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ORIGINAL ARTICLE

Arsenic levels in the groundwater of Korea and the urinary excretion among contaminated area

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Drinking water is a main source of human exposure to arsenic. Hence, the determination of arsenic in groundwater is essential to assess its impact on public health. Here, we report arsenic levels in the groundwater of 722 sites covering all six major provinces of Korea. Water was sampled in two occasions (summer, 722 sites and winter, 636 sites) and the arsenic levels were measured with highly sensitive inductively coupled plasma-mass spectrometry method (limit of detection, 0.1 μg/l) to encompass the current drinking water standard (< 10 μg/l). Seasonal variation was negligible, but the geographical difference was prominent. Total arsenic in groundwater ranged from 0.1 to 48.4 μg/l. A 88.0–89.0% of sites were < 2.0 μg/l and the remaining ones generally did not exceed 10 μg/l (6.4–7.0%, 2.0–4.9 μg/l; 2.4–3.0%, 5.0–9.9 μg/l). However, some areas (1.0–9.2%) exhibited > 10 μg/l. Notably, urinary arsenic excretion of people around these regions was markedly higher compared with non-contaminated areas (< 5 μg/l) (79.7 ± 5.2 μg/g ($N = 122$) *vs* 68.4 ± 5.4 μg/g ($N = 65$) creatinine, $P = 0.052$). All stratified analysis also revealed higher urinary excretion, where a statistically significant difference was noted for non-smokers (85.9 ± 12.7 *vs* 54.0 ± 6.3, $P = 0.030$), suggesting that arsenic-contaminated groundwater may contribute to its systemic exposure.

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INTRODUCTION

Arsenic (As) is a toxic metalloid ubiquitously distributed in soil and water. Arsenic occurs naturally from rock and volcanic eruption, and also from anthropogenic activities that include mining, smelting of ores, and agricultural chemicals.[1,2] Arsenic exists in the environment predominantly as water-soluble inorganic arsenite (As^{III}) or arsenate (As^{V}),[3,4] and drinking water is the major source of human exposure. Chronic exposure to As through the ingestion of contaminated water was demonstrated to cause various health problems in several countries such as Bangladesh, West Bengal, Vietnam, and Taiwan.[5–8]

A strong association of the ingestion of arsenic-contaminated water with non-carcinogenic diseases, such as skin pigmentation, keratosis, cardiovascular disease, diabetes, and peripheral neuropathy, as well as cancers in the skin, lung, and bladder is well established.[9–11] Based on a wealth of epidemiological evidence supporting the potent carcinogenicity of arsenic, it is classified as group I (carcinogenic to human) by the International Agency for Research on Cancer. Arsenic has also ranked the first in the priority list of hazardous substances by the Agency for Toxic Substances and Disease Registry, which is decided based on the toxicity, frequency of occurrence, and probability of human exposure.[12]

In an effort to protect human health from the hazardous impacts of arsenic, World Health Organization and several countries have attempted to strengthen the standard of arsenic contamination in drinking water. United States Environmental Protection Agency (EPA) has reinforced a new maximum contamination level (MCL) of arsenic in drinking water at 10 μg/l from the previous MCL of 50 μg/l in 2001. Currently, EPA and World Health Organization agreed on the regulation levels of arsenic in drinking water at 10 μg/l, but there is a movement to decline it down to 2 μg/l.[13] Korea also fortified the regulation of arsenic level to 10 μg/l from 50 μg/l in accordance with the global trend in 2008.

Groundwater is still a major source of drinking water, especially in rural areas. It is also being extensively used for agriculture, food processing, and washing, suggesting its additional contribution to systemic arsenic exposure via contaminated foods or utensils. Therefore, arsenic contamination of groundwater may be a major threat to public health, indicating an urgent need for the accurate monitoring of arsenic levels nationwide ideally with a sensitive quantitative method to meet the current standard (10 μg/l, 10 ppb). Indeed, many countries regularly monitor arsenic contamination in drinking water and groundwater.[7,14,15]

Here, we monitored arsenic concentrations in the groundwater of Korea nationwide and evaluated its geographical differences and seasonal variation with a highly sensitive analytical method, inductively coupled plasma-mass spectrometry (ICP-MS) with the limit of detection of 0.1 μg/l, which was 100-fold lower compared with the current drinking water standard, 10 μg/l. In addition, we measured and compared the urinary arsenic excretion of the people around contaminated groundwater

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sites (As $>10\,\mu g/l$) with geographically matched non-contaminated areas (As $<5\,\mu g/l$) to determine the contribution of contaminated groundwater to the systemic arsenic exposure.

METHODS

Study Area

South Korea is located in-between China and Japan in East Asia, which is further divided into six provinces as follows: Seoul and Gyeonggi (capital), Gangwon (east), Chungcheong (west), Gyeongsang (south east), Jeolla (south west), and Jeju (volcanic island). Groundwater sampling sites were selected randomly and distributed evenly all over the country that referred to "The result of management about the quality of groundwater in 2002" by the Ministry of Environment. Groundwater sampled from 722 selected sites of six areas were collected as follows: 107 sites in Seoul and Gyeonggi, 117 sites in Gangwon, 103 sites in Chungcheong, 123 sites in Gyeongsang, 233 sites in Jeolla, and 39 sites in Jeju during 2003–2004 (Table 1 and Figure 1).

Sampling of Groundwater

Sampling bottle was used precleaned EPA vials (Cole Parmer U99535-15; Cole Parmer, Vernon Hills, IL) with septum coated by Teflon. Sampling of groundwater was performed by a grab method twice in each during summer and winter. Of 722 sites, 98% and 88% were successfully sampled in the summer and the winter, respectively (Table 1). The number of sampling sites was smaller in the winter (636 sites) than in the summer (708 sites), because of frozen or close-down of water pump. Groundwater of selected sites were used mainly for drinking and also for agriculture, washing, and industry. Sampled groundwater were treated with concentrated nitric acid (0.2% (v/v)) and stored at 4 °C until analysis.

Analysis of Arsenic Concentration in Groundwater

The concentration of arsenic in groundwater was analyzed by ICP-MS (Elan 6100 DRC plus; Perkin-Elmer, Shelton, CT, USA). Analytical condition is presented in Table 2. For the calibration and verification of the analytical method, commercial multielement standard solution purchased from Perkin-Elmer was used. The analysis of arsenic in the groundwater was validated in terms of linearity of standard curve, precision, accuracy, and using a standard reference material (NIST SRM 1640a; NIST, Atlanta, GA, USA). The result was recovery = 99.7% and CV = 2.28% for NIST SRM 1640a reference. The limit of detection of this method was 0.1 $\mu g/l$ for arsenic, which is sufficiently sensitive considering 10 ppb (10 $\mu g/l$) standard.

Analysis of Arsenic Levels in Urine of the Population Around As-Contaminated Groundwater Sites *vs* Non-Contaminated Sites

Selection of sampling population. The target area was selected (Gosung, Gyeongsang, Dang-Jin, Chungcheong and Gok-sung, Jeolla) such that the arsenic contamination level exceeded 10 $\mu g/l$ and the groundwater was the major source of drinking water, and the floating population was small. Control, that is, non-contaminated area was selected in the same provincial region to match the geographical location and to control the potential contribution of arsenic exposure from food sources. The purpose of the study was explained to the inhabitants of the target area in a town meeting and volunteers were collected. Study subjects were enrolled such that they lived more than 10 years at the target area and have not been occupationally exposed to arsenic. An informed consent form was signed before the final enrollment. Information on background such as disease history, alcohol drinking, and smoking was obtained with a lifestyle questionnaire under the guidance of a surveyor. Urine sample (spot urine) was collected into the EPA vial as described above, and stored at −70 °C until analysis. Demographic data is presented in Table 4. Total arsenic concentration in urine was determined by using inductively coupled-plasma dynamic reaction cell-mass spectrometry (ICP-DRC-MS) (Perkin-Elmer; Elan 6100 DRC plus) after wet digestion with nitric acid. Briefly, urine samples were diluted at 10x-folds in 1% nitric acid, before analysis. The analysis of arsenic in the urine was validated in terms of linearity of standard curve, precision, accuracy, and using an SRM (Bio-Rad, Irvine, CA, USA) with an international quality control program (EQUAS, Germany). The result was recovery = 98.9% and CV = 2.76% for the SRM solution. Urinary arsenic excretion was presented as $\mu g/g$ creatinine. Urinary creatinine was determined by the modified Jaffe reaction method.[16]

Table 1. Number of groundwater sampling sites by area in summer and winter, respectively.

Area	*No. of target sampling site*	*No. sampled in summer*	*No. sampled in winter*
Seoul and Gyeonggi	107	107 (100%)	92 (86%)
Gangwon	117	117 (100%)	106 (91%)
Chungcheong	103	103 (100%)	100 (97%)
Gyeongsang	123	123 (100%)	76 (62%)
Jeolla	233	229 (98%)	231 (99%)
Jeju	39	29 (74%)	31 (79%)
Total	722	708 (98%)[a]	636 (88%)

[a]Sampling rate was 98% and 88% in summer and winter, respectively.

Simulation and Statistics

Data were expressed as the number and percentage or mean ± SEM otherwise indicated. Distribution of arsenic levels in groundwater among groups was analyzed by χ^2 test. Comparison of urinary arsenic excretion was carried out by Student's *t*-test. Statistical significance was set at $P<0.05$. For geographical analysis, H-likelihood method for the spatial data was used as described by Lee *et. al.*[17]

RESULTS

The concentration of arsenic in groundwater sampled from 722 selected sites of six areas ranged from 0.1 to 48.4 $\mu g/l$ (0.12–41.9 $\mu g/l$ in summer, 0.1–48.4 $\mu g/l$ in winter). The levels of arsenic in groundwater were divided into four categories: group I ($<2.0\,\mu g/l$ /l), group II (2.0–4.9 $\mu g/l$), group III (5.0–9.9 $\mu g/l$), and group IV ($>10\,\mu g/l$) (Table 3). In summer, the number of group I was the largest where 624 sites (88.1%) fell, whereas 49 sites (6.9%) were group II, 20 sites (2.8%) group III, and 15 sites (2.1%) group IV. Similar patterns of arsenic levels were observed in winter. In all, 566 sites (89.0%) were group I, 41 sites (6.4%) group II, 15 sites (2.4%) group III, and 14 sites (2.2%) group IV in winter. These data indicated that the seasonal variation in arsenic levels of groundwater was insignificant ($X^2=0.43$, $P>0.1$).

In contrast, geographical variation was prominent. In Gangwon area, there was no site belonging to group IV but 4.9% and 9.2% of groundwater of Gyeongsang area were group IV in summer and winter, respectively (Table 3). A national distribution of arsenic concentration in groundwater of study sites in summer and winter were presented in Figure 1. In addition, a simulated nationwide geographical distribution of arsenic in groundwater of Korea were presented based on the arsenic concentrations of studied sites (Figure 2).

To examine the contribution of arsenic-contaminated drinking waters to systemic exposure, we measured the urinary arsenic excretion of the people around the contaminated groundwater (As $>10\,\mu g/l$) and compared with geographically matched non-contaminated area ($<5\,\mu g/l$). The urinary arsenic excretion of the people around three contaminated groundwater (11.0–42.2 $\mu g/l$) was measured to be markedly higher ($79.7\pm5.2\,\mu g/g$ ($N=122$) *vs* $68.4\pm5.4\,\mu g/g$ ($N=65$) creatinine, $P=0.052$), although a statistical significance was borderline (Table 4). However, all stratified analysis also suggested higher urinary arsenic excretion of the contaminated areas where that of non-smokers achieved a statistically significant difference ($85.9\pm12.7\,\mu g/g$ *vs* $54.0\pm6.3\,\mu g/g$ creatinine, $P=0.030$), suggesting that arsenic-contaminated drinking waters might contribute to its systemic exposure in human, at least in part.

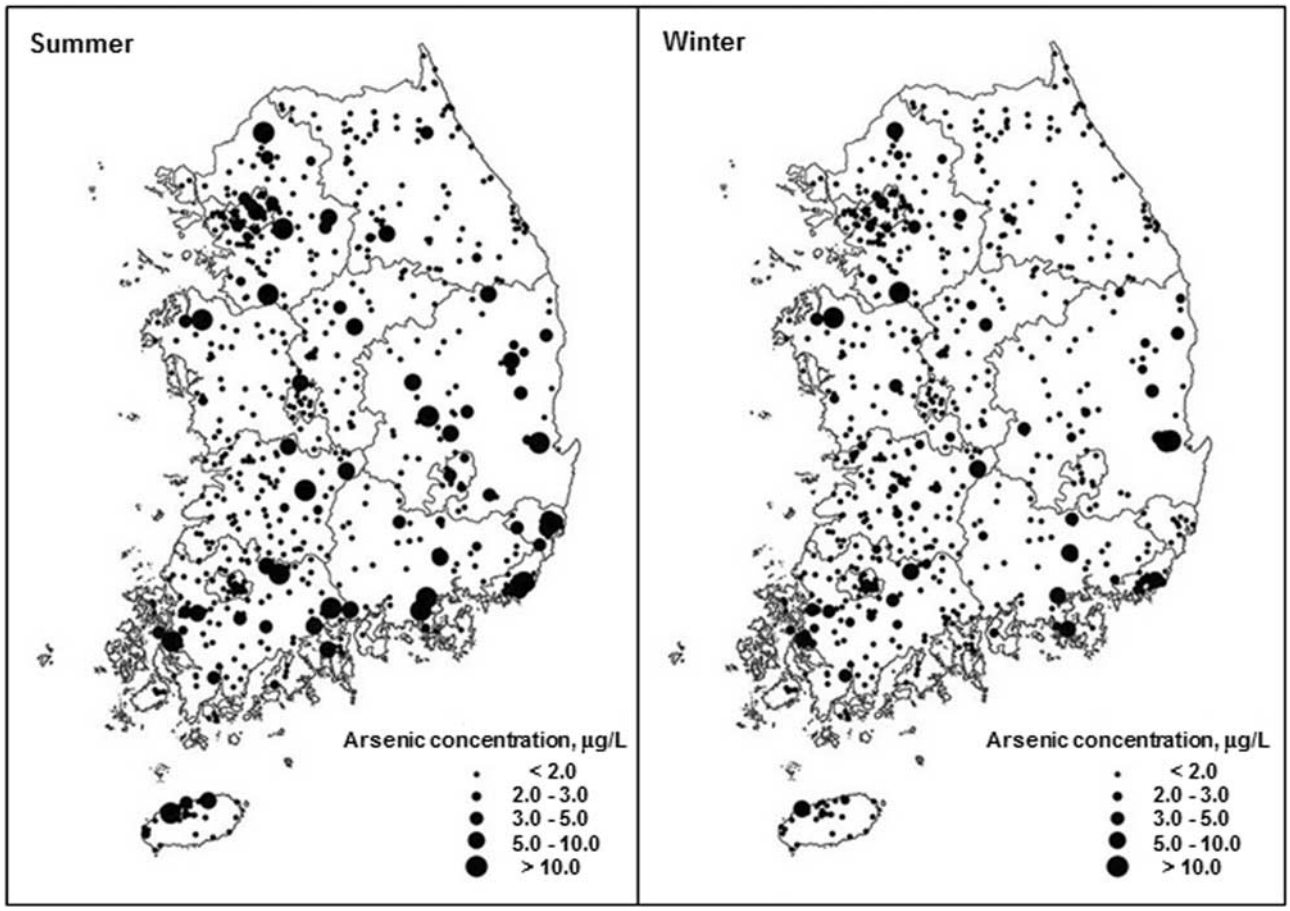

Figure 1. Nationwide distribution of arsenic concentration in the groundwater in summer and winter, respectively.

Table 2. Analytical conditions of ICP-MS for arsenic quantitation.

Description	*Conditions*
RF power	1000 W
Sampling depth	7 mm from load coil, on center
Coolant gas flow rate	1 5.0 l/min
Auxiliary gas flow rate	0.85 l/min
Nebulizer gas flow rate	0.92 l/min
Sample uptake flow	l.0 ml/min
Nebulizer	Cross-flow type
Torch	Demountable
Interface cones	Nickel
Mass analyzer	Quadrupole
Quadrupole chamber	5×10^{-7} Torr
Quantitative mode	
Replicate time (ms)	300
Dwell time (ms)	100
Sweeps/reading	3
Reading/replicate	1
Number of replicates	5
Points/spectral peak	3
As/mass	75

Abbreviations: ICP-MS, inductively coupled-mass spectrometry; RF power, radio frequency power.

DISCUSSION

Here, we provided a comprehensive data of arsenic levels in the groundwater of Korea nationwide with the selected 722 sampling sites. The concentrations of arsenic in the groundwater of Korea were determined to be from 0.1 to 48.4 μg/l. Most of samples investigated (88–89%) exhibited low arsenic levels ($< 2\ \mu$g/l). However, $> 2\%$ of groundwater (15 sites) exceeded the current MCL of arsenic, 10 μg/l, suggesting that the management or regulation of arsenic-contaminated groundwater may be necessary in some areas.

Arsenic concentration in groundwater is influenced by natural environment as well as by anthropogenic activities such as mining, industrialization, and pesticides. Several studies reported that high concentrations of arsenic in groundwater are observed around a specific geochemical environment such as oxidation–reduction reaction and ligand exchange, or aquifer environment.[18–20] Arsenic concentrations are generally well correlated with other anions and elements such as F, Fe and Mn, and high arsenic-contaminated waters often have a high salinity.[21] Consequently, As levels in the groundwater may vary substantially from countries to countries or from area to area depending on the geographical location within a country.

Bangladesh and West Bengal are known to exhibit high Arsenic concentrations. Arsenic concentrations in groundwater range from non-detectable to 2040 μg/l in Bangladesh and < 10 to 3400 μg/l in West Bengal.[22,23] Also, the high levels of arsenic in drinking water of artesian wells were reported in Taiwan. Epidemics of chronic arsenic poisoning, the so-called black foot disease, were prevalent in the Southwestern and Northeastern areas of Taiwan.[24] The Northern central area of Mexico exhibited exceedingly high levels of arsenic in the groundwater, ranging from 8 to 624 μg/l.[25] In the United States, EPA monitored arsenic

Table 3. Distribution of groundwater according to the level of arsenic (As) by area, in summer and winter, respectively.

Area	*Summer (As μg/l)*				*Winter (As μg/l)*			
	Below 2.0 (group I)	*2.0–4.9 (group II)*	*5.0–9.9 (group III)*	*Above 10.0 (group IV)*	*Below 2.0 (group I)*	*2.0–4.9 (group II)*	*5.0–9.9 (group III)*	*Above 10.0 (group IV)*
Seoul and Gyeonggi	92 (86.0%)	10 (9.3%)	2 (1.9%)	3 (2.8%)	81 (88.0%)	6 (6.5%)	3 (3.3%)	2 (2.2%)
Gangwon	113 (96.6%)	3 (2.6%)	1 (0.8%)	0 (0.0%)	106 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chungcheong	99 (96.1%)	2 (1.9%)	1 (1.0%)	1 (1.0%)	92 (92.0%)	4 (4.0%)	3 (3.0%)	1 (1.0%)
Gyeongsang	88 (71.5%)	21 (17.1%)	8 (6.5%)	6 (4.9%)	51 (67.1%)	14 (18.4%)	4 (5.3%)	7 (9.2%)
Jeolla	207 (90.0%)	11 (5.0%)	7 (3.0%)	4 (2.0%)	207 (90.0%)	17 (7.0%)	4 (2.0%)	3 (1.0%)
Jeju	25 (86.0%)	2 (7.0%)	1 (3.5%)	1 (3.5%)	29 (93.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)
Total	624 (88.0%)	49 (7.0%)	20 (3.0%)	15 (2.1%)	566 (89.0%)	41 (6.4%)	15 (2.4%)	14 (2.2%)

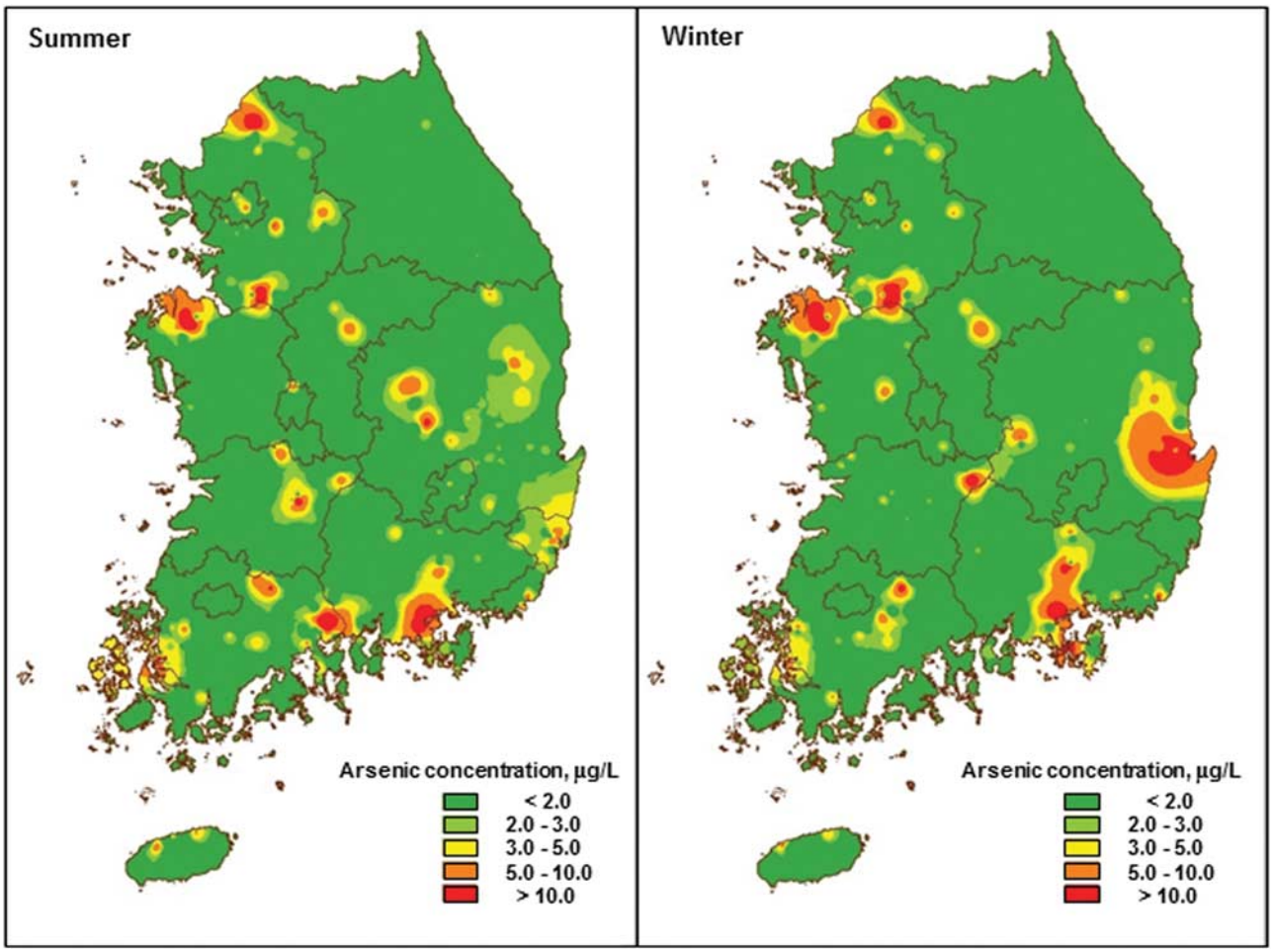

Figure 2. Simulated geographical distribution of arsenic concentration in groundwater in Korea, in the summer and the winter, respectively.

contamination of the community water supply (CWS) and non-transient, non-community water supply (NTNCWS) systems in 25 states of the United States.[26] Of 43,443 groundwater sites of CWS, 11,873 sites (27.3%) exceeded 2 μg/l, in which 5252 sites (12.1%) exceeded 5 μg/l and 2302 sites (5.3%) were beyond 10 μg/l. Similarly, of 19,635 sites in the groundwater of NTNCWS system, 6306 sites (32.1%) exceeded 2 μg/l, where 3064 sites (15.6%) exceeded 5 μg/l and 1050 sites (5.3%) were beyond 10 μg/l. Namely, ~5% of groundwater in the United States were contaminated with arsenic at >10 μg/l. From the United States EPA study, arsenic concentration in water tends to be higher in the Western area such as Utah, California and Oregon, compared with the Eastern or Midwestern areas, which might be explained by geological factors.

Recently, public health threat from arsenic-contaminated groundwater in China has attracted a large attention even though the portion of people at stake is ~2% of the whole population.[15,27] In the present study, we found that 2.2% of sampled sites of Korea exceeded 10 μg/l, which was comparable to other countries. In addition, we could also confirm that the geographical variation

Table 4. The concentration of arsenic in urine (As μg/g creatinine).[a]

Variable	*Group*	*All*		*Population around As-contaminated groundwater sites (> 10 ppb)*		*Population around non-contaminated groundwater sites (< 5 ppb)*		*Statistical significance*	
		N	*As conc. (μg/g creatinine)*	*N*	*As conc. (μg/g creatinine)*	*N*	*As conc. (μg/g creatinine)*	*P-value*	*Difference (95% CI)*
Sex	Male	76	76.7 ± 7.4	47	85.5 ± 10.6	29	62.5 ± 8.2	0.091	− 3.7, 49.7
	Female	111	79.23 ± 4.7	75	82.0 ± 6.1	36	73.1 ± 7.2	0.336	− 9.59, 27.78
Age (years)	< 60	69	70.9 ± 6.6	39	77.8 ± 11	30	62.0 ± 6.4	0.208	− 9.0, 40.4
	12–60	118	82.5 ± 5.2	83	86.1 ± 6.4	35	73.8 ± 8.3	0.244	− 8.6, 33.3
Smoking	Current	117	78.43 ± 4.8	77	80.6 ± 6.1	40	74.2 ± 7.9	0.525	− 13.5, 26.3
	Ex-smoker	24	84.5 ± 14.5	16	91.9 ± 21.0	8	69.5 ± 11.0	0.360	− 27.3, 72.1
	None	45	73.82 ± 8.5	28	85.9 ± 12.7*	17	54.0 ± 6.3	0.030	3.2, 60.6
Alcohol drinking	Yes	110	74.2 ± 4.7	52	87.7 ± 9.3	24	75.6 ± 11.1	0.406	− 16.9, 41.2
	No	77	83.9 ± 7.3	69	80.2 ± 6.6	41	64.1 ± 5.6	0.067	− 1.14, 33.24
Total		187	78.2 ± 4.1	122	79.7 ± 5.2	65	68.4 ± 5.4	0.052	−0.12, 30.31

Abbreviations: As, arsenic; CI, confidence interval. [a]By demographic characteristics in the subjects around the As-contaminated groundwater sites (> 10 μg /l) and non-contaminated sites (< 5 μg/l). *$P < 0.05$.

was evident: in the Gangwon area, no groundwater sites showed arsenic levels exceeding 10 μg/l, whereas in the Gyeongsang area, 4.9% and 9.2% sites were determined to be > 10 μg/l during summer and winter season, respectively, suggesting that regional management of arsenic contamination is necessary.

More than 88.0% of groundwater exhibited low arsenic contamination (< 10 μg/l), suggesting that health problems associated with high-dose arsenic exposure are unlikely. However, 2% of groundwater sites sampled exceeded 10 μg/l, indicating that potential health problems associated with exposure to arsenic could not be precluded. Strongly supporting this, we could find that compared with non-contaminated area (< 5 μg/l), the urinary arsenic excretion in the population around three groundwater sites with high arsenic levels (11.0–42.2 μg/l) was measured to be markedly higher with a borderline significance (79.7 ± 5.2 μg/g ($N = 122$) *vs* 68.4 ± 5.4 μg/g ($N = 65$) creatinine, $P = 0.052$). Actually in all subgroups, average urinary arsenic excretion of people near the contaminated groundwater was higher compared with those of non-contaminated area (109–159% of non-contaminated). Especially in non-smokers, urinary arsenic excretion was significantly higher around contaminated groundwater (85.9 ± 12.7 μg/g ($N = 28$) *vs* 54.0 ± 6.3 μg/g ($N = 17$) creatinine, $P = 0.030$, Student's *t*-test), the results of which may be attributable to the removal of potential interference of variable arsenic exposure from tobacco smoking.[28] Overall, these data suggest that arsenic-contaminated groundwater could contribute to systemic exposure of arsenic, at least in part, although more extensive epidemiological studies with proper control of confounding factors from other arsenic sources-like diet are needed. This may be from the wide use of groundwater in agriculture, food processing and washing as well as drinking, which can further contribute to human exposure to arsenic.[29] Rice, a major food source in Asia, contains relatively high level of inorganic arsenic from soil or water, and accordingly the consumption of arsenic-contaminated rice may have also contributed to inorganic arsenic exposure in human,[30–32] which might ultimately stem from arsenic-contaminated groundwater.

The nationwide survey in groundwater for arsenic contamination with the highly sensitive analytical method was the first report in Korea to our best knowledge. Our results suggest that ingestion of the groundwater contaminated with arsenic even at minimal extents (11.0–42.2 μg/l) may contribute to the increased systemic exposure of arsenic in human, indeed. However, it is yet to be elucidated whether the increased arsenic exposure from contaminated groundwater has any toxicological implication, as the number of subjects was small, other arsenic sources-like diet was not considered and the accurate speciation of urinary excreted arsenic was not conducted, which is necessary both to confirm the contribution from inorganic arsenic and to exclude those from nontoxic organic arsenicals, such as arsenobetaine from seafood.[33] However, we believe that our study may have provided an important initiative for a larger-scaled epidemiology study with the proper control of various confounding factors and the exact speciation of urinary arsenic excretion, which would be fundamental for the protection of public health against arsenic contamination.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Halder D, Bhowmick S, Biswas A, Chatterjee D, Nriagu J, Guha Mazumder DN *et al.* Risk of arsenic exposure from drinking water and dietary components: implications for risk management in rural Bengal. *Environ Sci Technol* 2013; **47**: 1120–1127.
2 WHO. *Arsenic and Arsenic Compounds*, 2nd edn. Environmental Health Criteria 224. World Health Organization: Geneva, Switzerland, 2001.
3 Hughes MF, Beck BD, Chen Y, Lewis AS, Thomas DJ. Arsenic exposure and toxicology: a historical perspective. *Toxicol Sci* 2011; **123**: 305–332.
4 Le XC, Cullen WR, Reimer KJ. Determination of urinary arsenic and impact of dietary arsenic intake. *Talanta* 1993; **40**: 185–193.
5 Berg M, Tran HC, Nguyen TC, Pham HV, Schertenleib R, Giger W. Arsenic contamination of groundwater and drinking water in Vietnam: a human health threat. *Environ Sci Technol* 2001; **35**: 2621–2626.
6 Guha Mazumder DN. Chronic arsenic toxicity: clinical features, epidemiology, and treatment: experience in West Bengal. *J Environ Sci Health A* 2003; **38**: 141–163.
7 Nordstrom DK. Public health. Worldwide occurrences of arsenic in groundwater. *Science* 2002; **296**: 2143–2145.
8 Smith AH, Lingas EO, Rahman M. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. *Bull World Health Organ* 2000; **78**: 1093–1103.

9 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**: 295–302.
10 Wu M-M, Kuo T-L, Hwang Y-H, Chen C-J. Dose–response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am J Epidemiol* 1989; **130**: 1123–1132.
11 Yoshida T, Yamauchi H, Fan Sun G. Chronic health effects in people exposed to arsenic via the drinking water: dose–response relationships in review. *Toxicol Appl Pharmacol* 2004; **198**: 243–252.
12 ASTDR. *The Priority List of Hazardous Substance*. Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services, Public Health Service: Atlanta, GA, USA, 2013.
13 EPA. *Implementation Guidance for the Arsenic Rule: Drinking Water Regulations for Arsenic and Clarification to Compliance and New Source Contaminants Monitoring*. United States Environmental Protection Agency: Washington DC, USA, 2002.
14 Mandal BK, Suzuki KT. Arsenic round the world: a review. *Talanta* 2002; **58**: 201–235.
15 Rodríguez-Lado L, Sun G, Berg M, Zhang Q, Xue H, Zheng Q *et al.* Groundwater arsenic contamination throughout China. *Science* 2013; **341**: 866–868.
16 Taussky HH. A microcolorimetric determination of creatine in urine by the Jaffe reaction. *J Biol Chem* 1954; **208**: 853–862.
17 Lee Y, Nelder JA, Pawitan Y. *Generalized Linear Models with Random Effects: Unified Analysis via H-likelihood*. CRC Press: Boca Raton, FL, USA, 2006.
18 McArthur J, Ravenscroft P, Safiulla S, Thirlwall M. Arsenic in groundwater: testing pollution mechanisms for sedimentary aquifers in Bangladesh. *Water Resour Res* 2001; **37**: 109–117.
19 Smedley P, Kinniburgh D. A review of the source, behaviour and distribution of arsenic in natural waters. *Appl Geochem* 2002; **17**: 517–568.
20 Ahn J-S, Ko K-S, Chon C-M. Arsenic Occurrence in Groundwater of Korea. *J Soil Groundw Environ* 2007; **12**: 64–72.
21 Nicolli HB, Bundschuh J, Blanco Mdel C, Tujchneider OC, Panarello HO, Dapena C *et al.* Arsenic and associated trace-elements in groundwater from the Chaco-Pampean plain, Argentina: results from 100 years of research. *Sci Total Environ* 2012; **429**: 36–56.
22 Guha Mazumder DN, Haque R, Ghosh N, De BK, Santra A, Chakraborty D *et al.* Arsenic levels in drinking water and the prevalence of skin lesions in West Bengal, India. *Int J Epidemiol* 1998; **27**: 871–877.
23 Tondel M, Rahman M, Magnuson A, Chowdhury IA, Faruquee MH, Ahmad SA. The relationship of arsenic levels in drinking water and the prevalence rate of skin lesions in Bangladesh. *Environ Health Perspect* 1999; **107**: 727–729.
24 Tseng WP, Chu HM, How SW, Fong JM, Lin CS, Yeh S. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J Natl Cancer Inst* 1968; **40**: 453–463.
25 Armienta M, Segovia N. Arsenic and fluoride in the groundwater of Mexico. *Environ Geochem Health* 2008; **30**: 345–353.
26 EPA. *Arsenic Occurrence in Public Drinking Water Supplies*. United States Environmental Protection Agency: Washington DC, USA, 2000.
27 Martinez VD, Vucic EA, Lam S, Lam WL. Emerging arsenic threat in Canada. *Science* 2013; **342**: 559.
28 Caruso RV, O'Connor RJ, Stephens WE, Cummings KM, Fong GT. Toxic metal concentrations in cigarettes obtained from U.S. smokers in 2009: results from the International Tobacco Control (ITC) United States survey cohort. *Int J Environ Res Public Health* 2014; **11**: 202–217.
29 Navas-Acien A, Umans JG, Howard BV, Goessler W, Francesconi KA, Crainiceanu CM *et al.* Urine arsenic concentrations and species excretion patterns in American Indian communities over a 10-year period: the Strong Heart Study. *Environ Health Perspect* 2009; **117**: 1428–1433.
30 Carbonell-Barrachina AA, Wu X, Ramirez-Gandolfo A, Norton GJ, Burlo F, Deacon C *et al.* Inorganic arsenic contents in rice-based infant foods from Spain, UK, China and USA. *Environ Pollut* 2012; **163**: 77–83.
31 Wei Y, Zhu J, Nguyen A. Rice consumption and urinary concentrations of arsenic in US adults. *Int J Environ Health Res* 2014; **24**: 459–470.
32 Wong WW, Chung SW, Chan BT, Ho YY, Xiao Y. Dietary exposure to inorganic arsenic of the Hong Kong population: results of the first Hong Kong total diet study. *Food Chem Toxicol* 2013; **51**: 379–385.
33 Leffers L, Ebert F, Taleshi MS, Francesconi KA, Schwerdtle T. *In vitro* toxicological characterization of two arsenosugars and their metabolites. *Mol Nutr Food Res* 2013; **57**: 1270–1282.