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Original Scientific Paper

ARSENIC IN DRINKING WATER AND URINE AND ITS RELATIONSHIP WITH MALIGNANT TUMORS OF URINARY TRACT IN OSIJEK-BARANJA COUNTY, CROATIA

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SUMMARY – Increased values of arsenic in potable water in eastern Croatia has been a matter of scientific interest for the past two decades due to numerous health effects, including carcinogenic ones. This study investigated whether prolonged exposure to increased arsenic from water could be detectable through increased arsenic in urine, and whether it influenced the incidence of kidney and bladder cancer in Osijek-Baranja County. Inductively coupled plasma mass spectrometry (ICP-MS) was used for analysis of water samples from available water sources (wells, aqueducts). In addition, examinees from Osijek, Našice, Vladislavci, Čepin and Dalj gave their urine samples for analysis. Data on cancer incidence were obtained from the Institute for Public Health Registry and cumulative incidence of kidney and bladder cancer was calculated for the period between January 1, 2000 and December 31, 2018. Elevated arsenic concentration in drinking water was recorded in Vladislavci, Čepin and Osijek area with values above the allowed maximum according to the EU standards (10 μg L-1) and as a result, arsenic levels in urine of the inhabitants were also elevated. Cumulative incidence for bladder cancer showed correlation between increased arsenic in water and urine in the areas affected by increased arsenic in water. Epidemiologic data suggest a conclusion that elevated arsenic could be considered at least as a cofounding factor for urinary tract cancer.

Key words: *Water; Urine; Arsenic; Kidney; Bladder*

Introduction

Arsenic (As) represents one of the most dangerous geocontaminants of modern times. Presence of elevated arsenic in local water supplies poses significant public health problems, raising public concern. For the past two decades, arsenic in the east Slavonian water supply, in particular wider Osijek and Vinkovci area, was investigated and published, causing great concern among local inhabitants[1,2]. Arsenic contaminated water sources have been reported across Europe, from Hungary, Romania, northern Serbia to Greece, from Slovakia to Spain and United Kingdom.

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Arsenic contaminated water (with measured arsenic in water above 10 μg L^{-1}) is still being used as drinking water in local aqueducts for public use, with local exemptions such as Zrenjanin, Vojvodina, which has banned using drinking water from local aqueduct since 2004[3-6]. In the Osijek wider area, using arsenic filtered water started in 2021.

Groundwater (and surface water) can be contaminated mainly because of the natural contamination and, rarely, due to anthropogenic activities. Natural contamination can be considered as natural hydrogeological characteristics of wider Pannonian region.

Increased concentrations of arsenic in water sources of eastern Croatia are considered as a hydrogeochemical quality of the soil in aqueducts of Drava and Danube basin. Recent geological surveys suggest that water sources around Sava have 10 times lower arsenic concentrations than Danube or Drava basins[7]. Environmental arsenic pollution due to human activities includes metal industry, fossil fuels, wood, pharmaceutical or glass industry. Use of pesticides, herbicides and veterinary antibiotics based on arsenic also is an important source, as well as improper disposal of contaminated agricultural or industrial waste[8,9].

The problem of elevated arsenic in waterways from parts of eastern Croatia represents a significant health problem and a potential risk to the health of the population. First reports of arsenic in drinking water of eastern Croatia were published in water and hair of the population of Vinkovci and Osijek area in 2005[1,2]. According to previous research, elevated arsenic in the soil and green leafy vegetables (cabbage) was recorded mainly because of crop irrigation with arsenic contaminated water[10,11].

In a study by Ćavar *et al.* in 2005[1], the measured values of arsenic in the hair of examinees from Vinkovci and Osijek ranged from 1.74 to 4.31 μg kg^{-1}, and those examinees were using water with arsenic levels ranging from 17.60 up to 611.89 μg L^{-1}, respectively. In 2005, state regulations prescribed maximum allowed concentration of arsenic in water of 50 μg L^{-1}, while the European Union (EU) allows 10 μg L^{-1} [12].

In a recently published paper, the authors correlated elevated arsenic in contaminated water in eastern Croatia with elevated arsenic concentrations in hair as an indicator of long-term exposure[13].

Studying arsenic levels is mainly important for its possible health effects, which are many. Health effects can be divided into acute and chronic. Arsenic has multiorgan toxic effects, including lung, bladder and skin cancers, gastrointestinal, cardiovascular and cerebrovascular disease, respiratory and vision systems[8,14-16]. Peripheral polyneuropathy is a common consequence of acute oral arsenic poisoning. Peripheral neuritis, cognitive and memory impairment have also been reported[17].

A special clinical entity and the most striking consequence of chronic arsenic exposure is blackfoot disease. This rare condition consists of circulatory impairment in the arms and legs, finally resulting in ischemia and gangrene. It is an endemic disease that occurs exclusively in Taiwan, where inhabitants are using water with high arsenic concentrations which usually range from 170 to 800 μg L^{-1} (an equivalent to a daily dose of 0.014 to 0.065 mg kg^{-1})[18,19].

Arsenic is carcinogenic and prolonged exposure is linked with bladder and kidney cancer, particularly uroepithelium[20,21]. Winemakers from the Moselle area who consumed wine contaminated with pesticides containing arsenic from grapes had increased mortality from bladder cancer[22]. Environmental studies have confirmed a correlation between mortality from bladder and kidney cancer and elevated arsenic in water of Taiwan. Subjects with signs of chronic arsenic exposure (skin cancer, blackfoot disease, etc.) also have a higher risk of bladder cancer, as do workers in copper smelters in the United States (US) and Japan[23-25].

Materials and Methods

Area of investigations

This research was part of the project entitled Investigation of the Long-Term Consequences of the War on the Health of the Population, launched by the Ministry of Science and Education, Republic of Croatia. The area of research is shown in Figure 1. Water and urine samples were collected from the locations in two towns, Osijek and Našice, and five neighboring municipalities/villages of Čepin, Dalj and Vladislavci (including Hrastin and Dopsin). In previous studies, some of these locations had elevated arsenic values in drinking water[1,2,7,13].

Urine sampling

Urine samples of 385 subjects were collected by a nurse and analyzed using inductively coupled plasma mass spectrometry (ICP-MS) with standardized protocol for arsenic[2,13].

Water sampling

According to standardized protocol, water sam-

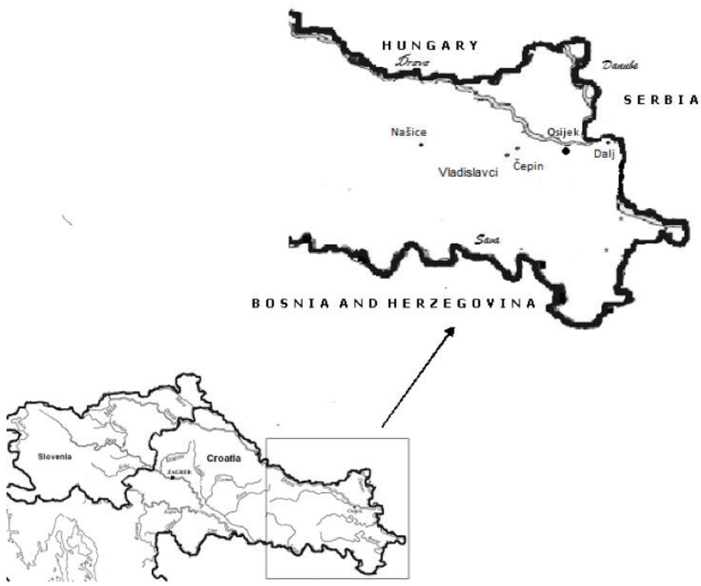

Fig. 1. Map of sampling sites (author: Assist. Prof. V. Gvozdić, MD, PhD).

ples were taken from local aqueducts or wells used for drinking water and analyzed using ICP-MS. Sampling was performed during a one week period[2,13].

Epidemiological data

Epidemiological data on the number and location of uropoietic cancer cases (kidney and bladder cases, *in situ* cancer of the bladder) were obtained from the National Cancer Registry kept at the Croatian Institute of Public Health in Zagreb, for the period from January 1, 2000 to December 31, 2018, for the examined locations. The number of inhabitants was determined using the national 2011 Census and total incidence rate was calculated *per* 100 000 inhabitants for a 19-year period giving cumulative incidence for the period[27].

Data analysis

Besides results on the mean arsenic concentrations in water and urine, data on cumulative incidence of uropoietic malignancies according to site *per* 100 000 inhabitants over the 19-year period (Table 1) were calculated by the principal component analysis method (PCA). Statistica software package, version 14.0.0.15 was used on data analysis.

Results

Arsenic concentrations in urine and drinking water presented in Figures 2-4 show similar pattern, thus leading to the conclusion that water and urine concen-

Table 1. Mean arsenic concentrations in water and urine and cumulative incidence of uropoietic malignancies according to site per 100 000 inhabitants over a 19-year period (ICD 10)

Parameter / Location	N	Water (mean) μg L^{-1}	N	Urine (mean) μg L^{-1}	Urine (median) μg L^{-1}	Urine (max) μg L^{-1}	C64	C67	D09.01
Osijek	16	26.3	64	38.8	32.4	130.4	241	438	32.4
Našice	10	0.4	80	23.3	19.8	73.2	160	277	6.2
Čepin	13	184.5	52	114.8	70.2	351	172	370	17.2
Dalj	19	1.5	106	27.3	29.5	86.3	123	328	13.7
Vladislavci	12	16.3	83	34.5	24.2	108.8	158	371	0

C64 = kidney cancer; C67 = bladder cancer; D09.01 = urinary bladder *in situ* carcinoma

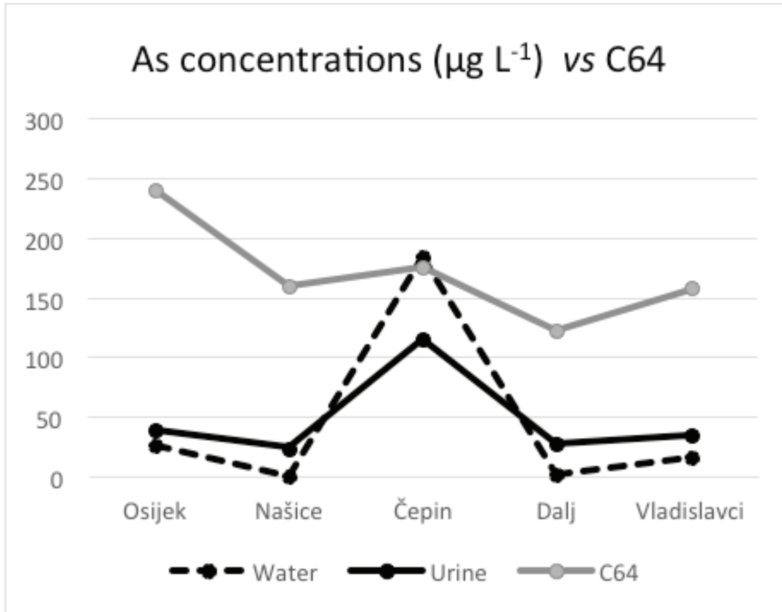

Fig. 2. Mean arsenic concentrations in water and urine according to kidney cancer cases.

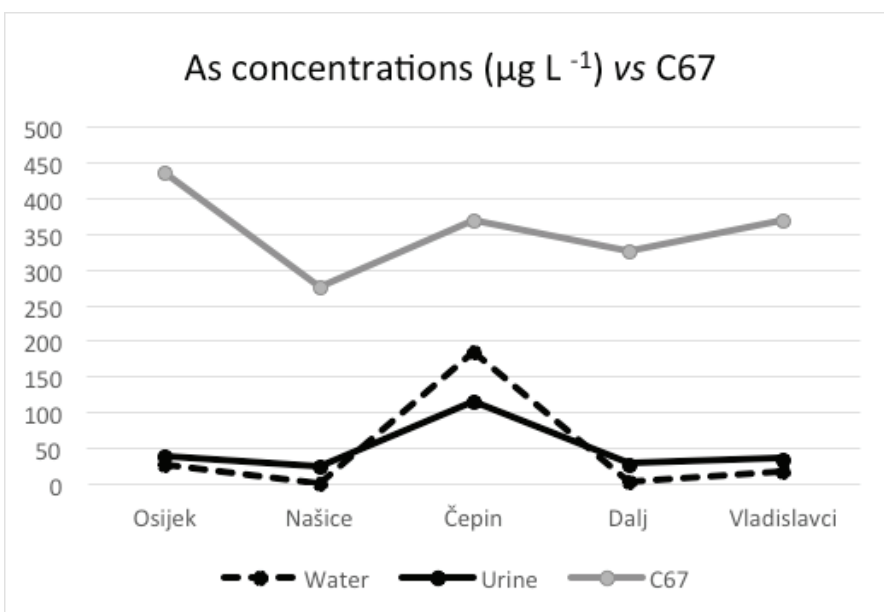

Fig. 3. Mean arsenic concentrations in water and urine according to bladder cancer cases.

trations are strongly correlated. When these data are compared with the 19-year incidence of bladder cancer and *in situ* bladder cancer, it is visible that locations with higher arsenic concentrations in both urine and water have a higher incidence of these cancers, which is depicted in Figures 3 and 4. Kidney cancer, on the other hand, shows weaker pattern that could indicate possible relation with other carcinogenic sources (Fig. 2).

Principal component analysis

Principal component analysis results are shown in Figure 5. A combination of variables allowed 88%

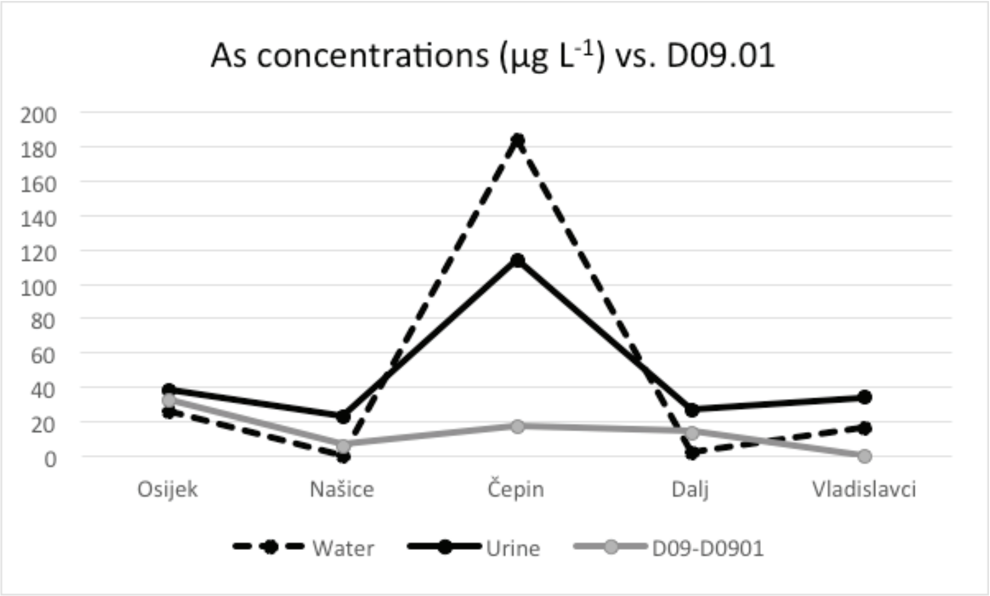

Fig. 4. Mean arsenic concentrations in water and urine according to in situ bladder cancer cases.

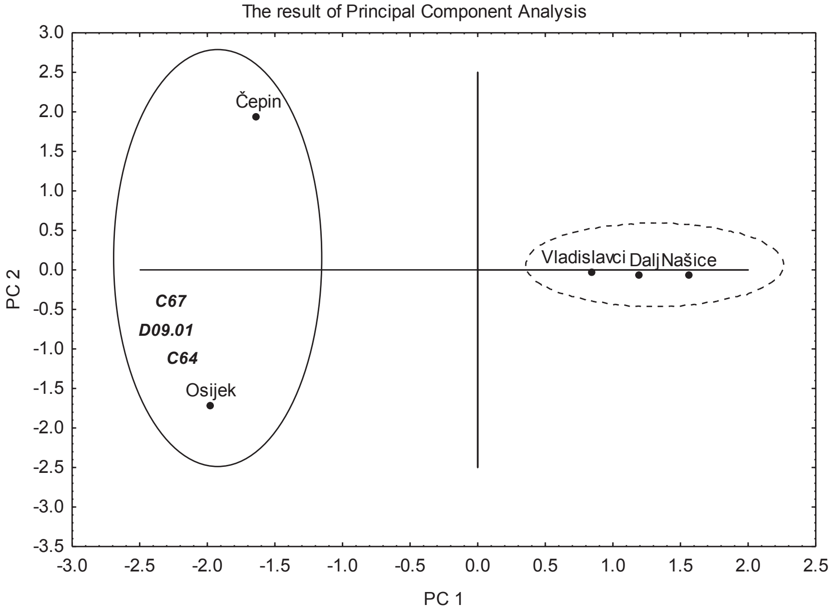

Fig. 5. Principal component analysis (PCA) biplot in the PC1/PC2 coordinate system. The result of PCA shows relationship between arsenic concentrations in water and urine according to kidney cancer, bladder and in situ bladder cancer cases at five locations in Osijek-Baranja County, Croatia.

of variance, highly sufficient for explanation of data variations. Sampling sites are divided into two clusters; the right part of Figure 5 depicts the locations of Našice, Vladislavci and Dalj with low arsenic values in water and urine and lower cumulative incidence of uropoietic malignancies, whereas the two-member elongated cluster in the left part of Figure 5 contains the locations of Osijek and Čepin with higher arsenic concentrations and higher incidence of uropoietic malignancies.

Discussion

Renal and bladder cancer are the 13th and 14th most common newly detected cancer cases in Croatian population according to data from the 2018 Cancer Registry in Croatia, accounting for approximately 10% of all cancer cases in males (5% of renal and 5% of bladder cases). In Croatia, 873 new cases of renal and 1019 new cases of bladder cancer were registered in 2018. The standardized incidence rates were 24.9/100 000 for bladder cancer, (38.1 male *vs*. 12.6 female) and 21.4/100 000 for renal cancer (29.7 male *vs*.13.6 female). In Osijek-Baranja County, 53 new cases of bladder cancer and 49 new cases of renal cancer were reported in 2018, yielding the standardized incidence rate of 17.7/100 000 (male 24.0 *vs*. 11.8 female) and 19.1/100 000 (24.7 male *vs*. 13.9 female), respectively[28].

Renal cancer accounts for 2.4% of all cancer cases, with annual incidence of 330.000 new cases in the world, making it the 13th most common cancer worldwide[29]. It is more common in the United States, Europe, Australia and Japan, twice more often in male than in female, and it is the 7th most common cancer in developed countries[30]. The age standardized incidence rate for male is 15.6/100 000 in the US, 21.9/100 000 in Czech Republic and 18.7/100 000 in Lithuania[31]. Croatia, however, has the renal cancer age standardized incidence rate of 21.4/100 000 for general population, with a higher incidence in males of 29.7/100 000[28]. Renal cancer is associated with tobacco smoking, alcohol consumption, occupational exposure to trichloroethylene, hypertension, chronic kidney disease, and diabetes mellitus[32].

Bladder cancer has annual incidence of 430 000 cases worldwide, making it the 9th most often cancer[33], predominantly in male (7th most common male cancer in the world)[34]. Bladder cancer is considered as the 4th most common in US male population. In developed western countries, it has a 3-fold higher incidence as compared with developing countries of the third world[35]. The US, Europe and Asia have the highest incidence rates, but mortality is significantly higher in developing countries, mainly due to the low level of health care[35]. The risk factors for bladder cancer are tobacco and opium smoking, professional exposure (metal and dye industry, tobacco companies), alcohol consumption or presence of *Schistosoma* in endemic areas[36,37].

In Croatia, bladder cancer has the incidence of 24.9/100 000 (male 38.1 and female 12.6/100 000)[28], higher than Latvia (12.5/100 000) but lower than China (35.1/100 000)[38,39]. Arsenic toxicity and carcinogenicity from arsenic in water is well documented but only at very high levels >200 µg L^{-1}. At lower levels, especially under 50 µg L^{-1} or even 10 µg L^{-1}, the risks and potential mechanisms are not so clear, especially from epidemiological perspective and it still needs to be established. Epidemiological studies suggest the possible relationship of bladder, liver, kidney and lung cancer with arsenic exposure[40,41].

The maximal allowable concentration (MAC) of arsenic in drinking water is still a matter of discussion. In 2001, the United States Environmental Protection Agency (USEPA) declared it to be 10 µg L^{-1}, but recently the same institution has proposed even lower dose-response slope for carcinogenic risk[5,26]. Meta regression analysis performed by Lynch *et al*. presented even lower values for risk assessment than the one proposed by USEPA, based on bladder and lung cancer epidemiological studies[42,43] .

In their comprehensive study, Tsuji *et al*.[44] performed a dose-response study to determine the risk of cancer and its relationship with arsenic in water. Based on animal models and *in vitro* study, they established a threshold for water at 65 µg L^{-1} and found it to correlate to *in vivo* effects that can cause bladder, lung and skin cancer. Finally, they suggest, with strong evidence, that the threshold for arsenic in potable water is ranging from 50 to 150 µg L^{-1} [44].

Jayasumana *et al*. investigated chronic kidney disease in Sri Lanka and found that fertilizers based on phosphates were the main sources of arsenic and important cause of the disease[45]. Bofetta and Borron[46] in their meta-analysis determined that, even in measured arsenic concentrations of up to 150 µg L^{-1} , there was no evidence for increased lung or bladder cancer risk.

The population of east Croatia, based on water arsenic levels that exceed 10 µg L^{-1}, are under prolonged exposure, and therefore, are at risk of potential toxic effects that arsenic causes[20,47]. Capak estimated that 74 177 men and 83 295 women from Osijek- Baranja County were to be considered at risk due to elevated arsenic in potable water, if applying MAC of 10 µg L^{-1} [48].

As shown in Figure 5, correlation between two locations known for higher arsenic in water (Čepin and Osijek) and arsenic concentrations in drinking water and urine, when correlated with the incidence of malignant tumors of uropoietic tract, clearly shows that higher arsenic concentrations in water and urine are linked with the increased incidence of renal and bladder cancer, and *in situ* cancer of the bladder.

Similar to this, Smith *et al.* explored cancer mortality in northern Chile, wider Antofagasta region, 40 years after the incident with arsenic in drinking water[49]. They concluded even after reduction and 40-year period, there still was elevated incidence of cancer mortality, demonstrating long latency of arsenic carcinogenicity[49]. Saint-Jacques *et al.* in their study investigated the relationship between measured arsenic in water under 50 μg L^{-1} and bladder cancer. They concluded that there was an 83% likelihood of elevated incidence and 74% likelihood of higher mortality. At higher values (150 μg L^{-1}), mortality rates were about 30% higher than those at 10 μg L^{-1} for bladder and renal cancer. According to their study, even exposure to 10 μg L^{-1} (MAC according to Croatian, EU and US legislation) can elevate the risk of bladder cancer by 40%[50].

Conclusion

Cumulative incidence of bladder and renal cancer indicates the possible relationship between elevated arsenic in water and urine over the 19-year period. Despite the fact that standardized and total incidence rates *per* year in Osijek-Baranja County do not exceed other national and international levels, a long-term epidemiological study still indicates the possible link between elevated values of arsenic in potable water and bladder cancer in larger, or kidney cancer in smaller extent for the population of Čepin, Vladislavci and Osijek. With the introduction of arsenic filtered water in public water supply, trends in the number and incidence of arsenic related urinary tract cancer should be reduced over a longer period of time. All this should be implemented in a broader frame of public health measures, preventive actions at the levels of family medicine, primary health care and population of these areas in general. Further extended epidemiological research is needed.

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Sažetak

POVEZANOST ARSENA U PITKOJ VODI I MOKRAĆI S MALIGNIM TUMORIMA MOKRAĆNOG SUSTAVA NA PODRUČJU OSJEČKO-BARANJSKE ŽUPANIJE, HRVATSKA

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Povećane vrijednosti arsena u pitkoj vodi istočne Hrvatske predmet su znanstvenog interesa posljednja dva desetljeća zbog brojnih zdravstvenih učinaka uključujući i kancerogene. Svrha rada bila je utvrditi postoji li povezanost između dugotrajne izloženosti povišenim vrijednostima arsena iz vode za piće s povišenim koncentracijama u mokraći i posljedičnom incidencijom raka bubrega i mokraćnog mjehura u Osječko-baranjskoj županiji. Masena spektrometrija induktivno spregnutom plazmom (ICP-MS) je primijenjena za analizu uzoraka vode iz dostupnih izvora vode za piće (bunari, vodovod). Uzorci mokraće prikupljeni su od stanovnika Osijeka, Našica, Vladislavaca, Čepina i Dalja. Podaci o incidenciji raka dobiveni su iz Registra za rak te je izračunata kumulativna incidencija raka bubrega i mokraćnog mjehur za razdoblje od 1. siječnja 2000. do 31. prosinca 2018. godine. Povišene razine arsena u pitkoj vodi (iznad 10 $\mu g\ L^{-1}$) zabilježene su na području Vladislavaca, Čepina i Osijeka, a kao rezultat toga razine arsena u mokraći stanovnika također su bile povišene. Kumulativna incidencija raka mokraćnog mjehura pokazuje njihovu povezanost s povišenim vrijednostima arsena u vodi i mokraći. Prema dobivenim epidemiološkim podacima, povišeni arsen u vodi se može smatrati zbunjujućim čimbenikom za tumore uropoetskog sustava.

Ključne riječi: *Voda; Mokraća; Arsen; Bubreg; Mjehur*