



Research Article

Chronic Arsenic Exposure through Drinking Water and Risk of Type 2 Diabetes Mellitus: A study from Bangladesh

Mst Karimon Nesha^{1*}, Md. Nazrul Islam², Nira Ferdous³, Fahid Bin Nazrul⁴, Johannes J. Rasker⁵

¹Department of GIS and Earth Observation for Natural Resources Management, University of Twente, The Netherlands

²Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

³Department of Medicine, MH Samorita Medical College, Tajgaon, Dhaka, Bangladesh

⁴Modern One Stop Arthritis Care & Research Center®, Dhaka, Bangladesh

⁵Department of Psychology, Health & Technology, University of Twente, Enschede, The Netherlands

***Corresponding author:** Mst Karimon Nesha, Department of GIS and Earth Observation for Natural Resources Management, University of Twente, Netherlands. Tel: +31687640579; Email: m.k.nesha@student.utwente.nl

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Summary

It has been well-documented that chronic arsenic exposure can lead to skin lesions, atherosclerotic diseases and cancers. The findings of association between arsenic exposure and diabetes mellitus indicate additional risk to human health. However, some studies reported inconsistent association.

The aim of this study was to assess the association of chronic arsenic exposure through drinking water with risk of type 2 diabetes mellitus. To this end, a cross-sectional study was conducted among randomly selected 300 individuals aged 30 years and older in Comilla and Jhenaidah District of Bangladesh. Individuals with arsenic-related skin lesions were defined as subjects exposed to arsenic. This study included 150 exposed subjects and recruited from Comilla district where drinking water (groundwater) is heavily contaminated with arsenic. Likewise, 150 subjects unexposed to arsenic were recruited as reference population from Jhenaidah district where groundwater is known not to be contaminated by arsenic. Diabetes was defined if fasting blood glucose (FBG) > 6.1 mmol/L following World Health Organization (WHO) guidelines.

The common odds ratio for diabetes mellitus among subjects exposed to arsenic was 3.5 (95% confidence interval 1.1-10.9). After adjustment for age, sex and BMI, the Mantel-Haenszel weighted prevalence ratio was 3.5 (95% CI: 1.1-11.1), 3.7 (95% CI: 1.1-11.8) and 4.4 (95% CI: 1.1-17.2) respectively. The indicated relationships were significant ($P < 0.05$). These observations suggested that chronic arsenic exposure through drinking water maybe a risk factor of type 2 diabetes mellitus.

Keywords: Arsenic; Bangladesh; Diabetes Mellitus; Drinking Water

Introduction

The contamination of groundwater with arsenic (As) is a big threat in various countries including Argentina, Australia, Bangladesh, Chile, China, Hungary, India, Mexico, Peru, Taiwan, and the United States of America exceeding the U.S. Environmental Protection Agency's (EPA) maximum contaminant level (MCL) of 10 µg/L [1]. However, the worst case scenario has been reported in

Bangladesh and West Bengal of India [2]. Approximately 56% of the tube wells (out of 34,000) throughout Bangladesh contain arsenic more than 10 µg/L and some 37% have greater than 50 µg/L [3]. It has been estimated that about 50 million people in Bangladesh are chronically exposed to arsenic through drinking water [4-6]. Public health problems related to chronic arsenic exposure through drinking water have been linked to increased risks of skin cancer [7] bladder, lung, and liver cancers [8,9] as well as cardiovascular diseases [10,11]. In addition, arsenic exposure has been suggested to be associated with development of diabetes mellitus as well

[12]. A cohort study in Taiwan stated that a long-term exposure to arsenic is associated with diabetes mellitus in humans [13]. Similar findings have also been reported in the state of Coahuila, Mexico [14]. More recently, a cross-sectional study from National Health and Nutrition Examination Survey (NHANES) reported that the OR for diabetes was 3.6 (95% CI, 1.2-10.8) when they compared participants at the 80th percentile with those at the 20th percentile for urinary arsenic [15]. As far as Bangladesh is concerned, a dose-response relationship between prevalence of diabetes mellitus and exposure to arsenic through drinking water was reported only in few studies [16,17].

Apart from arsenic exposure through drinking water, several studies reported occupational chronic arsenic exposure association with diabetes mellitus. For example, Swedish copper smelter workers revealed an increased risk of dying from diabetes mellitus with increasing arsenic exposure as compared to an unexposed control group [18]. In another study on Swedish art glass workers, the odds ratio of dying from diabetes mellitus was 1.8 for the exposed glass workers compared to unexposed ones [19]. Occupational exposure to arsenic was associated significantly with an increased level of glycosylated hemoglobin in Denmark [20]. Other studies showed an increased morbidity and mortality of diabetic patients having exposed to arsenic at work when compared with general population or unexposed workers [18,19,21,22].

However, many studies opposed such association between chronic arsenic exposure and diabetes mellitus. For instance, no significant association was observed in a community-based studies in areas of low arsenic exposure in the USA [23,24]. A study indicated no association between chronic arsenic exposure and diabetes, glycosuria, or blood HbA1c level in Bangladesh [25]. Similarly, a couple of studies also reported no association of occupational arsenic exposures with increasing mortality of diabetes mellitus in arsenic-exposed workers than the general population [26-29].

This exploratory study further aimed at determining the possible association between chronic arsenic exposure and type 2 diabetes mellitus in Bangladesh taking into account demographic, social and medical risk factors.

Methodology

This study was designed as a comparison of the prevalence of diabetes mellitus among subjects living in areas with and those without exposure to arsenic through drinking water. The total sample size was 300 including subjects exposed to arsenic (exposed subjects) and those not exposed to arsenic (unexposed subjects). Individuals aged 30 or more with skin manifestations such as keratosis, leucomelanosis and melanosis were defined as the exposed subjects in this study as skin lesions are a marker of prolonged arsenic exposure. The skin lesions were confirmed by the

physicians of local health centre. A total of 150 exposed subjects were randomly recruited from four villages viz. Eruen, Madhaya Eruen, Rajapur and Nagrapa from Lacksam Upazila of Comilla district where groundwater is heavily contaminated with arsenic as reported from the national survey of Bangladesh Arsenic Mitigation Water Supply Project (BAMWSP). The arsenic concentration of artesian well water in these villages ranged from 0.07 to 1.4ppm with a mean concentration of 0.15 ppm. The standard for arsenic in drinking water set by the U.S. Environmental Protection Agency is 0.05 mg/L for Bangladesh [9].

A sum of 150 unexposed subjects was arbitrarily recruited through door-to-door visit in a village Vespara, from Kaliganj Upazila of Jhenaidah district. The population of Jhenaidah was not known to be exposed to arsenic through drinking water according to the Water and Sewage Agency, Bangladesh. The unexposed subjects were recruited by matching age (≥ 30 years) and sex with the exposed subjects.

One exposed subject and two unexposed subjects with family history of hypertension were excluded from the study. Three exposed subjects and one unexposed subject denied taking part in the study. A semi-structured questionnaire was used to obtain information on socioeconomic, demographic characteristics, history of arsenic contaminated water consumption, height, weight, alcohol intake, cigarette smoking, physical activities, as well as personal, family history of hypertension and diabetes. The arsenic content of tube well water was taken from the report of BAMWSP survey. Type 2 diabetes was screened by a Glucometer. Diagnosis of DM was defined using the diagnostic criteria (FBG ≥ 6.1 mmol/L) from the WHO guidelines.

Statistics

The data were stratified according to age (30-44, 45-59, and >60 years), sex, and Body Mass Index (BMI). The BMI categories were <19 , 19-22, and >22 . Mantel-Haenszel weighted prevalence ratios (MH-PR) with 95 percent confidence intervals were calculated to determine the association of chronic arsenic exposure with type 2 diabetes mellitus. All the potential confounders were adjusted during the analysis.

Ethics

The study was approved by Khulna University, Khulna, Bangladesh as part of the graduation study. The study was performed following the Declaration of Helsinki principles and informed consent was given by all study participants before taking part in the survey.

Results

This study was carried out in areas of high arsenic contamination in drinking water and compared with areas not

containing arsenic in drinking water. The mean age of the exposed subjects was 45.5 years and unexposed subjects 45.7 years. The number of male and female accounted for 26% and 74% respectively in the exposed subjects. The corresponding figures for male and female in the unexposed subjects were 30% and 70% respectively. The major occupations were housewife (74%) and farmer (12%) in the exposed subjects. In the unexposed subjects, the main occupations were also housewife (69%) and farmer (12%). In the exposed subjects, the age of most of the participants (53%) ranged from 30 to 44 years. While the corresponding figure for this age group in the unexposed subjects accounted for 51%. Participants aged between 45 and 60 years were stood at 35% and 37% in the exposed and unexposed subjects respectively. Among the exposed subjects, 74% had no formal education while the corresponding figure was 70% in the unexposed subjects. The comparison of socio-demographic characteristics between the exposed subjects and unexposed subjects are presented in (Table 1).

The exposed subjects had lower BMI compared to the unexposed subjects (Table 1). The history of alcohol intake, cigarette smoking, physical activities, as well as personal and family history of hypertension and diabetes in the family of the exposed subjects was comparable to those in the unexposed subjects (Table 1)

Variables	Exposed group (n=150)		Non-exposed group (n=150)	
	No	(%)	No	(%)
Age (years)				
30-44	80	53.3	76	50.7
45-60	53	35.3	56	37.3
>60	17	11.3	18	12
Sex				
Male	39	26	45	30
Female	111	74	105	70
Occupation				
Cultivator	18	12	17	11.3
Day labor	5	3.3	11	7.3
House wife	111	74	103	68.7
Business	7	4.7	15	10
Service	6	4	2	1.3
*Others	3	0.21	2	1.3
Education				
No formal Education	111	74	105	70
Primary School	21	14	17	11.3
High School	12	8	21	14

SSC	5	3.3	4	2.7
HSC	1	0.7	3	2
Religion				
Islam	147	98	52	34.7
Hinduism	3	2	98	65.3
Marital Status				
Married	134	89.3	130	86.7
Widowed	14	9.3	20	13.3
Divorced	1	0.7	0	
Never Married	1	0.7	0	
Body Mass Index (BMI)				
<19	90	60	33	22
19-22	36	24	51	34
>22	24	16	66	44
Physical Activities				
Light	40	26.6	38	25.3
Moderate	79	52.6	73	48.6
Vigorous	31	20.6	39	20
Alcohol Intake	0	0	0	0
Cigarette Smoking	17	11.3	14	9.3
*Others=Rickshaw puller, Union Member, Tuition				

Table 1: Socio-demographic characteristics of participants: exposed and unexposed subjects to arsenic through drinking water (n=300).

Diabetes mellitus was diagnosed in 13 individuals among the exposed subjects and in four persons among the subjects not exposed to arsenic through drinking water. The crude prevalence ratio for diabetes mellitus was 3.5 (95%CI, 1.1-10.9) stating that the probability for developing diabetes mellitus for subjects exposed to arsenic contaminated drinking water is 3.5 times higher than those not exposed to arsenic through drinking water (Table 2). In order to find out a precise association between chronic arsenic exposure and diabetes mellitus, the effects of potential confounding factors viz. Age, Sex and BMI were adjusted. After adjusting for age (Table 3), the Mantel-Haenszel weighted prevalence ratio (MH-PR) was 3.5 (95% CI: 1.1-11.1, p=0.031). With adjustment for sex, MH-PR was 3.7 (95%CI: 1.1-11.8, p=0.029) (Table 4). When adjusted for BMI, MH-PR increased to 4.4 (95% CI: 1.1 - 17.2) p=0.032 (Table 5).

Arsenic exposure	Diabetes		
	Diabetic	Non-diabetic	Total
Exposed	13 (8.7%)	137 (91.3%)	150 (100%)
Not exposed	4 (2.7%)	146 (97.3%)	150 (100%)
Total	17 (5.7%)	283 (94.3%)	300 (100%)

Fisher's Exact Test	0.043		
Mantel-Haenszel Common Odds Ratio	3.5		
95% Confidence Interval	1.1-10.9		

Table 2: Type 2 Diabetes in exposed and unexposed subjects to arsenic through drinking water (n=300).

Age	Arsenic exposure	Diabetic status		
		Diabetic	Not diabetic	Total
30-44	Exposed	5 (6.2%)	75 (93.8%)	80 (100%)
	Not exposed	1 (1.3%)	75 (98.7%)	76 (100%)
Total		6 (3.8%)	150 (96.2%)	156 (100%)
45-60	Exposed	5 (9.4%)	48 (90.6%)	53 (100%)
	Not exposed	3 (5.4%)	53 (94.6%)	53 (100%)
Total		8 (7.3%)	101 (92.7%)	109 (100%)
>60	Exposed	3 (17.6%)	14 (82.4%)	17 (100%)
	Not exposed	0 (0%)	18 (100%)	18 (100%)
Total		3 (8.6%)	32 (91.4%)	35 (100%)
Mantel-Haenszel Common Odds Ratio				3.5
Exact Sig. (2-sided)				0.031
95% Confidence Interval				1.1-11.1

Table 3: According to age, type 2 diabetes mellitus in exposed and unexposed subjects to arsenic through drinking water (n=300).

Sex		Diabetic	Non-diabetic	Total
Male	Exposed	4 (10.3%)	35 (89.7%)	39 (100%)
	Not exposed	3 (6.7%)	42 (93.3%)	45 (100%)
Total		7 (8.3%)	77 (91.7%)	84 (100%)
Female	Exposed	9 (8.1%)	102 (91.9%)	111 (100%)
	Not exposed	1 (1.0%)	104 (99.0%)	105 (100%)
Total		10 (4.6%)	206 (95.4%)	216 (100%)
Mantel-Haenszel Common Odds Ratio				3.7
Exact Sig. (2-sided)				0.029
95% Confidence Interval				1.1-11.8

Table 4: According to sex, type 2 diabetes mellitus in exposed and unexposed subjects to arsenic through drinking water (n=300).

BMI		Diabetic	Non-diabetic	Total
<19	Exposed	9 (10.0%)	81 (90.0%)	90 (100%)
	Not exposed	0 (0%)	33 (100%)	33 (100%)
Total		9 (7.3%)	114 (92.7%)	123 (100%)
19-22	Exposed	2 (5.6%)	34 (94.4%)	36 (100%)
	Not exposed	1 (2.0%)	50 (98.0%)	51 (100%)
Total		3 (3.4%)	84 (96.6%)	87 (100%)
>22	Exposed	2 (8.3%)	22 (91.7%)	24 (100%)
	Not exposed	3 (4.5%)	63 (95.5%)	66 (100%)
Total		5 (5.6%)	85 (94.4%)	90 (100%)
Mantel-Haenszel Common Odds Ratio				4.4
Exact Sig. (2-sided)				0.032
95% Confidence Interval				1.1-17.2

Table 5: According to BMI, type 2 diabetes mellitus in exposed and unexposed subjects to arsenic through drinking water (n=300).

Discussion

The results of this study support the association between chronic arsenic exposure and diabetes mellitus, as observed by other investigations [12,13,16,18,19]. Exposure to inorganic arsenic, as indicated by animal and in vitro model systems, can potentially increase the risk of developing diabetes through its implications on the inhibition of insulin-dependent glucose uptake [30], insulin signaling [31], impairment of insulin secretion, transcription in pancreatic beta cells [32] and modification of the expression of genes involved in insulin resistance [33]. However, the concentrations of arsenic in most of these experiments are high, and the resulting effects may not be pertinent to populations chronically exposed to arsenic in the environment.

Nevertheless, the epidemiologic literature suggests that diabetes is an adverse outcome associated with prolonged exposure to high levels of arsenic (>500 µg/L) in drinking water [17] among patients with skin lesions, a marker of prolonged exposure, the OR for diabetes in association with 500-1,000 µg/L and >1,000 µg/L was 2.2 and 2.6 respectively [17]. In a cohort study in southwestern Taiwan, the OR of diabetes was 2.1 comparing individuals with cumulative arsenic exposure >17,000 µg/L-years to those with <17,000 µg/L-years [13].

On the other hand, the relation between inorganic arsenic exposure and diabetes mellitus has been reported yet to be inconclusive particularly at low to moderate levels of exposure to

arsenic [34]. Even no evidence of an association was found in a study in Bangladesh where 90% of study population was exposed to well water arsenic (<300 µg/L) when comparing the highest level of exposure (176-864 µg/L; mean, 291.2 µg/L) with the lowest (0.1-8 µg/L; mean, 2.4 µg/L) [25].

Occupational studies have also been inconclusive. While in the studies at a copper smelter [18] and an art glass industry [19] in Sweden, an association between occupational arsenic exposure and diabetes has been reported, no relation has been observed in a US copper smelter [26] and in a UK tin smelter [35]. The experimental and epidemiologic evidence suggest that the adverse effects on diabetes may be dose specific and limited to population with prolonged exposure to very high levels of arsenic exposure.

One of the main problems of published epidemiological studies is related to measurement errors. In several studies, only glycosuria [16,17] or statistical records [36-39] were used as a diagnosis of the disease. Only a couple of studies used glucose measurement after an oral glucose tolerance test [12,13] but in one of them the comparison group was not studied concurrently with the exposed group [13]. In our study, glucose measurement after an oral glucose tolerance test was used to diagnose diabetes as advised by WHO.

Deficiencies of trace elements such as copper and zinc have been suggested to play a role in the pathogenesis of diabetes mellitus [40]; administration of cadmium has been shown also to cause hyperglycemia [41]. Arsenic has been reported to interact with these chemicals. Arsenic exposure can lead to a significant increase in renal copper excretion and can potentiate the effects of cadmium when arsenic and cadmium are used together [42]. Arsenic may also compete with zinc in metal-binding proteins that display vicinal dithiols contained in zinc fingers of DNA binding and repair proteins. This competitive binding causes conformational change and altered biological function in proteins [43]. Due to financial restrictions in this explorational study, no other trace elements could be studied in the drinking water which is a limitation of this study.

In this study, all subjects were recruited from rural villages of almost similar occupation, socioeconomic status, and lifestyle. Therefore, these variables were reasonably similar between exposed and unexposed subjects and it was, therefore, unlikely to influence glycosuria either in the presence or absence of skin lesions. The subjects unexposed to arsenic had higher BMI than those exposed to As. This might indicate that a low body mass may be ascribed to the effect of arsenic exposure for long time.

Availability of data on environmental exposure to arsenic is a great strength of our study. Unlike previous studies [15,23,24] this study population was well described with detailed data on the duration, source, and form of exposure. This study also considered social and clinical risk factors as well as other risk factors like

alcohol intake, cigarette smoking, physical activities, plus personal and family history of hypertension and diabetes.

Conclusions

This exploratory study suggests a possibility of association of chronic arsenic intake with type 2 diabetes mellitus. As such we recommend an organized large-scale study to address this public health issue. In such a study, one may consider measuring other trace elements like Cadmium, Zinc and Copper in the drinking water.

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References

1. WHO (2001) Arsenic in drinking water. Fact sheet 210.
2. Roychowdhury T (2008) Impact of sedimentary arsenic through irrigated groundwater on soil, plant, crops and human continuum from Bengal delta: special reference to raw and cooked rice. *Food Chem Toxicol* 46: 2856-2564.
3. Chakraborti D, Sengupta MK, Rahman MM, Chowdhury UK, Lodh D, et al. (2003) Groundwater arsenic exposure in India. the book "Arsenic Exposure and Health Effects, Edited by WR Chappell, CO Abernathy, RL Calderon Publisher: Elsevier science, Amsterdam-Lausanne-New York-Oxford-Tokyo.3-24.
4. BGS-DPHE (1999) Groundwater Studies for Arsenic Contamination in Bangladesh. Final Report. Mott MacDonald Ltd, British Geological Survey, UK.
5. EPA US (2000) Arsenic Occurrence in Public Drinking Water Supplies. EPA-815-R-00-023.
6. EPA US (2001) Fact Sheet about the January 2001 Arsenic Rule. EPA 815-F-00-015.
7. Hsueh YM, Chiou HY, Huang YL, Wu WL, Huang CC, et al. (1997) Serum beta-carotene level, arsenic methylation capability, and incidence of skin cancer. *Cancer Epidemiol Biomarkers Prev* 6: 589-596.
8. Chen CJ, Kuo TL, Wu MM (1988) Arsenic and cancers. *The Lancet* 331: 414-415.
9. Chen Y, Ahsan H, Parvez F, Howe GR (2004) Validity of a food-frequency questionnaire for a large prospective cohort study in Bangladesh. *Br J Nutr* 92: 851-859.
10. Chen CJ, Chiou HY, Chiang MH, Lin LJ, Tai TY (1996) Dose-response relationship between ischemic heart disease mortality and long-term arsenic exposure. *Arterioscler Thromb Vasc Biol* 16: 504-510.
11. Chen CJ, Hsueh YM, Lai MS, Shyu MP, Chen SY, et al. (1995) Increased prevalence of hypertension and long-term arsenic exposure. *Hypertension* 25: 53-60.
12. Lai MS, Hsueh YM, Chen CJ, Shyu MP, Chen SY, et al. (1994) Ingested inorganic arsenic and prevalence of diabetes mellitus. *Am J Epidemiol* 139: 484-492.

13. Tseng CH, Tai TY, Chong CK, Tseng CP, Lai MS, et al. (2000) Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis-hyperendemic villages in Taiwan. *Environ Health Perspect* 108: 847-51.
14. Coronado-González JA, Del Razo LM, García-Vargas G, Sanmiguel-Salazar F, Escobedo-de la Peña J (2007) Inorganic arsenic exposure and type 2 diabetes mellitus in Mexico. *Environ Res* 104: 383-389.
15. Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, Guallar E (2008) Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA* 300: 814-822.
16. Rahman M, Tondel M, Ahmad SA, Axelson O (1998) Diabetes mellitus associated with arsenic exposure in Bangladesh. *Am J Epidemiol* 148: 198-203.
17. Rahman M, Tondel M, Chowdhury IA, Axelson O (1999) Relations between exposure to arsenic, skin lesions, and glucosuria. *Occup Environ Med* 56: 277-281.
18. Rahman M, Axelson O (1995) Diabetes mellitus and arsenic exposure: a second look at case-control data from a Swedish copper smelter. *Occupational and environmental medicine* 52: 773-774.
19. Rahman M, Wingren G, Axelson O (1996) Diabetes mellitus among Swedish art glass workers: an effect of arsenic exposure? *Scandinavian journal of work, environment & health* 146-149.
20. Jensen GE, Hansen ML (1998) Occupational arsenic exposure and glycosylated haemoglobin. *Analyst* 123: 77-80.
21. Lagerkvist BJ, Zetterlund B (1994) Assessment of exposure to arsenic among smelter workers: A five year follow up. *American journal of industrial medicine* 25: 477-488.
22. Tollestrup K, Frost FJ, Harter LC, McMillan GP (2003) Mortality among children residing near the American Smelting and Refining Company (ASARCO) copper smelter in Ruston, Washington. *Arch Environ Health* 58: 683-691.
23. Lewis DR, Southwick JW, Ouellet-Hellstrom R, Rench J, Calderon RL (1999) Drinking water arsenic in Utah: A cohort mortality study. *Environ Health Perspect* 107: 359-365.
24. Zierold KM, Knobeloch L, Anderson H (2004) Prevalence of chronic diseases in adults exposed to arsenic-contaminated drinking water. *Am J Public Health* 94: 1936-1937.
25. Chen Y, Ahsan H, Slavkovich V, Peltier GL, Gluskin RT, et al. (2010) No association between arsenic exposure from drinking water and diabetes mellitus: a cross-sectional study in Bangladesh. *Environ Health Perspect* 118: 1299-1305.
26. Lubin JH, Pottern LM, Stone BJ, Fraumeni JF (2000) Respiratory cancer in a cohort of copper smelter workers: results from more than 50 years of follow-up. *American Journal of Epidemiology* 151: 554-565.
27. Bartoli D, Battista G, De Santis M, Iaia TE, Orsi D, et al. (1998) Cohort study of art glass workers in Tuscany, Italy: mortality from non-malignant diseases. *Occup Med (Lond)* 48: 441-445.
28. Enterline PE, Marsh GM (1982) Cancer among workers exposed to arsenic and other substances in a copper smelter. *Am J Epidemiol* 116: 895-911.
29. Mabuchi K, Lilienfeld AM, Snell LM (1980) Cancer and occupational exposure to arsenic: a study of pesticide workers. *Prev Med* 9: 51-77.
30. Walton FS, Harmon AW, Paul DS, Drobná Z, Patel YM, et al. (2004) Inhibition of insulin-dependent glucose uptake by trivalent arsenicals: possible mechanism of arsenic-induced diabetes. *Toxicol Appl Pharmacol* 198: 424-433.
31. Paul DS, Harmon AW, Devesa V, Thomas DJ, Stýblo M (2007) Molecular mechanisms of the diabetogenic effects of arsenic: inhibition of insulin signaling by arsenite and methylarsonous acid. *Environ Health Perspect* 115: 734-742.
32. Diaz-Villasenor A, Sanchez-Soto MC, Cebrian ME, Ostrosky-Wegman P, Hiriart M (2006) Sodium arsenite impairs insulin secretion and transcription in pancreatic beta-cells. *Toxicol Appl Pharmacol* 214: 30-34.
33. Diaz-Villasenor A, Burns AL, Hiriart M, Cebrian ME, Ostrosky-Wegman P (2007) Arsenic-induced alteration in the expression of genes related to type 2 diabetes mellitus. *Toxicol Appl Pharmacol* 225: 123-133.
34. Navas-Acien A, Silbergeld EK, Streeter RA, Clark JM, Burke TA, et al. (2006) Arsenic exposure and type 2 diabetes: a systematic review of the experimental and epidemiologic evidence. *Environ Health Perspect* 114: 641-648.
35. Binks K, Doll R, Gillies M, Holroyd C, Jones SR, et al. (2005) Mortality experience of male workers at a UK tin smelter. *Occup Med (Lond)* 55: 215-226.
36. Chiu HF, Chang CC, Tsai SS, Yang CY (2006) Does arsenic exposure increase the risk for diabetes mellitus? *J Occup Environ Med* 48: 63-67.
37. Tsai SM, Wang TN, Ko YC (1999) Mortality for certain diseases in areas with high levels of arsenic in drinking water. *Arch Environ Health* 54: 186-193.
38. Wang SL, Chiou JM, Chen CJ, Tseng CH, Chou WL, et al. (2003) Prevalence of non-insulin-dependent diabetes mellitus and related vascular diseases in southwestern arseniasis-endemic and nonendemic areas in Taiwan. *Environ Health Perspect* 111: 155-159.
39. Wang SL, Chou WL, Wang CC, Chen CJ (2003) Cardiovascular Disease Profile and Its Relation to Diabetes in Arseniasis-Endemic Area in Southwestern Taiwan. *Isee-388. Epidemiology* 14: S77.
40. Group WHOS (1985) Report of diabetes mellitus technical report series. No 727. World Health Organisation Geneva.
41. Bell RR, Early JL, Nonavinkere VK, Mallory Z (1990) Effect of cadmium on blood glucose level in the rat. *Toxicol Lett* 54: 199-205.
42. Mahaffey KR, Capar SG, Gladen BC, Fowler BA (1981) Concurrent exposure to lead, cadmium, and arsenic. Effects on toxicity and tissue metal concentrations in the rat. *J Lab Clin Med* 98: 463-481.
43. Engel RR, Hoppenhayn-Rich C, Receveur O, Smith AH (1994) Vascular effects of chronic arsenic exposure: a review. *Epidemiol Rev* 16: 184-209.