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Original Scientific Paper

EXPOSURE TO ARSENIC IN DRINKING WATER AND RISK OF BLADDER CANCER

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SUMMARY – The municipality of Bogatić, part of Mačva District, belongs to the Pannonian Basin, where high concentrations of arsenic in artesian wells were detected. Numerous epidemiological studies have confirmed the association of exposure to arsenic in drinking water and bladder cancer (C67). This retrospective ten-year analysis included age-standardized incidence rates (ASRs) and age-specific incidence rates of C67 in the municipality of Bogatić and rural municipalities of Mačva District. The concentration of arsenic in drinking water was determined at Šabac Public Health Institute (PHI) laboratories in 2015. ASRs were estimated using data from regional cancer registries at Šabac PHI and compared by use of the Mann-Whitney U test. Control population was recruited from an area where there were no artesian wells or hydrogeological conditions that would indicate elevated concentrations of arsenic in drinking water. Arsenic levels in all artesian wells in Bogatić municipality were 1.4 to 41 times higher than the maximum permissible concentration (mean 120 μg/L±165). Female subjects from Bogatić municipality had higher ASRs of C67 compared with the populations in rural municipalities of Mačva District ($p<0.01$), while the incidence of bladder cancer was by 13% greater than that in central Serbia (standardized incidence ratio, 113; 95% CI 96.97-131.35). Male subjects from Bogatić municipality had higher ASRs of C67 but the difference was not statistically significant ($p>0.05$). Our analyses suggested that exposure to arsenic in drinking water could triple the risk of bladder cancer. These results support the conclusions of previous studies that there may be an association between higher concentrations of arsenic in drinking water and higher ASRs of bladder cancer in both male and female subjects.

Key words: *Mačva District; Arsenic; Bladder cancer; Artesian wells; Ten-year analysis*

Introduction

The presence of arsenic in groundwater used for water supply is a problem faced by many countries in the world[1]. The presence of inorganic arsenic in groundwater in the Pannonian Basin has been known for decades[2,3], and its penetration into groundwater occurs as a consequence of the process of dissolution under different hydrogeological conditions[4]. In this study, the term 'artesian well' denotes deep drilled well

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used for water supply where groundwater flows to the land surface under pressure. Chronic exposure to inorganic arsenic >10 μg/L is related to an increased incidence of type 2 diabetes[5-8], cardiovascular and respiratory diseases[9,10], skin hyperpigmentation[11,12], and malignant neoplasms (lung, bladder, kidney, skin)[13-18]. Argos *et al*.[19] estimated that the contribution of arsenic from drinking water was 21.4% in total mortality and 23.5% in mortality from chronic diseases in Bangladesh population for concentrations of arsenic >10 μg/L. Mortality from cancer of the bladder, kidney and lung due to chronic arsenic exposure has a very long latency, with increased risks manifesting up to 40 years after a decrease in arsenic exposure[20]. Key evidence for arsenic carcinogenicity exists in epidemiological studies with arsenic >10 μg/L, but there still are insufficient epidemiological studies to evaluate the carcinogenic effects of arsenic at low to moderate concentrations in drinking water. A meta-analysis conducted by Mink *et al*. in 2007 found no association between exposure to low levels <10 μg/L of arsenic in drinking water and bladder cancer[21]. However, an environmental study conducted in the United States supports the association between low and moderately elevated concentrations of arsenic in drinking water (1.5-15.4 μg/L) and an increase in the incidence of bladder cancer[22].

Based on the 2018 Globocan estimates at International Agency for Research on Cancer (IARC), the incidence of malignant bladder neoplasms is 6th in male, 17th in female, and 10th overall, with an age-standardized incidence rate (ASR) of 5.7 *per* 100,000 inhabitants (male to female, 9.6:2.4)[23]. According to data reported by the Institute of Public Health of Serbia (2006-2015)[24], the incidence of malignant bladder neoplasms in central Serbia is 4th in male and 8th in female. The incidence cannot be accurately estimated due to significant heterogeneity in the way it is reported in national registries and different methodologies used on data analysis across countries.

Material and Methods

Research area

The municipality of Bogatić is one of eight municipalities in the Mačva District, part of central Serbia, belonging to the Pannonian Basin. The presence of arsenic in mineral and thermal waters, as hydrological deposits, in the area of Bogatić municipality has been described in previous studies indicating the presence of arsenic in rocks and clay layers, which enables its easy penetration into groundwater as a result of the process of dissolution under different hydrogeological conditions[2], while data on its presence in artesian wells, which have been used for alternative or regular water supply to the population for about 40 years, did not exist until 2015. The municipality of Bogatić decided to organize control of water quality in artesian wells and asked the Šabac Public Health Institute for assistance. The Šabac Public Health Institute then conducted extended analyses for the first time with respect to the parameter that could be expected in high-depth drinking water, as well as stipulated parameters in the Book of Regulations on the Hygienic Quality of Drinking Water 98/42 (1998)[25]. Given the specificity of artesian wells, the parameters of hygienic-epidemiological significance (suspected presence of arsenic above the maximum permissible concentration (MPC) in drinking water) were determined to check their suitability as a source of water supply. Previously, controls were carried out on inspection orders for basic stipulated parameters by the rule book (A range of analyses), which do not imply determination of arsenic concentration, although according to the Constitution of the Republic of Serbia (2006)[26], access to an appropriate water supply as a fundamental human right presents a failure to monitor artesian wells by local authorities as owners. According to the 2002 census, the population in the territory in which there were artesian wells included 15,359 inhabitants out of a total of 32,990 inhabitants in the territory of the municipality of Bogatić[27]. The 2002 census reported that out of 9510 inhabited apartments in the municipality of Bogatić, 6492 had public and individual water supply facilities, whereas 3018 inhabited dwellings in Bogatić municipality did not own water objects in 2002 (31.7%)[28]. Based on this information, we can assume that the population of these housing units used artesian wells as sources of water supply, whereby we cannot exclude the possibility of using drinking water from artesian wells by other households.

The rural municipalities of the Mačva District include municipalities with less than 30,000 inhabitants; these are Bogatić, Vladimirci, Koceljeva, Krupanj, Mali Zvornik and Ljubovija (Fig. 1).

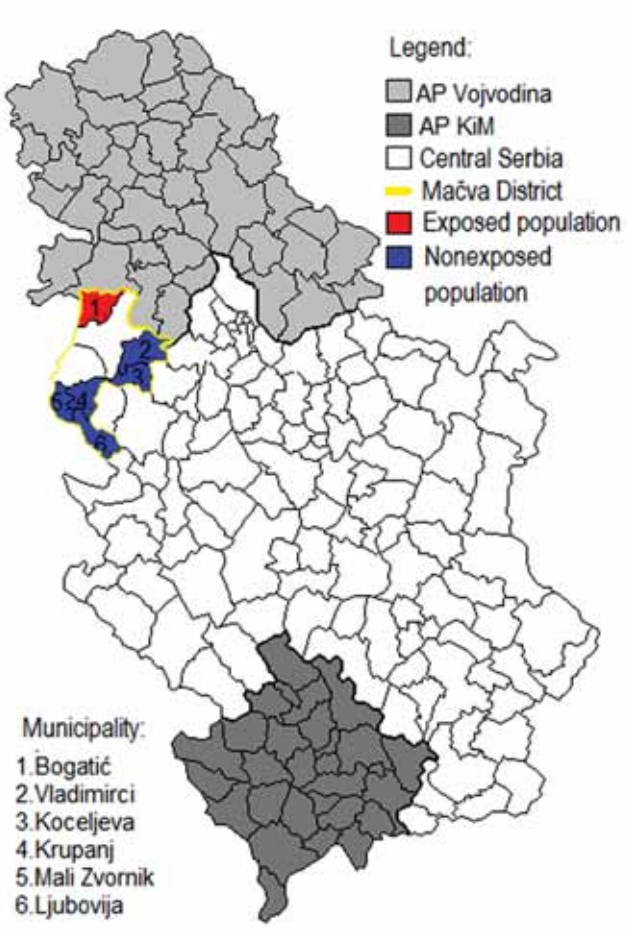

Fig. 1. Map of the research area: rural municipalities of the Mačva District.

Methods

Laboratory testing of water samples for arsenic content from all 8 artesian wells in the territory of Bogatić municipality in 2015 was performed in the following places: Crna Bara (two artesian wells), Sovljak, Bogatić, Glušci, Uzveće, and Banovo Polje (two artesian wells), which represented the sources of water supply. Water sampling for the analysis of arsenic was carried out by an accredited laboratory according to SRPS ISO/IEC 17025[29] and SRPS ISO 9001 standards[30]. Current Serbian regulations limit arsenic levels at 10 μg/L[25]. Ten-year ASRs for bladder cancer in the municipality of Bogatić, in the territory where arsenic concentrations >10 μg/L were detected in drinking water, and in the rural municipalities of the Mačva District where there were no artesian wells for water supply (Koceljeva, Krupanj, Ljubovija, Mali Zvornik and Vladimirci) were tested by Mann-Whitney U test. Control population of the Mačva District were recruited from a rural area with demographic characteristics similar to the exposed area and where there were no industries or artesian wells or hydrogeological conditions that would indicate elevated concentrations of arsenic in drinking water. Ten-year linear trend of ASRs (time trend) was presented and the standardized rate ratio (SRR) and standardized incidence ratio (SIR) in the municipality of Bogatić were calculated.

Results

Arsenic values in all artesian wells in the municipality of Bogatić were 1.4 to 41 times greater than MPC (mean 120±165 μg/L; range 14-410 μg/L) (Table 1). During the observed period, 156 bladder cancer patients were registered in the surveyed rural municipalities of the Mačva District, of which 140 were males and 33 females. The mean ten-year ASRs *per* 100,000 population for bladder cancer in the municipality of Bogatić were higher than in the surveyed municipality of the Mačva District (Table 2). No cases of bladder cancer disease were reported in young people under 30 in rural municipalities of the Mačva District. Considering ASRs for bladder cancer in the study populations, the risk of developing bladder cancer was calculated. On average, the population of Bogatić municipality was 3 times more likely to develop bladder cancer than the Mačva District surveyed population over a ten-year observation period. In the male population, the risk of bladder cancer was 1.33 times higher in the municipality of Bogatić (ranging from 1.04 to 1.53), whereas in females this risk was 4.65 times higher (ranging from 1.24 to 9.1) (Table 3). Among females, ASRs for bladder cancer were higher in Bogatić municipality than in the surveyed municipalities of the Mačva District, where there are no artesian wells with high arsenic concentration (p=0.01) (Table 4). The incidence rates were higher for males in Bogatić municipality compared to the male population of other surveyed municipalities in the Mačva District, but these differences were not statistically significant (p>0.05) (Table 5).

Table 1. Arsenic values in all artesian wells in the municipality of Bogatić

Artesian well	AW I	AW II	AW III	AW IV	AW V	AW VI	AW VII	AW VIII	Mean	SD
Arsenic (μg/L)	52	45	22	18	14	40	360	410	120	±165

AW = artesian well; SD = standard deviation

Table 2. Mean ten-year ASRs per 100,000 population for bladder cancer in the municipality of Bogatić in the Mačva District (2006-2015)

Municipality	Sex	Number of cases	Crude rate	ASR	M:F
Bogatić	Male	49	30	16.16	2.96
	Female	15	33.27	5.46	
Koceljeva	Male	17	22.65	10.59	2.36
	Female	6	8.15	4.42	
Krupanj	Male	17	17.65	10.59	7.06
	Female	5	4.27	1.5	
Ljubovija	Male	19	23.58	13.48	10.06
	Female	3	3.85	1.34	
Mali Zvornik	Male	14	20.7	15.55	14.81
	Female	1	1.48	1.05	
Vladimirci	Male	24	24.39	11.99	19.98
	Female	3	3.12	0.6	

ASR = age-standardized incidence rate; M:F = male to female ratio

Table 3. Standardized rate ratio (SRR) for bladder cancer (C67) in the municipality of Bogatić compared with rural municipalities of the Mačva District (2006-2015)

Municipality/ sex	Bogatić and Koceljeva	Bogatić and Ljubovija	Bogatić and Mali Zvornik	Bogatić and Vladimirci	Bogatić and Krupanj
SRR males	1.53	1.2	1.04	1.35	1.53
SRR females	1.24	4.07	5.2	9.1	3.64

Table 4. Identified differences in standardized incidence rates for bladder cancer among females in the municipality of Bogatić compared with rural municipalities of the Mačva District (2006-2015)

Municipality (females)	As group	N	Median	Minimum	Maximum	p-value*
Bogatić/Koceljeva	As >10	10	5.100	0.0	12.9	0.45
	As <10	10	1.450	0.0	12.2	
	Total	20	4.450	0.0	12.9	
Bogatić/Ljubovija	As >10	10	5.100	0.0	12.9	0.001
	As <10	10	0.000	0.0	2.0	
	Total	20	1.250	0.0	12.9	
Bogatić/Mali Zvornik	As >10	10	5.100	0.0	12.9	0.003
	As <10	10	0.000	0.0	10.5	
	Total	20	0.750	0.0	12.9	
Bogatić/Vladimirci	As >10	10	5.100	0.0	12.9	0.002
	As <10	10	0.000	0.0	2.0	
	Total	20	2.000	0.0	12.9	
Bogatić/Krupanj	As >10	10	5.100	0.0	12.9	0.01
	As <10	10	0.000	0.0	9.7	
	Total	20	2.950	0.0	12.9	

*Mann-Whitney U test; As = arsenic

Table 5. Identified differences in standardized incidence rates for bladder cancer among males in the municipality of Bogatić compared with rural municipalities of the Mačva District (2006-2015)

Municipality (males)	As group	N	Median	Minimum	Maximum	p-value*
Bogatić/Koceljeva	As >10	10	14.700	7.2	25.1	0.15
	As <10	10	10.850	0.0	19.9	
	Total	20	13.900	0.0	25.1	
Bogatić/Ljubovija	As >10	10	14.700	7.2	25.1	0.13
	As <10	10	10.500	4.7	34.9	
	Total	20	13.450	4.7	34.9	
Bogatić/Mali Zvornik	As >10	10	14.700	7.2	25.1	0.13
	As <10	10	8.350	0.0	64.9	
	Total	20	13.450	0.0	64.9	
Bogatić/Vladimirci	As >10	10	14.700	7.2	25.1	0.17
	As <10	10	9.350	0.0	24.8	
	Total	20	13.800	0.0	25.1	
Bogatić/Krupanj	As >10	10	14.700	7.2	25.1	0.11
	As <10	10	8.600	0.0	28.3	
	Total	20	13.450	0.0	28.3	

*Mann-Whitney U test; As = arsenic

Study results suggest that the ten-year incidence of bladder cancer among females in the municipality of Bogatić was by 13% higher than expected based on average age-specific incidence rates for central Serbia (SIR=113; 95% CI=96.97-131.35). Among males, there was no significant difference in bladder cancer between Bogatić and central Serbia (SIR=100.58; 95% CI=92.37-109.32). In female population from Bogatić municipality, the peak in developing the disease was 55-59 years, which was not the case in other municipalities, where the peak was recorded at the age above 75 years. Males from the municipality of Bogatić had higher age-specific incidence rates in older age groups (>70 years) than in the surveyed municipalities of the Mačva District.

Figures 2 and 3 show that the number of patients affected by age varied irregularly due to the small number of new patients and small population (one

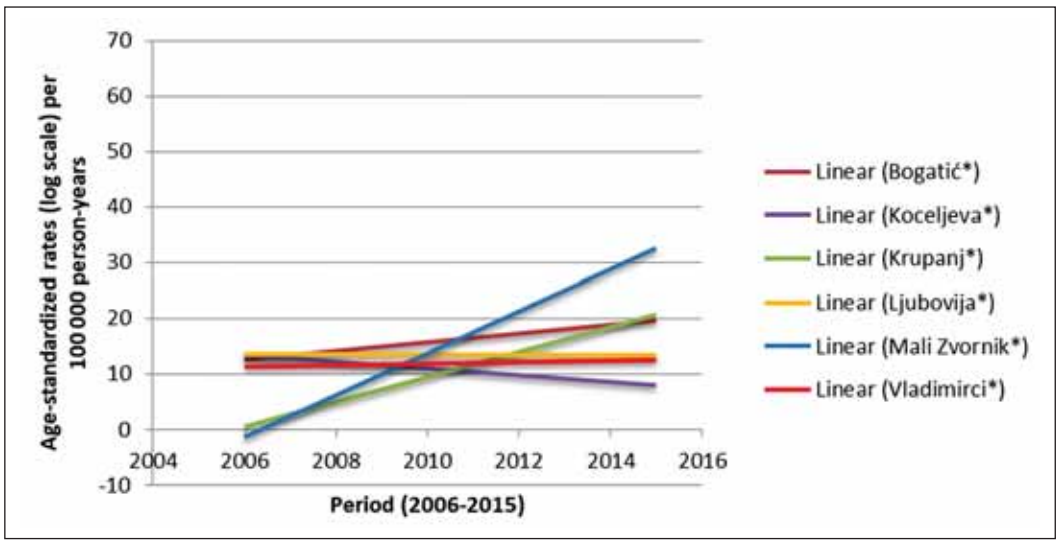

Fig. 2. Bladder cancer trends: age-standardized incidence rates among males in the Mačva District (2006-2015).

*Incidence rates were estimated using aggregated data from regional cancer registries

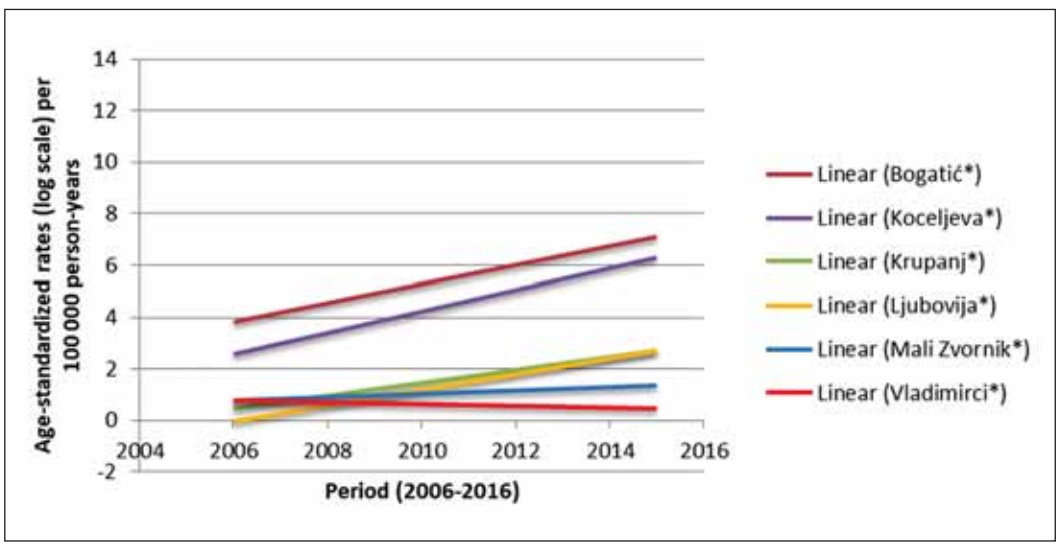

Fig. 3. Bladder cancer trends: age-standardized incidence rates among females in the Mačva District (2006-2015).

*Incidence rates were estimated using aggregated data from regional cancer registries

year it rose, and declined in the next year), so we cannot claim with confidence the growing trend of ASRs for bladder cancer, except that ASRs for bladder cancer were on average greater in the municipality of Bogatić than in other rural municipalities of the Mačva District. An exception was the municipality of Mali Zvornik, which recorded a linear upward trend of 24% (R2=0.33) in the male population due to high ASRs for C67 in 2014 and 2015, whereas in previous years ASRs for C67 were lower in relation to the exposed population of the municipality of Bogatić. Therefore, the observed trend could not be considered statistically significant due to the small population and small number of registered new cases during the ten-year observation period. In the female population of Bogatić, significantly higher ASRs were observed for bladder cancer compared to other surveyed municipalities, where, based on a linear trend model, a 0.36 *per* 100,000 increase of ASRs for bladder cancer was observed in Bogatić municipality for each year of observation from 2006 to 2015.

Discussion

This is the first study on the distribution of arsenic in public water supply systems in the municipality of Bogatić and in Mačva District. The values of arsenic in all artesian wells in the municipality of Bogatić were 1.4 to 41 times higher than the MPC[25]. It shows large variation in arsenic levels in the region. The mean arsenic levels were much higher than those reported in other countries in the Pannonian Basin[31]. In some parts of the municipality of Bogatić, the arsenic content in drinking water is higher than in public water supply systems across ten municipalities in Vojvodina Region, Serbia (median ranged from 2 to 250 μg/L; maximum value ranged from 5 to 349 μg/L)[3]. The municipality of Bogatić population was largely supplied with water from individual water facilities or public drinking fountains (referred to as artesian wells in the paper), but accurate data on the number of those exposed to arsenic in drinking water and the length of exposure are not available. According to data from the local authority of the municipality of Bogatić and Statistical Office of the Republic of Serbia, artesian wells have been used for about 40 years, and over 30% of households out of the total number of households in the territory of the municipality of Bogatić have been supplied with water for drinking and cooking from artesian wells[28]. It should be emphasized that there are no data on concentrations of and exposure to arsenic from artesian wells used as individual water bodies, but it can be assumed that the percentage of exposure in the municipality Bogatić is higher.

Based on the average ten-year ASRs for bladder cancer, the highest ASRs were observed in the municipality of Bogatić compared to the surveyed municipalities in the Mačva District, which may be related to arsenic exposure in drinking water from artesian wells as one of the predictors of high rates of bladder cancer[32]. Inorganic arsenic belongs to the first group of carcinogens according to the IARC classification[33] and group A of carcinogens according to the US Environmental Protection Agency[4]. Toxic effects of arsenic on the human body depend on a number of factors, such as the concentration of arsenic or its compounds in water, its valence, the length of exposure, the way of intake into the body, individual sensitivity of the human body, methylation capacity, age, gender, nutritional status, smoking status, etc.[34-39]. Trends in age-specific incidence rates in our study showed similarity to the available literature data, which report an increase in the incidence with age, most often after 55 years in both sexes, with the highest incidence in the population aged over 65[40]. Data showed the peak age-specific incidence of bladder cancer among females at the age 55-59 years in the municipality of Bogatić, which was not the case in other municipalities, where the peak was observed at the age above 75 years, which is in accordance with previous studies[40].

The ratio of male to female bladder cancer in the municipality of Bogatić was 2.96, lower than that in the examined municipalities of the Mačva District (mean 10.85±6.82) and may be associated with a small population of surveyed municipalities. Studies show that the rates in males are three to four times those in females, with ASR-W 10.1 *per* 100,000 for males and 2.5 *per* 100,000 for females worldwide[41].

Among residents of the Bogatić municipality, we found a significantly increased risk of developing bladder cancer in males and females, with SRRs of 1.33 and 4.65, respectively. The findings were consistent with those reported previously in the arseniasis-endemic area in southwestern and northeastern Taiwan[42,43]. A very high risk of bladder cancer has been reported in a previously conducted study in rural areas of Argentina (males 13.8 and females 12.7)[44]. The SIR for females

was by 13% higher than in central Serbia, while this trend was not observed in males. The results of a study conducted in 22 rural Victoria municipalities do not support the association between arsenic exposure and bladder cancer in both sexes, but the study was limited by low potency and exposure misclassification[45].

In our study, females in the Bogatić municipality had statistically significantly higher ASRs for bladder cancer than females in the rural parts of the Mačva District (p=0.01), which may be associated with hormone-dependent arsenic methylation and different enzyme metabolic activity[46-48]. It is also thought that the increased incidence in women may be related to their daily role in preparing food in rural families (cooking food). The mechanisms underlying these gender differences are not sufficiently known.

Where the concentration of arsenic in drinking water is 10 μg/L or greater, this will be the dominant source of intake, according to the World Health Organization report[49]. In circumstances where soups or similar dishes are a staple part of the diet, the contribution of drinking water through preparation of food will be even greater[50]. In its updated evaluation, the World Health Organization concluded that „… the concentration of arsenic in drinking water below which no effects can be observed remains to be determined, and there is an urgent need for identification of the mechanism by which arsenic causes cancer, which appears to be the most sensitive toxicity end-point"[51].

Conclusion

This ten-year study found an association between higher levels of arsenic in drinking water and higher ASRs for bladder cancer in men and women. These results support the findings of previous studies suggesting an association between higher concentrations of arsenic in drinking water and higher ASRs for bladder cancer in males and females. Timely detection of exposure to arsenic and other harmful substances found in drinking water in rural areas, as well as the implementation of public health measures by the competent authorities, local authorities and water facility owners should be a priority in reducing the risks of drinking water to human health.

References

1. Van Halem D, Bakker SA, Amy GL, Van Dijk JC. Arsenic in drinking water: not just a problem for Bangladesh. Drink Water Eng Sci Discuss. 2009;2:51-64. doi: 10.2147/RMHP.S153188.
2. Dangić A. Arsenic in surface- and groundwater in central parts of the Balkan Peninsula (SE Europe). Trace Metals and Other Contaminants in the Environment. 2007;9:127-56. doi: 10.1016/S0927-5215(06)09005-9.
3. Jovanović D, Jakovljević B, Rašić-Milutinović Z, Paunović K, Peković G, Knežević T. Arsenic occurrence in drinking water supply systems in ten municipalities in Vojvodina Region, Serbia. Eviron Res. 2011;111(2):315-8. doi: 10.1016/j.envres.2010.11.014.
4. US Environmental Protection Agency (EPA). The Risk Assessment Guidelines of 1986. EPA/600/8-87/04. Washington, DC: Office of Health and Environmental Assessment, US EPA; 1987.
5. Jovanovic D, Rasic-Milutinovic Z, Paunovic K, Jakovljevic B, Plavsic S, Milosevic J. Low levels of arsenic in drinking water and type 2 diabetes in Middle Banat region, Serbia. Int J Hyg Environ Health. 2013;216(1):50-5. doi: 10.1016/j.ijheh.2012.01.001.
6. Rahman M, Tondel M, Ahmad SA, Axelson O. Diabetes mellitus associated with arsenic exposure in Bangladesh. Am J Epidemiol. 1998;148(2):198-203. doi: 10.1093/oxfordjournals.aje.a009624.
7. Bruce KD, Byrne CD. The metabolic syndrome: common origins of a multifactorial disorders. Postgrad Med J. 2009;85(1009):614-21. doi: 10.1136/pgmj.2008.078014.
8. Coronado-Gonzalez JA, Del Razo LM, Garcia-Vargas G, Sanmiguel-Salazar F, Escobedo-de la Pena J. Inorganic arsenic exposure and type 2 diabetes mellitus in Mexico. Environ Res. 2007;104(3):383-92. doi: 10.1016/j.envres.2007.03.004.
9. Huda N, Hossain S, Rahman M, Karim MR, Islam K, Mamun AA, *et al*. Elevated levels of plasma uric acid and its relation to hypertension in arsenic-endemic human individuals in Bangladesh. Toxicol Appl Pharmacol. 2014;281(1):11-8. doi: 10.1016/j.taap.2014.09.011.
10. Chen CJ, Chiou HY, Chiang MH, Lin LJ, Tai TY. Dose-response relationship between ischaemic heart disease mortality and long-term arsenic exposure. Arterioscler Thromb Vasc Biol. 1996;16(4):504-10. doi: 10.1161/01.atv.16.4.504.
11. Rahman M, Vahter M, Wahed MA, Sohel N, Yunus M, Streatfield PK, El Arifeen S, Bhuiya A, Zaman K, Chowdhury AM, Ekström EC, Persson LA. Prevalence of arsenic exposure and skin lesions. A population based survey in Matlab, Bangladesh. J Epidemiol Community Health. 2006;60(3):242-8. doi: 10.1136/jech.2005.040212.
12. Rahman MM, Sengupta MK, Ahamed S, Chowdhury UK, Lodh D, Hossain A, *et al*. Arsenic contamination of groundwater and its health impact on residents in a village in West Bengal, India. Bull World Health Organ. 2005;83(1):49-57. doi: /S0042-96862005000100014.

13. Ferreccio C, Gonzalez C, Milosavljevic B, Marshall G, Sancha AM, Smith AH. Lung cancer and arsenic concentrations in drinking water in Chile. Epidemiology. 2000;11(6):673-9. doi: 10.1097/00001648-200011000-00010.
14. Naujokas MF, Anderson B, Ahsan H, Aposhian HV, Graziano JH, Thompson C, *et al*. The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem. Environ Health Perspect. 2013;121(3):295-302. doi: 10.1289/ehp.1205875.
15. Marshall G, Ferreccio C, Yuan Y, Bates MN, Steinmaus C, Selvin S, Liaw J, Smith AH. Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. J Natl Cancer Inst. 2007;99(12):920-8. doi: 10.1093/jnci/djm004.
16. Smith AH, Goycolea M, Haque R, Biggs ML. Marked increase in bladder and lung cancer mortality in a region of northern Chile due to arsenic in drinking water. Am J Epidemiol. 1998;147(7):660-9. doi: 10.1093/oxfordjournals.aje.a009507.
17. Tsuda T, Babazono A, Yamamoto E, Kurumatani N, Mino Y, Ogawa T, Kishi Y, Aoyama H. Ingested arsenic and internal cancer: a historical cohort study followed for 33 years. Am J Epidemiol. 1995;141(3):198-209. doi: 10.1093/oxfordjournals.aje.a117421.
18. Wu MM, Kuo TL, Hwang YH, Chen CJ. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am J Epidemiol. 1989;130(6):1123-32. doi: 10.1093/oxfordjournals.aje.a115439.
19. Argos M, Karla T, Rathouz PJ, Chen Y, Pierce B, Parvez F, Islam T, Ahmed A, Rakibuz-Zaman M, Hasan R, Sarwar G, Slavkovich V, van Geen A, Graziano J, Ahsan H. Arsenic exposure from drinking water, and all-cause and chronic disease mortalities in Bangladesh (HEALS): a prospective cohort study. Lancet. 2010;376(9737):252-8. doi: 10.1016/S0140-6736(10)60481-3.
20. Cohen SM, Arnold LL, Beck BD, Lewis AS, Eldan M. Evaluation of the carcinogenicity of inorganic arsenic. Crit Rev Toxicol. 2013;43(9):711-52. doi: 10.3109/10408444.2013.827152.
21. Mink PJ, Alexander DD, Barraj L M, Kelsh MA, Tsuji JS. Low-level arsenic exposure in drinking water and bladder cancer: a review and meta-analysis. Regul Toxicol Pharmacol. 2008;52 (3):299-310. doi: 10.1177/1559325819863634.
22. Mendez Jr WM, Eftim S, Cohen J, Warren I , Cowden J , Lee JS, *et al*. Relationships between arsenic concentrations in drinking water and lung and bladder cancer incidence in U.S. counties. J Expo Sci Environ Epidemiol. 2017;27(3):235-43. doi: 10.1038/jes.2016.58.
23. International Agency for Research on Cancer, World Health Organization. Estimated age-standardized incidence rates (World) in 2018. GLOBOCAN; 2018. Available from: http://globocan.iarc.fr.
24. Institute of Public Health of Serbia „Dr Milan Jovanović Batut". 2006-2015. Cancer incidence and mortality in central Serbia. Retrieved from: http://www.batut.org.rs/index.php?content=185 (Accessed May 5, 2019).
25. Book of Regulations on the Hygienic Correctness of Drinking Water, 1998. Sl. list SRJ 42/98, Belgrade. (in Serbian)
26. The Constitution of the Republic of Serbia. Službeni glasnik RS 98/2006.
27. Statistical Office of the Republic of Serbia. 2004. Statistical Year book of Serbia. Statistical Office of the Republic of Serbia, Belgrade. Retrieved from: http://publikacije.stat.gov.rs/G2002/Pdf/G20024432.pdf (in Serbian)
28. Republički zavod za statistiku. Popis stanovništva, domaćinstava i stanova u 2002. godini. Veličina, kvalitet, godina izgradnje, svojina, domaćinstva i lica (drugi deo). Beograd 2004. Availablefrom: http://publikacije.stat.gov.rs/G2002/Pdf/G20024432.pdf (in Serbian)
29. ISO/IEC 17025:2005. General Requirements for the Competence of Testing and Calibration Laboratories. International Organization for Standardization, Geneva.
30. ISO 9001:2000. Quality Management System-Requirements. International Organization for Standardization, Geneva.
31. Lindberg AL, Goessler W, Gurzau E, Koppova K, Rudnai P, Kumar R, Fletcher T, Leonardi G, Slotova K, Gheorghiu, E, Vahter M. Arsenic exposure in Hungary, Romania and Slovakia. J Environ Monit. 2006;8(1):203-8. doi: 10.1039/b513206a.
32. Amin RW, Stafford B, Guttmann RP. A spatial study of bladder cancer mortality and incidence in the contiguous US: 2000-2014. Sci Total Environ. 2019;670:806-13. doi: 10.1016/j.scitotenv.2019.03.290.
33. IARC. Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1-42. Lyon, International Agency for Research on Cancer, 1987; pp. 100-6 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7).
34. Hopenhayn-Rich C, Biggs ML, Kalman DA, Moore LE, Smith AH. Arsenic methylation patterns before and after changing from high to lower concentrations of arsenic in drinking water. Environ Health Perspect. 1996;104(11):1200-7. doi: 10.1289/ehp.961041200.
35. US Environmental Protection Agency (EPA). EPA Chemical Profiles: Arsine. US Environmental Protection Agency, 2006.
36. Valenzuela OL, Borja-Aburto VH, Garcia-Vargas GG, Cruz-Gonzalez MB, Garcia-Montalvo EA, Calderon-Aranda ES, *et al*. Urinary trivalent methylated arsenic species in a population chronically exposed to inorganic arsenic. Environ Health Perspect. 2005;113(3):250-4. doi: 10.1289/ehp.7519.
37. Sams R2nd, Wolf DC, Ramasamy S, Ohanian E, Chen J, Lowit A. Workshop overview: arsenic research and risk assessment. Toxicol Appl Pharmacol. 2007;222(3):245-51. doi: 10.1080/10408444.2019.1573804.
38. Cohen SM, Arnold LL, Beck BD, Lewis AS, Eldan M. Evaluation of the carcinogenicity of inorganic arsenic. Crit Rev Toxicol. 2013;43(9):711-52. doi: 10.3109/10408444.2013.827152.
39. Moe B, Peng H, Lu X, Chen B, Chen LWL, Gabos S, *et al*. 2016. Comparative cytotoxicity of fourteen trivalent and pentavalent arsenic species determined using real-time cell sensing. J Environ Sci. 2016;(11):113-24. doi.org/10.1016/j.jes.2016.10.004.
40. Horstmann M, Witthuhn R, Falk M, Stenzl A. Gender-specific differences in bladder cancer: a retrospective analysis. Gend Med. 2008;5:385-94.

41. Parkin DM. The global burden of urinary bladder cancer. Scand J Urol Nephrol Suppl. 2008;42:12-20. doi: 10.1016/j.genm.2008.11.002.
42. Chen CJ, Kuo TL, Wu MM. Arsenic and cancers. Lancet. 1988;20:414-5. doi: 10.1016/s0140-6736(88)91207-x.
43. Chiou HY, Chiou ST, Hsu YH, Chou YL, Tseng CH, Wei ML, Chen CJ. Incidence of transitional cell carcinoma and arsenic in drinking water: a follow-up study of 8,102 residents in an arseniasis-endemic area in northeastern Taiwan. Am J Epidemiol. 2001;153:411-8. doi: 10.1093/aje/153.5.411.
44. Aballay LR, Díaz M del P, Francisca FM, Muñoz SE. Cancer incidence and pattern of arsenic concentration in drinking water wells in Córdoba, Argentina. Int J Environ Health Res. 2012;22(3):220-31. doi: 10.1080/09603123.2011.628792.
45. Hinwood AL, Jolley DJ, Sim MR. Cancer incidence and high environmental arsenic concentrations in rural populations: results of an ecological study. Int J Environ Health Res. 1999;9:131-41. doi: 10.1080/09603129973272.
46. Jansen RJ, Argos M, Tong Lin, Li JiaBei, Rakibuz-Zaman M, Islam MT, *et al*. Determinants and consequences of arsenic metabolism efficiency among 4,794 individuals: demographics, lifestyle, genetics, and toxicity. Cancer Epidemiol Biomarkers Prev. 2016;381-90. doi: 10.1158/1055-9965.EPI-15-0718.
47. Fischer LM, da Costa KA, Kwock L, Stewart PW, Lu TS, Stabler SP, Allen RH, Zeisel SH. Sex and menopausal status influence human dietary requirements for the nutrient choline. Am J Clin Nutr. 2007;85(5):1275-85. doi: 10.1093/ajcn/85.5.1275.
48. Wolff I, Brookman-May S, May M. Sex difference in presentation and outcomes of bladder cancer: biological reality or statistical fluke? Curr Opin Urol. 2015;25:418-26. doi: 10.1097/MOU.0000000000000198.
49. WHO. Arsenic in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality. Geneva: World Health Organization, 2011 (WHO/SDE/WSH/03.04/75/Rev/1).
50. FAO/WHO. Evaluation of certain contaminants in food. 72nd report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: World Health Organization, 2011 (WHO Technical Report Series, No. 959).
51. World Health Organization. Guidelines for drinking-water quality: fourth edition incorporating the first addendum (978-92-4-154995-0). Geneva: World Health Organization, 2017.

Sažetak

IZLOŽENOST ARSENU U VODI ZA PIĆE I RIZIK OD RAKA MOKRAĆNOG MJEHURA

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Općina Bogatić, dio Mačvanskog okruga, pripada Panonskom bazenu gdje su otkrivene visoke koncentracije arsena u arteškim bunarima. Brojne epidemiološke studije su potvrdile povezanost izloženosti arsenu u vodi za piće i raka mokraćnog mjehura (C67). Ova retrospektivna desetogodišnja analiza obuhvatila je standardizirane stope incidencije (ASRs) i za dob specifične stope incidencije C67 u općini Bogatić i ruralnim općinama Mačvanskog okruga. Koncentracija arsena u vodi za piće određena je u laboratoriju Zavoda za javno zdravlje Šabac (ZZJZ) 2015. godine. ASRs su procijenjene korištenjem podataka iz regionalnog registra za rak ZZJZ Šabac i uspoređene korištenjem Mann-Whitney U testa. Kontrolna populacija je regrutirana iz područja gdje nije bilo arteških bunara ili hidrogeoloških uvjeta koji bi ukazivali na povišene koncentracije arsena u vodi za piće. Razine arsena u svim arteškim bunarima u općini Bogatić bile su 1,4 do 41 puta više od maksimalno dozvoljene koncentracije (prosjek 120±165 μg/L). Ženske ispitanice iz općine Bogatić su imale više ASRs za C67 u usporedbi s populacijama u ruralnim općinama Mačvanskog okruga ($p<0,01$), dok je incidencija raka mjehura bila za 13% veća nego u centralnoj Srbiji (standardizirani odnos incidencije, 113; 95% CI 96,97-131,35). Muški ispitanici iz općine Bogatić su imali više ASRs za C67, ali razlika nije bila statistički značajna ($p>0,05$). Naše analize su ukazale na to da izloženost arsenu u vodi za piće može utrostručiti rizik od raka mjehura. Ovi rezultati podupiru zaključke prethodnih studija da može postojati povezanost između viših koncentracija arsena u vodi za piće i viših ASRs raka mjehura kod oba spola.

Ključne riječi: *Mačvanski okrug; Arsen; Rak mokraćnog mjehura; Arteški bunari; Desetogodišnja analiza*