5.9 (95% confidence interval 2.9-11.6).

One of the other studies performed in Bangladesh (1481 exposed individuals, 430 exhibiting keratosis) showed a somewhat higher prevalence rate of skin lesions in males (31%) than females (26%) due to chronic arsenic toxicity. The crude overall prevalence was 29% in the studied villages, and there was a distinct dose-response relationship between arsenic concentrations in drinking water and skin lesions ($p < 0.01$). A clear dose-response relationship was also observed between arsenic exposure and glucosuria for subjects both with and without skin lesions ($p < 0.01$). However, the appearance of dermatological signs of chronic arsenic toxicity proved to be a poor marker in this respect, because glucosuria also occurred in the absence of skin lesions.

A third Bangladeshi study indicated a significantly increased risk of hypertension in connection with exposure to inorganic arsenic in drinking water (1481 exposed and 114 unexposed subjects). The overall crude prevalence ratio of hypertension amounted to 1.7, and the adjusted (for age, sex, and BMI) ratio was 1.9 (95% confidence interval 1.0-3.6). A significant trend in risk ($p << 0.001$) was observed between an approximate time-weighted mean exposure to arsenic, considered in milligrams per liter or milligram-years per liter, which strengthens the possibility of a causal association.

Key word: arsenic, diabetes mellitus, drinking water, epidemiology, exposure, keratosis, public health, hypertension.

A link between arsenic in drinking water and the occurrence of diabetes mellitus and hypertension has been suggested rather recently (1, 2), and these chronic diseases represent novel health risks associated with arsenic exposure. Arsenic is a classical poison, however, but has also been used in medical treatments until our time, and occurred as late as in 1959 on the list of drugs in Sweden (3). Arsenic tetrasulfide seems to have been used already in antiquity in a paste for ulcer treatment (4, 5), and in 1786, Fowler introduced his solution, which contains 1% of As_2O_3 .

From an occupational and environmental health point of view, arsenic exposure has attracted great interest in the past few decades, especially regarding the risk of lung cancer among copper smelter workers, but also the risk of skin and bladder cancer seen in connection with exposure through drinking water. Characteristic skin lesions such as keratosis have been taken as a hallmark for chronic arsenic ingestion and seem to constitute a pre-cancerous condition (6, 7)

The newly proposed risk of diabetes mellitus and hypertension may relate more or less closely to the peripheral vascular disease and cardiovascular disease that have been associated with arsenic in drinking water. Here we summarise some epidemiological findings made in studies of diabetes mellitus and hypertension both in worker groups and in a general population with arsenic exposure and briefly discuss the relations of these diseases to the degree of exposure and the risks of cancer.

Studies of worker groups with exposure to arsenic

In the report of a study from Taiwan (1) on diabetes mellitus in relation to arsenic exposure through drinking water, a Swedish study on copper smelter workers was referred to (8). It was suggested that an excess of cardiovascular disease among these Swedish workers could have been secondary to diabetes mellitus as induced through the exposure to arsenic. Diabetes mellitus had not been considered in the original study, however, but as the records had been preserved, it was decided to evaluate further whether diabetes mellitus was associated with arsenic exposure among these workers (9). The records also included exposure information from the company whether the air concentrations at the work places had been about or had been higher or lower than the Swedish occupational standard at the time, i.e., $500 \mu\text{g}/\text{m}^3$ in 1975 (later the standard was lowered to $50 \mu\text{g}/\text{m}^3$). On the average, workers enrolled in the study had been exposed for 23 years.

The available data for the extended case-control analysis included the death records and some clinical information about chronic diseases. The register of deaths and burials in the parishes around the copper smelter was used as the source of subjects. The parish registers of deaths and burials used to be of a high quality in Sweden with complete diagnoses from the death certificates along with data on occupation. Nowadays, the registration system has been changed and there are no longer any such local registers. All subjects were men in ages 30-74 years and only those ever employed at the smelter were considered in this analysis. No comparison was made with the external population as there was no clinical information for the general population.

The number of subjects who been employed included only 12 cases of diabetes mellitus. As cancer, cardiovascular and cerebrovascular disease had been associated with arsenic exposure in the original study and elsewhere, only 31 subjects remained without such diagnoses and could be utilised as controls. Taking the unexposed employees as the reference, the odds ratios found for

diabetes mellitus with increasing arsenic exposure categories were (reference level = 1), 2.0, 4.2, and 7.0, but the corresponding 95% confidence intervals all included unity. A test for trend was weakly significant, $P = 0.03$, however.

Although based on small numbers, the findings provided some support for the suggestion that arsenic exposure could be a risk factor for diabetes mellitus. To obtain further insight into this issue we decided to also supplement some earlier studies of art glass workers (10) with a further analysis regarding diabetes mellitus and exposure to arsenic (11). Glass workers are inherently exposed, as glass manufacturing requires arsenic trioxide as a fining and decolouring agent. There are also many other potentially toxic agents used in art glass production including lead, cadmium, antimony, copper, selenium, chromium, sulfuric acid and hydrofluoric acid. The exposure levels for arsenic were not assessable in the glass industry, however, but presumably much lower than for the copper smelters.

Our case-control analysis included the death records of 5498 individuals in the art glass producing part of south-eastern Sweden. The data were obtained from the registers of deaths and burials in 11 parishes. All men were deceased in the period of 1950-1982 and only subjects in ages of 45 years or more were included. Out of all the subjects included, 888 were art glass workers. According to occupational title, glassblowers, foundry workers, and unspecified workers were regarded as potentially exposed to arsenic. Persons with a diagnosis of diabetes mellitus either as an underlying or contributing cause of death were considered cases. Referents were decedents without any indication of cancer or cardiovascular disease, as these disorders were considered associated with arsenic exposure.

A slightly elevated risk [Mantel-Haenszel odds ratio (MH-OR) 1.2, 95% confidence interval (95% CI) 0.82-1.8] was found for diabetes mellitus among the glassworks employees, especially in combination with cardiovascular disease (MH-OR 1.4, 95% CI 0.81-2.3). For glassblowers, other foundry workers and unspecified art glass workers, who were probably those exposed to arsenic, the M-H odds ratio was 1.4 (95% CI 0.92-2.2). Unspecified glass workers, who probably included persons with high exposure, carried the higher risk (MH-OR 1.8, 95% CI 1.1-2.8).

The observations from these two studies of workers with exposure to arsenic provide some but still limited support for the possibility that occupational arsenic exposure could play a role in the development of diabetes mellitus. Hence, the study of copper smelter workers clearly suffer from the small numbers involved and the rather poor exposure information hampers the study of the glass workers. Many other metallic compounds are also used in art glass production, however, with subsequent risk of uncontrolled confounding.

Studying general populations with arsenic exposure

Arsenic is a ubiquitous element with metalloid properties and it is a constituent of many different minerals. The concentrations of arsenic occurring in the in the environment is highly variable. Soil has been reported to contain 0.03-0.25 ppm, plants 0.023-0.25 ppm, ground water up to 55 ppm, sea water 0.0001-0.08 ppm, fish food 3-170 ppm, wine 0.008-0.85 ppm and urban air up to 0.00049 or 0.63 $\mu\text{g}/\text{m}^3$ (12). Some areas in the world are reported to have very high concentrations of arsenic in drinking water and large populations exposed, table 1.

We noted the recently discovered high concentrations of arsenic in drinking water in Bangladesh and decided to investigate whether the indications of an increased risk of diabetes mellitus

among exposed workers in Sweden as well as in the general population in Taiwan could be confirmed in further studies. Also the possibility of a risk of hypertension attracted our interest, again based on some primary observations from Taiwan.

The source of arsenic contamination in Bangladesh is probably geological from the fine alluvial sediments of the Ganges delta. The duration of arsenic exposure is uncertain, but it probably first started in the late 1960s through the introduction of drilled tubewells. Until the early 1970s, more than 100 million inhabitants of Bangladesh and the neighbouring Indian province West Bengal drank from shallow hand dug wells, rivers and ponds, but bacterial contamination was causing epidemics of cholera.

Considering diabetes mellitus

In 1996, a survey was conducted regarding the prevalence of diabetes mellitus among 163 subjects with keratosis who were recruited by a door to door visit in villages known to have a high arsenic content in the drinking water. Subjects with keratosis were selected because such skin lesions clearly indicate exposure, the characteristic skin effects from chronic arsenic exposure starting with initial changes in pigmentation followed by keratosis. This sequence has been observed under a variety of circumstances involving chronic exposure, e.g., in using potassium arsenate for medical treatment, in vineyard workers spraying and/or dusting powders containing arsenic compounds, in drinking arsenic-contaminated wine, and in using arsenate as a sheep-dip (6, 7).

For comparison, 854 unexposed individuals were selected from the suburban area of Dhaka, where there is no arsenic contamination of the drinking water. Diabetes mellitus was determined in the two compared population groups by history of symptoms, previously diagnosed diabetes, glucosuria, and blood sugar level after glucose intake. The crude prevalence ratio for diabetes mellitus among keratotic subjects exposed to arsenic was 4.4 (95% confidence interval 2.5-7.7) and increased to 5.2 (95% confidence interval 2.5-10.5) after adjustment for age, sex, and body mass index. On the basis of a few earlier measurements of arsenic concentrations in drinking water by the authorities in Bangladesh and another 20 new ad hoc analyses, approximate time-weighted exposure levels to arsenic in drinking water could be estimated for each subject. Three time-weighted average exposure categories were created, i.e., less than 0.5, 0.5-1.0, and more than 1.0 mg/liter. For the exposed subjects, the corresponding prevalence ratios were (reference =1.0) 2.6, 3.9, and 8.8, representing a significant trend in risk ($p < 0.001$). In this study age exerted a weak positive confounding effect and body mass index appeared as a negative confounder (15), the latter because the unexposed Dhaka population might have had a slightly better socio-economic situation and thereby a somewhat greater risk for developing diabetes mellitus.

A further study in Bangladesh was set up as based on existing surveys of arsenic in drinking water in four villages. The purpose was to study arsenic exposure and glucosuria as taken to indicate diabetes mellitus both in the absence and presence of keratosis. Also the occurrence of hypertension in relation to exposure and skin lesions was considered in view of the observations from Taiwan in this respect. A total of about 4000 individuals were found to have lived in the selected villages throughout their lifetime, but many of these individuals were younger than 30 years and unlikely to have developed hypertension or other effects of the exposure. The remaining part of the population, as eligible for an interview and examination, encompassed 1794 subjects; all of them had used the same well as long as it had existed. A total of 1595 finally accepted to participate in the study when contacted by a door to door visit. All subjects

were interviewed by means of a questionnaire filled in by the interviewer and they were also examined at their homes.

Urine samples from the study subjects were tested by means of a glucometric strip. People with positive tests were considered to be cases of glucosuria. A total of 430 (29%) of the exposed people were found to have skin lesions as diagnosed when one or more of the following signs were present, that is, changes in pigmentation of unexposed body surfaces and/or keratosis, especially on palms and soles.

Based on the history of consumption of well water and current arsenic concentrations, the arsenic exposure was estimated as time weighted mean arsenic concentrations and as mg-years/L. Out of the participating 1595 subjects, 114 turned out to be unexposed, i.e., to have used water from wells that had non-detectable arsenic levels. Both exposed and unexposed subjects were recruited in all of the four villages.

For those without skin lesions and corresponding to drinking water concentrations of arsenic of < 0.5, 0.5-1.0, and > 1.0 mg/L, the prevalence ratios for glucosuria, as adjusted for age and sex, were 0.8, 1.4, and 1.4 with the 114 unexposed subjects as the reference. For those with skin lesions the prevalence ratios were slightly higher, namely 1.1, 2.2, and 2.6 in comparison to the unexposed subjects. Taking exposure as < 1.0, 1.0-5.0, > 5.0-10.0 and > 10.0 mg-years/L of exposure to arsenic, the similarly adjusted prevalence ratios were 0.4, 0.9, 1.2, and 1.7 for those without and 0.8, 1.7, 2.1, and 2.9 for those with skin lesions. All series of risk estimates were significant for trend, $p < 0.01$.

These results, as summarised in table 2, indicate that skin lesions and diabetes mellitus, as here indicated by glucosuria, are largely independent effects of exposure to arsenic although glucosuria had some tendency to be associated with skin lesions. Importantly, however, glucosuria, that is, diabetes mellitus, may occur independently of skin lesions, which has the practical implication that any primary screening for this disease can not utilise the occurrence of skin lesions, which would have been useful in a developing country like Bangladesh.

Considering hypertension

The data set collected for the aforementioned study of glucosuria and arsenic exposure also included measurements of the blood pressure. Hypertension was defined as a systolic blood pressure of ≥ 140 mm Hg in combination with a diastolic blood pressure of ≥ 90 mm Hg. A prevalence comparison of hypertension between the 1481 subjects with arsenic exposure and those 114 without this exposure through the drinking water could therefore also be made in order to confirm or refute an earlier observation of a relation in this respect. Again the exposure was assessed as time-weighted mean arsenic levels in milligrams per litre and milligram-years per litre of arsenic.

Corresponding to the exposure categories with the unexposed subjects as the reference, the prevalence ratios for hypertension adjusted for age, sex, and body mass index were 1.2, 2.2, 2.5 in relation to the arsenic exposure categories in milligrams per litre, table 2. Considering the exposure in milligram-years per litre as <1.0 mg-y/L, 1.0 to 5.0 mg-y/L, >5.0 to ≤ 10.0 mg-y/L, and >10.0 mg-y/L, the prevalence ratios in relation to the unexposed individuals were 0.8, 1.5, 2.2, 3.0, respectively. The indicated dose-response relationships were significant ($P < 0.001$) for both series of risk estimates. These results confirm the findings reported from Taiwan and suggest that arsenic exposure may induce hypertension in humans.

The risk for hypertension was analysed also separately for subjects with and without skin lesions. Considering time-weighted mean arsenic exposure in the same categories as for glucosuria, and taking unexposed as the reference, the adjusted prevalence ratios for hypertension among the subjects without skin lesions were 0.8, 1.7 and 2.2. With the same reference and exposure categories, subjects with skin lesions had adjusted prevalence ratios of 1.4, 2.5, and 2.9, respectively. A dose-response trend was significant both for subjects with and without skin lesions $p < 0.001$, respectively. Considering mg-years/L of arsenic exposure, and using the unexposed as the reference, the adjusted prevalence ratios in subjects without skin lesions again showed a dose-response, with prevalence ratios 0.7, 1.1, 1.5, and 2.5. For subjects with skin lesions, the risk estimates were even higher 0.9, 1.9, 2.5, and 4.0, respectively. Both trends were highly significant, $p < 0.001$.

Epidemiological studies of workers exposed to arsenic by inhalation have provided results regarding mortality from vascular diseases. The studies include several occupations in different countries, such as sheep-dip manufacturing workers in Britain (16), smelter workers in United States (17-24), Sweden (8, 25, 26), and Japan (27). Also insecticides manufacturing workers in United States have been studied (28-30). While there is good epidemiological evidence supporting a causal association between well water containing inorganic arsenic and occurrence of black foot disease, the evidence for an increased mortality from vascular diseases independent of blackfoot disease is less compelling

A limitation of the studies in Bangladesh is the cross-sectional design as well as the lack of a comprehensive, systematic, long-term sampling of the water supplies in the study areas. Directly measured individual exposure data over time would have been even more useful. Arsenic concentrations not only vary from well to well in the same area but even in the same well with time and season. There are no data regarding such likely time and seasonal variations. Also the influence of various other circumstances are unknown, for example, the use of bottled water, but in this respect the effect would rather be that of a dilution and lead to an underestimation of the associations found. Within these various limitations, the series of studies suggest a causal relation between occupational or environmental arsenic exposure and chronic non-malignant health effects, such as diabetes mellitus and hypertension. The mechanism for inorganic arsenic induction of these disorders is still unclear, however. To investigate further these effects of arsenic, a variety of sources of exposure might be considered for further studies.

Non-malignant versus malignant effects from long term exposure to arsenic

Several cancer forms have been associated with exposure to arsenic, but it is currently unclear whether the cancer risk or some of the non-malignant effects of arsenic exposure should be determining permissible exposure levels. Inhalation of inorganic arsenic has been shown to cause lung cancer but less attention has been paid the possibility of a lung cancer risk from ingestion. Reports from Argentina and Taiwan have mentioned elevated rates of lung cancer in relation to arsenic in drinking water and Bowen's disease (31, 32). Cancer of the bladder and skin has been clearly associated with arsenic exposure through ingestion but there is also evidence for an increased risk of liver cancer including a few cases of angiosarcoma of the liver. (33-37). Risk estimates based on findings from Taiwan suggest that the risk of lung and bladder cancer might be greater than the risk of other cancers and to be about one percent at an intake of 10 micrograms per kilogram and day (38). There is also an observation from Taiwan of no excess risk at arsenic concentrations below 0.1 mg per litre (39). Others have estimated the risk of dying

from cancer of the liver, lung, kidney or bladder to be in the same range from the intake of 50 micrograms of arsenic drinking water per day (40).

Regarding other health effects from arsenic exposure than diabetes mellitus and hypertension, it may be noted here that cerebrovascular disease was found to have tripled among persons consuming well water with an arsenic content in the range of 0.1 to 50 micrograms per litre (41). The occurrence of ischemic heart disease was found to have more than doubled by a cumulative exposure to arsenic in drinking water of 0.1-9.9 mg/L-years (42). The risk of developing such non-malignant diseases as well as cancer therefore seems to increase in about the same range of arsenic exposure.

Regarding the occurrence of diabetes mellitus among keratotic subjects in Bangladesh we found a prevalence ratio of 2.6 (95% confidence interval 1.2-5.7) for those having used well water containing less than 0.5 mg/L in the first study. For this degree of exposure in the second study, we obtained prevalence ratios around unity, that is, 1.1 for subjects with skin lesions, including pigmentation changes and not only keratosis, and for those without skin lesions 0.8. For hypertension a prevalence ratio of 1.2 was obtained with a confidence interval including unity. A preliminary conclusion may therefore be that other effects than diabetes mellitus and hypertension should be determining permissible exposure levels, although these diseases might be considered in medical surveillance of exposed populations as rather early manifestations of a too high exposure.

Table 1. Arsenic concentrations in drinking water in different parts of the world. and the size of populations potentially exposed (13,14).

Country	Area	Concentrations in water ($\mu\text{g/L}$)	Number of individuals	Years of exposure
Argentina		up to 800 $\mu\text{g/L}$	20000	1938-81
Bangladesh*		up to 2040 $\mu\text{g/L}$	>67 million	1970-still
Chile		up to 800 $\mu\text{g/L}$	130000	1958-70
China		up to 800 $\mu\text{g/L}$	>400	1969-still
India		up to 3400 $\mu\text{g/L}$	>1 million	1978-still
Mexico		up to 800 $\mu\text{g/L}$	200000	1963-83
Taiwan		up to 600 $\mu\text{g/L}$	>100000	1961-85
Thailand		up to 800 $\mu\text{g/L}$	no data	1987-88

* Drilling of wells started in the late 1960s; first cases of keratosis known from around 1993

Table 2. Prevalence ratios (and 95% confidence intervals) obtained in three studies of diabetes mellitus and/or glucosuria and hypertension in relation to arsenic concentrations in drinking water in Bangladesh.

Study and disease	Arsenic concentrations in mg/ L		
	< 0.5	0.5 - 1.0	> 1.0
Rahman et al 1998 Diabetes mellitus among keratotic subjects	2.6 (1.2-5.7)	3.9 (1.8-8.2)	8.8 (2.7-28.4)
Rahman et al 1999 Glucosuria among subjects without skin lesions	0.8 (0.4-1.3)	1.4 (0.8-2.3)	1.4 (0.7-2.4)
Glucosuria among subjects with skin lesions	1.1 (0.5-2.0)	2.2 (1.3-3.8)	2.6 (1.4-4.6)
Rahman et al 1999 Hypertension	1.2 (0.6-2.3)	2.2 (1.1-4.3)	2.5 (1.2-4.9)

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