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Arsenic Content in Groundwater in Two Regions of the Republic of North Macedonia: The Hidden Public Health Threat

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Abstract

BACKGROUND: Arsenic groundwater contamination is a challenging public health threat in many regions globally, it also poses a threat to sustainable agriculture and food production. Hyperpigmentation, hyperkeratosis and skin lesions on the palms and feet are the first symptoms of the long term exposure, both, trough drinking water and food. In terms of its carcinogenic effect, long term exposure to Arsenic is associated with cancer of the bladder, lungs, skin, kidneys, nasal passages, liver and prostate.

AIM: The aim of the study was to analyze the effects of long-term exposure to low levels of arsenic in groundwater in two regions in the Republic of North Macedonia - Kumanovo municipality (Northeast Region) and Gevgelija municipality (Southeast Region), related to the cancer incidence rate and some other related diagnoses.

METHODS: The relationship between arsenic concentration in groundwater and the death rate due to various causes of deaths was investigated using Poisson Regression.

RESULTS: Our study despite the methodological limitations suggested important links between the chronic exposure to Arsenic in groundwater and adverse health outcomes such as diabetes mellitus, cancer of larynx, liver, bronchus and lung cancer, stomach cancer leukaemia, lymphoma and cancer of prostate, from total malignancies and malignancies of digestive organs.

CONCLUSIONS: The policy and actions in the RN Macedonia supposed to be focus on awareness raising of the local population about the adverse effects of groundwater used for irrigation, crop cultivation or even drinking, replacing high content arsenic sources (wells) with some more safe alternatives, regular monitoring of the arsenic content in the groundwater, drinking water and food (crops) or eventually, ban of the use of arsenic-contaminated wells as a last resort.

Introduction

Arsenic contamination of groundwater is a challenging public health threat in many regions globally but not only that, it also poses a threat to sustainable agriculture and food production. Natural sources are the main sources for its occurrence in the groundwater. Waters that come in contact with particular rocks and soils (arsenopyrite and pyrite minerals) that may contain Arsenic (As), also, some natural activities (volcanic eruption, erosions, forest fires) can lead to the further release of arsenic into the groundwater. High arsenic levels from anthropogenic sources come from wood processing industry (it is used as a wood preservative), processing of glass, textiles, paper, metal adhesives, from certain fertilizers and animal feeding operations, it is used in paints and dyes etc. Groundwater contains higher concentrations of arsenic than surface water (as lakes or reservoirs), therefore the demand on groundwater from municipal systems and private drinking water wells may cause water levels to drop and release arsenic from rock formations [1]. An estimated 140 million people in at least 70 countries have been drinking water containing arsenic at levels above the WHO provisional guideline value of 10 μg/L [2].

Arsenic is a metalloid, widely present in the environment and occurs in various organic and inorganic forms. In soil are mostly present inorganic forms of arsenic such as AsIII, trivalent arsenite and AsV, pentavalent arsenate which are more toxic than organic forms. While arsenite and arsenate habitually appears in water, the organic forms are rare in this medium. Two forms of organic arsenic are found in certain foods, dimethylarsinic acid (DMA) and monomethylarsonic acid (MMA). Although less toxic, they may be a health concern and are primarily found in seafood, algae and marine environments, consumption of meat, poultry, dairy products and cereals [3], [4].

After ingestion As is absorbed rapidly (45-80%) and being distributed in the body, easily crosses barriers such as placental barrier. Arsenic has a high toxicity reacting with sulfhydryl groups and affecting general protein metabolism. It is metabolized by reduction, oxidative methylation, thiolation and glutathiolation. Inorganic arsenic is a confirmed genotoxic carcinogen with additional epigenetic effects [5], [6]. According to EFSA, the degree of methylation is crucial for its toxic effects in humans. It is excreted through urine, and its half-life is about 2-3 days. In terms of arsenic carcinogenesis, increasing oxidative stress through generation of reactive oxygen species, arsenic damages the DNA and other macromolecules. Modification of epigenetic regulation of gene expression, and targets protein function due its ability to replace zinc in select proteins, is inhibiting the DNA repair. However, the strong association between arsenic and it carcinogenesis is being established in animal studies, while in humans is still not fully understood due to the complex nature of arsenic cancers [7].

The primary routes of human exposure to arsenic are via ingestion and inhalation. Dermal exposure is possible but is not considered as a primary route of exposure. Drinking contaminated water, or use of contaminated water for food preparation, for irrigation of food crops or eating contaminated food as well as tobacco smoking are the main public concerns regarding this contaminant [8].

Health effect

Human exposure to arsenic can cause both short and long term health effects. Short term exposure to high doses of arsenic can cause adverse health effects such as skin damage or problems with circulatory systems, and may have increased risk of getting cancer. WHO working group in 2005 defined the term arsenicosis as a "chronic health condition arising from prolonged ingestion (not less than 6 months) of arsenic above a safe dose, usually manifested by characteristic skin lesions, with or without involvement of internal organs" [9]. Hyperpigmentation, hyperkeratosis and skin lesions on the palms and feet are the first symptoms of the long term exposure, both, trough drinking water and food. These changes are considered as precancerous and occur after a minimum exposure of approximately five years.

In terms of its carcinogenic effect, long term exposure to Arsenic is associated with cancer of the bladder, lungs, skin, kidneys, nasal passages, liver and prostate. According to the International Agency for Research on Cancer (IARC), there is sufficient evidence in humans for cancer of the lung, urinary bladder, and skin, and limited evidence for cancer of the breast and pancreatic cancer, kidney, liver, and prostate [5], [10]. Although the inorganic arsenic does not directly interact with DNA, "induction of the oxidative stress plays a crucial role in formation of DNA base oxidation as well as both DNA single and double strand breaks". Chronic exposure to inorganic As in utero or adult life is also associated with epigenetic changes that may lead to aberrant gene expression [5].

The majority of studies come from the world regions where inorganic arsenic is naturally present in high concentration in the groundwater (Argentina, Bangladesh, Cambodia, Chile, China, India, Mexico, Pakistan, the United States of America and Viet Nam), analyzing cancer incidence after an exposure to high concentrations of arsenic. However, there is waist epidemiological evidence claiming sufficient and causal associations between low to moderate exposure to inorganic As (defined as concentrations of arsenic in water of less than 150 μg/l) [5] and other adverse health effects such as stillbirth, spontaneous abortion, infant mortality, congenital heart disease, neurodevelopmental effects, chronic kidney disease, ischemic heart disease and carotid artery atherosclerosis etc [5]. Limited and insufficient evidence exists also for the association between low to moderate exposure to As and male fertility, diabetes and metabolic syndrome, neurotoxicity, stroke and hypertension, arsenic-induced myocardial infarction, glucose metabolism [5]. Having in mind that most of those effects and evidence are generated from the studies conducted in regions with low or medium income (China, Bangladesh), the role of some important modifying factors has to be taken into the consideration especially nutrition or health status of the population.

Therefore, with this study we aim to analyze the effects of long-term exposure to low levels of arsenic in the groundwater in two regions in the Republic of North Macedonia - Kumanovo municipality (Northeast Region) and Gevgelija municipality (Southeast Region), related to the cancer incidence rate and some other related diagnoses. The adverse effects on the children development and pregnancy outcomes are not analyzed in this study.

Methods

Mortality data for the health outcomes of interest were provided by the State Statistical Office along with latest population Census data (2021). The water sampling and analysis were performed in the Institute of Public Health in compliance with the requirements of the ISO 5667-3 [11]. The samples were analyzed within the 24 hours from the time of the collection for the total presence of As, according to the ISO 15586. A flow injection atomic absorption spectrometry (FIAS) was employed for the determination of the total arsenic content [12]. Period covered by the study - 2017 to 2023.

Statistical analysis of the data is performed using the IBM Statistical Package for the Social Sciences (IBM SPSS Statistic for Windows, Version 19.0. Amonk, NY: IBM Corp.). Descriptive statistics is done in series with numerical marks (pollutants concentration), means and standard deviation; ±95% CI, minimum, and maximum. The relationship between arsenic concentration in groundwater and different health outcomes of interest - the death rate due to various causes of deaths was investigated using Poisson Regression at a significant level (P<0.05).

The study area

The Republic of North Macedonia is located in Southeast Europe, in the center of the Balkan Peninsula and covers an area of 25,713 km². For statistical, economic and administrative purposes, the territory of the RN Macedonia is divided into eight planning regions. Administratively, the territory is divided in 80 municipalities, 10 of which constitute the City of Skopje, as a separate unit of local self-government (Figure 1). According to the last Census conducted in 2021, there are 1.836.713 citizens [13], [14].

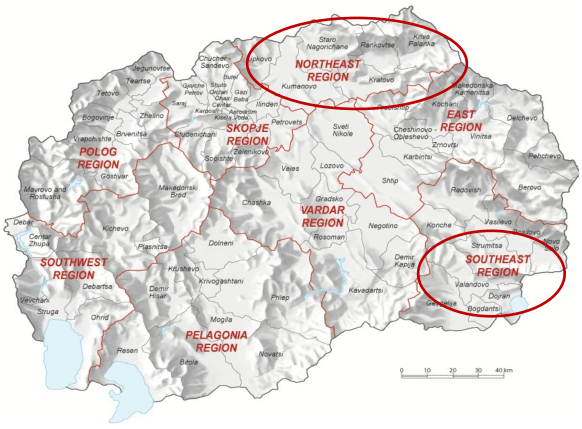

*Figure 1: Statistical regions in the Republic of North Macedonia (*Source: State Statistical Office, 2024)

Based on the data from the Census (2021), the total population of the Kumanovo municipality (comprise 47 villages and the city of Kumanovo) is 105 484, that presents 5.8% of total population of the country, and Gevgelija municipality (comprise 17 villages and the city of Gevgelija) with total population of 22 988 residents (1.3% of total population).

Geology

The selection of this two regions - the municipality of Kumanovo (Northeastern Region) and the municipality of Gevgelija (Southeastern Region), has been done based on the findings from the analysis of groundwater samples indicating increasing trends in arsenic concentration during the time, especially in the region of the municipality of Gevgelija. Agriculture and food production are among the main economic activities in both regions, but is also important to emphasize the tradition of the population to use the groundwater from private wells for irrigation, and in some cases even for drinking especially in the rural areas although there is an access to public water supply systems.

The relief of the RN Macedonia is mainly mountainous. According to Stafilov et al., the highest average content of arsenic in the country was found in soil from the areas with dominant occurrence of magmatic rocks in area of Paleogene and area of Neogene soil. The mean content of arsenic in topsoil in Macedonia is 9.2 mg/kg which is lower than European topsoil content (12 mg/kg). (Table 1).

Table 1: The mean values of arsenic in soil in different regions in the RN Macedonia

Region	Mean mg/kg	Md mg/kg	Min mg/kg	Max mg/kg
Pelagonian	5.6	6.0	<1.0	140.0
Southwestern	11.0	12.0	<1.0	290.0
Polog	14.0	15.0	3.0	160.0
Vardar	9.3	9.0	1.0	720.0
Skopje	11.0	10.0	3.0	30.0
Southeastern	9.7	9.0	2.0	120.0
Eastern	9.7	10.0	1.0	170.0
Northeastern	10.0	10.0	2.0	160.0

Source: Stafilov T, Shajn R. Geochemical atlas of the Republic of Macedonia. 2016.

The content of arsenic in soil is slightly higher than the country mean value in both regions - in the Southeastern Region 9.7 mg/kg (2.0-120.0 mg/kg) and Northeastern Region, with mean content of arsenic of 10.0 mg/kg (2.0-160.0 mg/kg) [15].

Results

Aiming to understand the relationship between arsenic concentration in the groundwater and mortality rate due to some cancers, Alzheimer disease and diabetes mellitus, we have analyzed 243 groundwater samples from the two selected regions. Analyzing the concentration of arsenic in groundwater samples over the observed seven-year period (2017-2023), along with other metals, we found increasing concentration of arsenic over time (although bellow the WHO provisional guideline value of 10 µg/L) (Table 2). This particularly applies to groundwater samples from the Southeastern Region (Gevgelija).

The average monthly concentration of arsenic is within the range of 1.3-8.9 µg/L in Gevgelija, with maximal concentrations ranging from 17.3-24.4 µg/L. In the municipality of Kumanovo, the average concentration of arsenic is lower, ranging from 1.3-2.7 µg/L, and the maximal ranging from 4.5-8.8 µg/L. In general, in the observed period, the highest concentration of arsenic has been reported from July to September with some exceptions (December or January).

Table 2: Concentration of arsenic (μg/L) in the groundwater samples, period observed 2017-2023

Region	N	Min	Max	Mean	Std. Deviation	Skewness		Kurtosis	
					Statistic	Statistic	Std. Error	Statistic	Std. Error
Gevgelija	127	0.00	24.41	5.34	7.397	1.375	0.215	0.482	0.427
Kumanovo	116	0.00	8.79	2.04	2.378	0.944	0.225	-0.687	0.446

Source: Institute of Public Health of the RNM. 2024

Aiming to compare the findings of our study with the countries or world regions which are at the top of the list in terms of the arsenic contamination and concentrations in groundwater such as China, India, Bangladesh, Iran and some other countries [16], we selected some health outcomes that have been used in the study from Iran (Table 3) [17].

In Table 3 is presented the death rate per 100 000 populations due to different types of cancer, Alzheimer disease and diabetes mellitus. In the observed seven-year period, Gevgelija municipality has higher all-cause mortality rate compared to the Kumanovo (1408.7 per 100 000 population vs 1156.0/100 000). Specific mortality shows that the highest mortality rate is observed due to total malignant (C00-C97) in both regions - Gevgelija 232.3/100 000 and Kumanovo 201.00/100 00, especially due to the lung cancer (Gevgelija 65.0/100 00 and 46.4 in Kumanovo) and malignant of the digestive system (Gevgelija 65.7/100 000 and 66.3 in Kumanovo). Also, high mortality rate is observed due to diabetes mellitus (101.4 and 71.4/100 000).

Table 3: Summary statistic of the mortality rate (per 100 000 population) in the regions observed, for the period 2017-2023

Mortality (disease, ICD 10 code)	GEVGELIJA				KUMANOVO			
	Min	Max	Mean	Std. Dev.	Min	Max	Mean	Std. Dev.
Alzheimer disease (G30–G30.9)	4.6	32.4	14.57	10.326	14.3	61.2	38.43	18.636
Bronchus and lung (C34, C34.1, C34.8, C34.9)	41.7	88.0	65.00	14.549	36.7	59.1	46.43	6.630
Bladder (C67, C67.9)	4.6	13.9	8.57	3.047	2.0	12.2	6.57	3.207
Breast (C50, C50.8, C50.9)	13.9	27.8	21.29	4.424	8.2	22.4	14.71	5.282
Cervix uteri, uteri (C53, C53.9, C54, C54.1, C54.9, C55)	0.0	18.5	6.86	5.956	5.1	12.2	7.43	2.699
Colon (C18, C18.8, C18.9, C19, C20, C21)	9.3	27.8	18.00	6.325	18.3	32.6	24.57	5.381
Gallbladder (C23)	0.0	4.6	.71	1.890	1.0	3.1	1.86	.900
Kidney, renal pelvis (C64, C65)	0.0	9.3	4.71	3.684	1.0	4.1	2.29	1.380
Leukaemia (C90.1–C95.9)	0.0	13.9	4.71	6.601	2.0	5.1	3.86	.900
Liver (C22, C22.0, C22.1, C22.4, C22.7, C22.9)	4.6	13.9	8.00	3.317	2.0	14.3	9.14	4.337
Lymphoma (C81, C81.9, C83, C83.0, C83.9, C85.9, C84.4, C85.1)	0.0	13.9	2.71	5.314	1.0	6.1	3.29	1.976
Larynx (C32, C32.9)	0.0	13.9	6.71	4.424	2.0	6.1	4.86	1.345
Meninges, brain (C70, C70.9, C71, C71.0, C71.9)	0.0	23.2	9.86	8.688	3.1	10.2	6.86	2.340
Malignant neoplasms (C00-C97)	190.0	264.1	232.29	23.908	174.3	225.3	201.00	18.111
Malignant neoplasms of digestive organs (C15-C26)	55.6	78.8	65.71	8.995	43.8	81.5	66.29	12.311
Oesophagus (C15, C15.9)	0.0	9.3	2.00	3.606	1.0	4.1	1.71	1.113
Ovary (C56)	0.0	9.3	4.71	3.684	1.0	5.1	2.86	1.574
Pancreas (C25, C25.0, C25.9)	9.3	32.4	19.29	8.159	9.2	19.4	13.29	3.147
Prostate (C61)	0.0	23.2	8.57	8.142	8.2	16.3	11.00	3.055
Stomach (C16.9, C16.8, C16)	9.3	27.8	17.29	8.077	8.2	15.3	11.86	2.968
Skin of scalp and neck (C44.4)	0.0	4.6	1.43	2.440	1.0	3.1	1.71	.951
Skin (C43.9, C44, C44.9, C44.7)	0.0	9.3	4.14	3.185	2.0	10.2	5.57	2.760
Unspecified diabetes mellitus (T1D+T2D) E10, E10.2, E10.7, E10.9, E11–E11.9, E14–E14.9	51.0	157.6	101.43	41.725	56.1	97.9	71.43	17.203

Source: State Statistical Office. 2024

According to the results of Poisson regression analysis (Table 4), the highest relationship with arsenic concentration and different causes of death at a significant level (p-value <0.05), in Gevgelija region is observed in terms of the cancer of the cervix uteri and uterus 1.54 (1.25-1.90), ovary 1.50 (1.17-1.93), larynx 1.38 (1.11-1.71), liver 1.30 (1.07-1.59), diabetes mellitus 1.25 (1.18-1.32), stomach cancer 1.23 (1.07-1.41), bronchus and lung cancer 0.92 (0.85-0.99), leukaemia 0.69 (0.49-0.99), lymphoma 0.58 (0.35-0.97) and cancer of prostate 0.58 (0.43-0.77).

In Kumanovo region, such a relationship is observed in terms of diabetes mellitus 1.46 (1.17-1.82), bronchus and lung cancer 1.33 (1.00-1.76) and as well as in terms of the mortality from total malignancies 0.85 (0.72-0.99), malignancies of digestive organs 0.63 (0.46-0.86) and liver cancer 0.19 (0.47-0.79).

Discussion

Inorganic arsenic is naturally present at high levels in the groundwater of a number of countries, including Argentina, Bangladesh, Cambodia, Chile, China, India, Mexico, Pakistan, Iran, the United States of America and Viet Nam. The biggest scientific evidence for the adverse effect of the arsenic actually come from the studies conducted in these area. Long-term exposures to concentrations of arsenic in water of less than 150 μg/L are considered as exposure to low to moderate levels of arsenic [5], [16]. In Europe, groundwater with high concentrations of arsenic and other elements like manganese, iron, ammonia and organic substances is reported in Austria and the eastern Croatia. The appearance of inorganic arsenic in groundwater in Croatia is mainly caused by arsenic from natural geological sources. Since the groundwater is the main source of drinking water for the population in this area, almost 200 000 people are daily drinking water with arsenic concentration ranging from 10 to 610 μg/L. The arsenic concentration in drinking water in water supply system of some Croatian cities such as Osijek is 40 μg/L, Èepin (170 μg/L) and Andrijaševci (610 μg/L) [18]. In Serbia, Zrenjanin municipality, the arsenic concentration is about 420 μg/L in the public water supply [19]. In Turkey, Boron and Arsenic were the two important contaminants determined in the groundwater around the Bigadiç borate mines. Arsenic is the major pollutant and it ranged from 33 to 911 μg/L in the groundwater samples [20], [21].

Table 4: Poisson Regression analysis, evaluation of the relationship between the arsenic concentration and mortality rate of selected health outcomes

Diseases (ICD10 code)	GEVGELIJA			KUMANOVO		
	IRR*	[95% CI]	P_value	IRR*	[95% CI]	P_value
Alzheimer disease, G30–G30.9	1.104	.944-1.292	.217	1.110	.799-1.543	.534
Bronchus and lung, C34, C34.1, C34.8, C34.9	.917	.845-.996	.039	1.331	1.004-1.764	.047
Bladder, C67, C67.9	.864	.684-1.090	.217	.273	.066-1.125	.072
Breast, C50, C50.8, C50.9	1.038	.908-1.187	.585	.867	.485-1.550	.630
Cervix uteri, uteri, C53, C53.9, C54, C54.1, C54.9, C55	1.542	1.253-1.897	.000	.638	.254-1.605	.340
Colon, C18, C18.8, C18.9, C19, C20, C21	.874	.745-1.025	.097	.745	.463-1.200	.226
Gallbladder, C23	.577	.211-1.578	.284	1.091	.242- 4.922	.910
Kidney, renal pelvis, C64, C65	1.223	.938-1.593	.136	.857	.195- 3.771	.838
Leukaemia, C90.1–C95.9	.692	.485- .988	.042	1.043	.361-3.017	.937
Liver, C22, C22.0, C22.1, C22.4, C22.7, C22.9	1.299	1.065-1.585	.010	.194	.047- .791	.022
Lymphoma, C81, C81.9, C83, C83.0, C83.9, C85.9, C84.4, C85.1	.577	.345-.967	.037	.900	.267-3.029	.865
Larynx, C32, C32.9	1.377	1.112-1.705	.003	1.034	.400-2.672	.944
Meninges, brain, C70, C70.9, C71, C71.0, C71.9	1.069	.880-1.297	.502	.400	.124-1.287	.124
Malignant neoplasms (C00-C97)	.997	.956-1.039	.880	.847	.722-.992	.040
Malignant neoplasms of digestive organs (C15-C26)	1.063	.986-1.146	.112	.629	.461-.857	.003
Oesophagus (C15, C15.9)	.845	.519-1.376	.497	1.200	.263- 5.477	.814
Ovary, C56	1.501	1.168-1.929	.001	1.500	.501-4.487	.468
Pancreas, C25, C25.0, C25.9	1.058	.920-1.216	.428	.643	.323- 1.278	.208
Prostate, C61	.577	.432-.772	.000	1.333	.747-2.379	.330
Stomach (C16.9, C16.8, C16)	1.227	1.069-1.408	.004	.640	.309-1.327	.640
Skin of scalp and neck (C44.4)	.948	.552-1.629	.848	.545	.070-4.225	.562
Skin, C43.9, C44, C44.9, C44.7	1.210	.912-1.607	.186	.500	.154-1.624	.249
Unspecified diabetes mellitus (T1D+T2D) E10, E10.2, E10.7, E10.9, E11–E11.9, E14–E14.9	1.250	1.181-1.322	.000	1.463	1.173-1.824	.001

*IRR (Incidence Rate Ratio).

In the Republic of North Macedonia, a region well known for high concentrations of arsenic is Kozuf metallogenic district in Southeast Region. As a result of past mining activities, there are dumps with anomalous concentrations of antimony, arsenic, lead, mercury and thallium at abandoned, that represent a significant environmental and health hazards. Here is located world-known Allchar (mine gold–arsenic–antimony–thallium deposit), ore deposits/mineral occurrences (Majdan - arsenic), Dudica - copper-gold and Arnicko - antimony) and other ore deposits are supposed to have existed here but have remained unknown due to the lack of exploration. Through the waterways the entire area is drained into the river Vardar, transition river shared with neighboring country Greece [1,22]. The city of Gevgelija used to face a severe arsenic contamination of the groundwater (Moin wells) and drinking water [23] until 2009, when the drinking water from the public water supply system has been banned for human consumption and use. The problem has been finally solved about 2018. In the Vardar Region near the city of Kavadarci actually the highest concentration was determined in the soil sample due to the lithogenic enrichment of arsenic minerals but also due to this longtime exploitation from the Allchar mine [15]. In Kumanovo Region, it was found that the distribution of most elements follows the lithology of the studied area, except for some elements (As, Pb, and Zn) whose higher contents were found in some specific parts of sub-areas, which is due to the current and past mining activities in the region [24].

Numerous studies have explored arsenic contamination in groundwater, particularly in South Asia (e.g., Bangladesh, India), where groundwater arsenic levels have been a major public health concern. These studies often mention how seasonal variations in water levels (due to monsoons or dry seasons) can influence arsenic concentrations [25,26]. As mentioned before, in our study, the highest concentration of arsenic has been reported from July to September in the observed period, with some exceptions (December or January). Among other contributing factors for variation of groundwater arsenic concentrations, intense agricultural activities due to the use of pesticides, sediment disturbances are also identified. Warmer temperatures can sometimes lead to increased microbial activity, which can affect the reduction or oxidation of arsenic in the groundwater as well [27], [28]. This could either mobilize or immobilize arsenic, depending on the local conditions.

The mean concentration of arsenic in analyzed samples of groundwater in the case of municipality Kumanovo and Gevgelija is bellow 10 µg/L. Still, there are samples exceeding the WHO limit values and reaching maximal concentrations up to 24.4 µg/L in Gevgelija region, and 8.8 µg/L in Kumanovo region respectively. Groundwater is a major source not only for water supply but also for irrigation globally, which is the case in both regions in North Macedonia. Hence, if arsenic polluted groundwater is used for irrigation and crop cultivation, serious problems may occur in agriculture production but as well as can impact the population health. Arsenic can accumulate in the topsoil making the soil unfit for agriculture production. Several studies have already proved that the consumption of rice and vegetables cultivated with As-elevated groundwater is a potential contributor to the human body globally. Some plants like cabbage, potatoes, rice, lettuce and carrot can accumulate it in the edible parts of the plant "making it unsuitable for human consumption or other intended use" [29], [30].

Regarding the health effects and impact of the Arsenic, the magnitude of this public health problem globally can not be estimated due to many factors: individual and population characteristics of the exposed in different geographical areas, lack of methodology to distinguish cases of cancer caused by arsenic from cancers induced by other factors as well as lack of universal definition of the disease caused by arsenic [4]. According to Joint FAO/WHO Expert Committee on Food Additives (JECFA) and their reevaluation, "in certain regions of the world where concentrations of inorganic arsenic in drinking-water exceed 50–100 µg/L, there is some evidence of adverse effects. In other areas, where arsenic concentrations in water are elevated (10–50 µg/L), there is a possibility of adverse effects. These would be at a low incidence that would be difficult to detect in epidemiological studies".

The findings of our present study are in line with the studies obtained from the most polluted regions worldwide. It showed a positive and statistically significant association between the arsenic concentration in groundwater and some of the selected health outcomes - mortality due to cancer of larynx, liver, diabetes mellitus, stomach cancer, leukaemia, lymphoma and cancer of prostate. In Kumanovo region, we found positive association with mortality due to diabetes mellitus, bronchus and lung cancer and from total malignancies and malignancies of digestive organs also.

The strongest scientific evidence for organ-specific arsenic carcinogenicity is in skin, lung, bladder and kidney with evidence for arsenic contributions to other cancers [31], [32]. In the Iranian study, a positive association has been found between arsenic concentration and mortality due to breast cancer, stomach, liver and other digestive organs, and leukemia as well [17]. Regarding the association with lung cancer, the strongest evidence has been derived from occupational exposure studies [32], [33]. However, other studies reported that the main source of human exposure to arsenic comes trough the chronic exposure to contaminated drinking water compared to the contaminated soil, where such an association has not been found [34]. Taiwan study confirmed that there is a dose-response association of lung cancer and arsenic exposure especially at higher concentrations (concentrations between 100 and 300 µg/L, with excess risk (RR 1.54, 0.97-2.46)). This study reported significant dose-response trends and the synergistic effect of arsenic exposure and cigarette smoking in the appearance of squamous and small cell carcinomas, but not in adenocarcinoma. The main contributing factor is the duration of exposure. Thus, this study showed that long-term exposure to even lower concentrations of arsenic will lead to lung cancer [35].

The evidence is more limited in terms of the increased gastrointestinal tract cancers, prostate and laryngeal cancer, and especially in terms of the breast cancer where other genetic factors can have strong modifying role in arsenic-associated risk [36], [37]. The role of environmental exposures to hormonal agents and other factors such as exposures to endocrine disrupting substances, indoor and outdoor air pollution, polycyclic aromatic hydrocarbons (PAHs), arsenic, accompanied with family history and genetic predisposition can induce epigenetic changes in an exposure or disease. They are "likely to contribute to the epigenetic dysregulation of oncogenes and tumor suppressor genes in breast cancer" [38].

Some studies suggest a potential association between long-term exposure to arsenic and ovarian cancer risk, the evidence is still inconclusive and further research is needed. Many of the studies are limited by small sample sizes, confounding factors, or lack of direct focus on ovarian cancer specifically [17,39,40].

In the present study we did not find association for the mortality due to skin cancer which is expected due to the fact that skin lesions and cancer appear to be more prevalent at exposures to drinking water levels in excess of 50 µg/L [41], [42]. According to the study conducted in Taiwan, skin cancer (mostly epidermoid and basal cell carcinoma) was considered as better indicator of long-term (at least 20 years) cumulative exposure to arsenic than the arsenic content in hair or urine [43].

Despite the findings reported by the IARC about the limited evidence that the liver is a target site for the carcinogenic effects of arsenic and arsenic compounds in humans (which is not a case in rodents), also the evidence is limited in terms of the kidney and prostate cancer in humans [10], [44]. Some other studies observed mortality due to liver cancer, pancreatic cancer, cancer of stomach and other digestive organs. The Taiwan study reported significantly high standardized mortality ratio (SMR) and cumulative mortality rate in blackfoot disease-endemic areas for cancers of bladder, kidney, skin, lung, liver, and colon [43].

Among the potential mechanisms in which arsenic induces cancer, gut microbe perturbations, genotoxic effects, and epigenetic modification are listed. They act synergistically and combinably. The gut microbe perturbations lead to inflammation that is the major factor for development of cirrhosis and hepatocellular carcinoma as a final outcome [46]. The systematic review of the carcinogenic effect of arsenic in relation to the digestive cancers suggested an association, particularly in hepato-pancreatico-biliary (HPB) malignancies. In summary of the findings of this systematic review was reported that 43% (3/7) and 48% (10/21) studies highlighted an association between arsenic and the incidence and mortality of digestive cancers, respectively [46]. The positive association was reported in study from Argentina in terms of the exposure trough drinking water and pancreatic and colon cancers in men and colon cancer in women [47]. In the present study, we found associations with liver cancer in Gevgelija region and a positive association for mortality due to the malignancies of the digestive organs in Kumanovo. The study conducted in Chile that observed the most common childhood cancers (leukemia and brain cancer among other), reported that exposures to arsenic in drinking water during early childhood may result in an increase in childhood liver cancer mortality, with the highest rate reported in the age group 0-19 (for males and females pooled, the RR was 10.6 (95% CI 2.9–39.2; p<0.001) [48]. In the US-based prospective cohort study, arsenic exposure (measured in urine) was associated with increased mortality from lung, pancreas and prostate cancer. The risk was statistically non-significant in terms of kidney cancer and liver cancer [49], [50].

The other health outcome that we observed was mortality due to leukaemia and lymphoma. Despite the main limitation of the study (low mortality rate from these malignancies 4.7/100 000 and 2.7/100 000 in Gevgelija and 3.9 and 3.3/100 000 in Kumanovo), we found a positive association between arsenic concentration and mortality only in Gevgelija region. In the US-based prospective cohort study, arsenic exposure was associated with decreased mortality from lymphatic and hematopoietic cancers. The study from Taiwan reported also a negative association between arsenic concentration in drinking water in both sexes, supporting the "dual effects of arsenic on carcinogenesis and also a protective effect against hematologic malignancies" [51]. This finding leads to the conclusion that "arsenic plays different roles in the carcinogenesis of solid cancers and hematologic malignances". Namely, it is well known fact that arsenic trioxide for example had been approved by the FDA as a chemotherapeutic for leukemia in 2000 "bringing an ancient drug into the modern era" again. Arsenic trioxide also has a therapeutically use in some type of ovarian cancers [52], [53], [54].

In our study, we found a positive association between arsenic concentration in the groundwater and total mortality for malignances (ICD10 code C00-C97) only in Kumanovo (0.85 (0.72-0.99). Overall, in some studies that have observed the same health outcome, reported that increasing urine arsenic concentrations showed a positive but non-significant association with total cancer mortality [49], [50]. The Chilean study on the childhood cancers, fund no associations between the arsenic exposures trough drinking water and mortality from the most common cancers in children - brain cancer and leukemia [48].

A systematic review of experimental and epidemiological studies analyzing the association of arsenic in drinking water and type 2 diabetes, in summary concluded that environmental arsenic exposure is related with some of the main characteristic od T2DM (insulin resistance, micro- and macrovascular complications of T2DM, compromised glucose tolerance also). Still, according to them, "the current available evidence is inadequate to establish a causal role of arsenic in diabetes", and further research is required in order to fully understand the complex interactions, mechanisms and contributing factors [55]. Some other studies have also revealed high rates of diabetes among other health outcomes (asthma, hepatomegaly, few cases of renal, skin, breast and cervix cancer in the exposed population) [56], [57], [58], while a Canadian and study conducted in Cyprus revealed no association between Arsenic in groundwater and risk of diabetes after some adjustments of the confounding factors (age, smoking, seafood consumptions etc. [59], [60]. In the present study, we have not found a significant relationship between arsenic exposure and mortality due to Alzheimer's disease.

Limitations

In the field of limitations of this study, lack of information about some factors that potentially could contribute to the diseases risk such as smoking, physical inactivity, BMI, diet, occupation, genetics, family history of cancers is the major ones. In this regard, this study could be a base for some further, more detailed studies that would encompass all these confounding and potentially contributing factors. Small number of death cases due to some malignancies such as gallbladder, lymphoma, oesophagus or cancer of skin of scalp and neck are reducing statistical significance of the analysis.

Conclusions

Despite extensive epidemiological evidence on the association between arsenic concentration in water and the increased risk of developing various types of cancer, studies on the effects of arsenic present in groundwater or drinking water from countries of the Balkan region are still lacking.

Our study despite the methodological limitations suggested important links between the chronic exposure to Arsenic in groundwater and adverse health outcomes such as diabetes mellitus, cancer of larynx, liver, bronchus and lung cancer, stomach cancer etc. in the RN Macedonia. Therefore, bearing in mind that the most effective and efficient strategy to decrease arsenic-induced cancer risk is to reduce arsenic exposure, the policy and actions in the RN Macedonia supposed to be focus on awareness raising of the local population about the adverse effects of groundwater use for irrigation, crop cultivation or even drinking. The latter is particularly important because both analyzed regions have access to safe drinking water in both, urban and rural areas. Replacing high content arsenic sources (wells) with some more safe alternatives (surface water or collected rainwater), blending low-arsenic water with higher-arsenic water and regular monitoring of the arsenic content in the groundwater, drinking water and food (crops) or eventually ban of the use of arsenic-contaminated wells as a last resort is recommended.

Author Contributions

Both authors contributed to the study's conception and design. Data collection was performed

by Atanas Minov. Mirjana Dimovska performed the computations and writing of the manuscript. Both authors read and approved the final manuscript.

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