Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2020 doi:10.20944/preprints202009.0501.v1

Elevated urinary arsenic level among residents of an arsenic-endemic area of southern Thailand and its related factors: three decades after mitigation attempts

Running title: Factors related with urinary arsenic level in southern Thailand

Udomsak Saengow [1,2,3]*, Surasak Vijitpongjinda [3], Supabhorn Yimthiang [4], Apichai Wattanapisit [3], Sirilak Thaicharoen [5]

[1] Center of Excellence in Health System and Medical Research (CE-HSMR), Walailak University, Tha Sala, Nakhon Si Thammarat 80160, Thailand

[2] Research Institute for Health Sciences, Walailak University, Tha Sala, Nakhon Si Thammarat 80160, Thailand

[3] School of Medicine, Walailak University, Tha Sala, Nakhon Si Thammarat 80160, Thailand

[4] School of Public Health, Walailak University, Tha Sala, Nakhon Si Thammarat 80160, Thailand

[5] Department of Disease Control 11, Mueang Nakhon Si Thammarat District, Nakhon Si Thammarat 80000, Thailand

* Correspondence: saengow.udomsak@gmail.com; Tel.: (+66)-83-656-4582

Abstract

Three decades ago, human arsenic (As) contamination has been recognized in, Ron Phibun, a sub-district with tin mining activity in southern Thailand. Since then different government bodies have attempted to mitigate the As-contamination problem by providing safe water in households. The most recent study conducted during 2000-2002 reported only a small fraction of population still had high urinary As level. Less attention has been paid to this issue afterwards. The present study aimed to re-assess the current situation, including human As contamination, water use behavior as well as identify risk factors of elevated As concentration among residents of Ron Phibun. The survey of 560 participants living in Ron Phibun with urinary As assessment was conducted. The median urinary As concentration of study participants was higher than normal. Consumption of shallow well water, a source generally considered as As-contaminated, was higher than a previous survey. A significant association was observed between urinary As concentrations and water sources for drinking and cooking. Gender and educational level were found to be associated with urinary As concentration. Significant associations between urinary As concentration and certain diseases (respiratory diseases, dermatitis, and dyslipidemia) were observed. The findings suggested further investigation of all water sources in the area for As contamination.

Keywords: Human arsenic exposure; water source; risk factors; Thailand

1. Introduction

Heavy metal contamination is a serious problem worldwide, affecting both ecosystems and human health. Arsenic (As) is one of the most toxic elements and also known as “the king of poisons” [1]. The occurrence of As in nature can be found in a

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2020 doi:10.20944/preprints202009.0501.v1

variety of different mineral forms in which around 60% are presented as arsenates, 20% are sulfies and sulfosalts, and the 20% remaining As are also in the form of arsenides, arsenites, oxides, silicates, and elemental As [2]. Generally, it is well known that the toxicity of inorganic As (iAs) forms are higher than the organic ones. The anthropogenic activities are considered as the main source of As contamination of the environment, including ore mining activity and smelting, application of fertilizers and pesticides, and burning of fossil fuel [3]. However, natural geological activities of As have been recently demonstrated its devastating impact on water quality, including desorption of alkaline, oxidation of sulfide, reductive dissolution, among others [4].

Normally, humans are exposed to As through drinking water, soil, and air. For populations residing on or near the geological source of As, drinking water could be the major source of As exposure [5]. According to the guidelines of World Health Organization (WHO), the range of As concentration from 10 to 50 µg/l in drinking water is considered as safe [6]. Globally, more than 200 million people in over 70 countries are exposed to high levels of As through drinking water [7]. Among these, areas in South and Southeast Asia are most affected including Bangladesh, Cambodia, China, India, Nepal, Pakistan, and Vietnam [8].

In Thailand, the first documented case of arsenic poisoning was reported in 1987, subsequently diagnosed with skin cancer case due to chronic arsenic exposure in Ron Phibun sub-district, Nakhon Si Thammarat province, southern Thailand [9,10]. Both surface waters and groundwater around mining sites were found to have a high concentration of As and the consumption of the water might be the main source of exposure. Ron Phibun is a part of the Southeast Asian Tin Belt, a famous region for tin (Sn) production. The occurrence of As contamination in this sub-district results from former bedrock and alluvial mining, and tin mining activities over the past century

[11]. Williams et al. [12] reported that As-contaminated surface waters in Ron Phibun were above 580 µg/l, while shallow groundwaters (<15 meter deep) from alluvial and colluvial deposits contained extremely high As concentrations up to 5100 µg/l. A survey conducted in 1991 by Choprapawan and Ajjimangkul [13] reported that over 1,000 cases were diagnosed with As-induced skin lesions. The chronic As poisoning affecting Ron Phibun residents, as indicated by the skin lesions, was 26.3%.

Many attempts have been made by different government bodies to solve the problem such as by closing mining sites, providing rainwater jars, installing water pipelines, and using algae in household filtration system [14]. After water without arsenic contamination has been supplied to the majority of households, high As-contaminated shallow wells were closed.

About a decade later, a survey conducted by Oshikawa et al. [15] in 2001 reported that only a small number of residents had used contaminated shallow well water for drinking or cooking in the last 10 years. The most recent survey conducted in 2000–2002 reported that an average urinary As concentration of residents living in highly-contaminated areas (>50 µg/l) was higher than that of residents living in low contaminated areas. This survey also reported that 6.33% of the investigated population had inorganic As above 50 mg/g creatinine [16].

Since then, less attention had been paid to As contamination in Ron Phibun from both government and the general public. There are no more reports concerning As contamination in humans from Ron Phibun. However, continuous monitoring is key to contain the problem and prevent further human exposure. Knowledge concerning a current situation of human As contamination and water use behaviors in Ron Phibun is important. Therefore, the present study aimed to re-assess the current situation, including human As contamination, water use behavior, and identify risk factors of

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2020 doi:10.20944/preprints202009.0501.v1

elevated As concentration among residents of Ron Phibun sub-district three decades after early mitigation attempts.

2. Materials and Methods

2.1. Study design and ethical consideration

This study was a cross-sectional survey using a simple random sampling technique conducted from December 2016 to February 2017. The study objectives and protocol were, fully, explained, and written informed consent was obtained from all the participants prior to the data collection. The protocol for this study was reviewed and ethical approval was issued by Human Research Ethics Committee of Walailak University (WUEC-16-009-0).

2.2. Site of study

The survey of the current situation of human As contamination and risk factors associated with urinary As concentration was conducted in the Ron Phibun sub-district, Nakhon Si Thammarat province, southern Thailand. In certain areas of the sub-district, arsenopyrite (AsFeS), the major waste from past mining activities and its leaching, has released As into groundwater that causes As contamination of shallow wells. Shallow-well As contamination was unevenly distributed within this area [15,16]. According to previous reports, three villages were considered high As-contaminated areas including village 2, 12, and 13, whereas other villages were classified as low contaminated areas [15,16].

2.3. Selection of participants and sample size

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2020 doi:10.20944/preprints202009.0501.v1

The participants were recruited from historically high and low As-contaminated areas. The inclusion criteria for enrollment were (i) aged 18 years or older; (ii) agreed to give consent to participate in the study; and (iii) continuous residency in the study area for at least 6 months at the time of the interview. Participants who were unable to communicate were excluded.

The sample size was calculated using a formula for proportion estimation based on the prevalence of urine As >50 μg/l obtaining from a previous study [16]. The prevalence of urinary As exceeding 50 μg/l was 6% in high contaminated areas. We assumed the prevalence of 1% in low contaminated areas. The required sample size was 250 participants from high As-contaminated areas and 250 from low As-contaminated areas. Thus, the total sample size was 500. To compensate for 10% potential missing data, the target sample size was increased to 556 participants. The sample size calculation was performed using epicalc package in R software version 2.15.1.0. [17,18].

2.4. Questionnaire interview and specimen collection

Participants who satisfied eligibility criteria were randomly selected from the population registry of Ron Phibun. Individuals on the participant list were approached by trained interviewers who conducted a door to door survey. In-person interviews were conducted to collect data using a structured questionnaire concerning the sociodemographic characteristics, length of stay in the area, history of chronic diseases, water-use information including cooking, drinking, cleaning food composites, showering or bathing, brushing the teeth, cleaning face, and hands, and cleaning utensils.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2020 doi:10.20944/preprints202009.0501.v1

At the end of an interview, an appointment was made for participants to provide urine specimen. All participants were asked to refrain from eating seafood products for 3 days before the specimen collection [19]. Each participant was given a sterile container to place their fresh morning urine specimen in the morning of the 4th day. Urine samples were collected from participants' houses in early morning, immediately placed in an ice box, and transported to a laboratory at Walailak University. The urine samples were stored frozen at -20 °C and analyzed within 3 weeks of collection according to a standardized protocol [20].

2.5. Sample preparation and urinary As determination

The urine samples were analyzed by using inductively coupled plasma tandem mass spectrometry (ICP-MS) according to the method described by Scheer et al. [21]. They were thawed at room temperature and a portion (170 ml) of the sample was transferred into a Plastibrand® microtube (Brand GmbH + Co KG, Wertheim Germany). Each sample was diluted with 10% (v/v) nitric acid (HNO_3) (Merck, Darmstadt, Germany) containing the mixed solution of internal elements of Ge, In, and Lu (CPI International, Santa Rosa, CA, USA) at a concentration of 44 µg/l. The mixture was centrifuged at 13,000 ×g for 10 min and supernatant was collect and filtrated through a 0.22 µm Nylon filter (Whatman GmbH, Dassel, German) before determination of total As content by ICP-MS (Agilent 7500 CS, Agilent Technologies, Tokyo-Japan).

2.6. Creatinine (Cr) determination in urine

Urine creatinine adjustment was applied to adjust for urine volume and concentration. Creatinine concentrations in urine samples were determined using

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2020 doi:10.20944/preprints202009.0501.v1

creatinine assay kit (Sigma, St. Louis, Mo, USA). Urinary As concentrations were divided by urine creatinine concentrations (mg/g creatinine) and expressed as creatinine adjusted urinary As (mg/g of creatinine). In addition, the normal value of creatinine-adjusted urinary As concentration is ≤ 50 mg/g of creatinine [22].

2.7. Statistical analysis

All statistical analyses were performed by using epicalc package R, version 2.15.1 [17,18]. Descriptive statistics (mean, standard deviation, median, interquartile range, and percentage) were applied according to types of data of each variable. In bivariate analysis, Kruskal-Wallis test was applied to test whether urinary As levels differed among the participants with different characteristics. Linear regression was employed to determine the factors associated with elevated urinary As level. The log-transformed urinary As level was a dependent variable in the regression model since urinary As levels were not normally distributed. A p-value of < 0.05 (two-sided) was considered statistically significant.

3. Results

3.1. Characteristics of the study population

In total, there were 560 participants: 280 of them were from historically high As-contaminated areas, while the rest resided in low As-contaminated areas. They consisted of 78.2% females and 21.8% males with a mean age of 53.6 years. More than half of the total participants had grade 11 education or lower. Three-quarters of the participants had resided in Ron Phibun before 1988 with an average 41.7 years of residence. Overall, 40.0% and 39.1% of participants rated their health status as fair and good, respectively. Most of the participants did not smoke. Nearly half of the total

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2020 doi:10.20944/preprints202009.0501.v1

participants had chronic diseases. The most prevalent disease was hypertension, followed by dyslipidemia and diabetes (Table 1).

3.2. Water sources in households and usage

A majority of the participants had access to tap water in their households. A third of the total participants reported having shallow wells at home. Most of them had purchased drinking water in households (Table 2). Half of the participants experienced water shortage in the past 12 months. Most of the participants (64.6%) purchased drinking water (Table 3). Tap water and purchased water were equally popular sources for cooking. Tap water was a primary source of water used for other purposes. Shallow well water was still in use by over 10% of the participants for various purposes.

3.3. Urinary As concentration and health conditions

The median urinary As concentration of total study participants was 75.0 µg/g creatinine (IQR: 52.5–111.4 µg/g creatinine), which was higher than the normal values of not exceeding 50.0 µg/g creatinine. In the bivariate analysis, high urinary As concentration was significantly correlated with respiratory diseases ($p < 0.001$), dermatitis ($p < 0.001$), and dyslipidemia ($p = 0.038$). For respiratory diseases and dermatitis, there was only one participant reported having such a condition. It is worth noting that the participants who described their health status poorer tended to have higher median urinary As concentration although the relationship was not statistically significant. Those rated their health as very poor had a median concentration of 91.6 µg/g creatinine; those rated their health as excellence had a median concentration of 59.7 6 µg/g creatinine (Table 4).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2020 doi:10.20944/preprints202009.0501.v1

3.4. Urinary As concentration, water source in households, and water usage

Associations between urinary As concentration in participants and water sources in their households shown in Table 5. Higher urinary As concentrations were significantly associated with having underground water in households (p = 0.020) and not purchasing drinking water (p = 0.039). Residing in historically high As-contaminated areas had no effect on urinary As concentration. The highest urinary As concentration was observed in participants using underground water for all purposes. Significant differences in urinary As concentration between participant using different water sources were observed for all purposes of water use except washing food (Table 6).

3.5. Factors associated with urinary As concentration

The results of the linear regression model are presented in Table 7. Female participants and participants in the highest education group had significantly higher urinary As concentration. Period of residence was associated with urinary As concentration but living in historically high contaminated areas was not associated with urinary As concentration. We found that water sources for drinking and cooking were significantly associated with urinary As concentration. However, the relationships were in opposite direction. Compared to shallow well water, those who drank water from other sources had higher urinary As concentration, whereas those used water from sources other than shallow well for cooking had lower urinary As concentration.

4. Discussion

This study demonstrated that three decades after mitigation attempts, exposure to As was still a problem for people living in Ron Phibun. Overall, the median urinary As concentration was higher than normal. Shallow well water, which was considered to have a high risk of contamination, was still in use for various purposes. Higher urinary As concentration was associated with worse health outcomes. Sources of water consumed and period of residence in Ron Phibun were associated with urinary As concentration as well as gender and educational level.

Urinary As is the biomarker of recent exposure. In the study site, the water sources that were considered as having no As contamination may be contaminated. The significant association between urinary As concentrations and water sources for drinking and cooking was found. The participants who used shallow well water for drinking showed lower urinary As concentration than those who drunk from other water sources. In contrast, using a shallow well water source for cooking showed higher urinary As concentration. These relationships were in the opposite direction. The possible explanations were that people were exposed to As through food materials and many participants could not totally avoid using shallow well water that contaminated with As for their cooking.

To solve the As contamination, different government bodies have provided safe-water sources to households. Shoko et al. [15] studied on type of water for each water-use activity among Ron Phibun residents and found that shallow well water contaminated with As was used for cooking by 2.5% of population and for drinking by none. Our study found that 7.0% and 3.6% of the participants used shallow well water for cooking and drinking, which was higher than the previous survey. Accordingly, our result showed median urinary As level was higher than normal for residents living in these areas. In Vietnam, As was removed in water using sand filter to reduce exposure in many households, nevertheless As-related health problems were still reported [23]. In India, highly As-contaminated water was switched to arsenic-free water using As removal filters. It found that As concentration in drinking/cooking water decreased (*p*

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2020 doi:10.20944/preprints202009.0501.v1

< 0.01) from 91 µg/L (Year-I) to 30 µg/L (Year-II), and 13 µg/L (Year-III) and drinking/cooking water were from safe water source arsenic intake through the water significantly decreased. However, people were still exposed to As through food materials instead of water [24].

Our study found that high urinary As concentration was significantly associated with certain diseases, including respiratory diseases, dermatitis, and dyslipidemia. This result was in agreement with with Sanchez et al. [25] who reported that inorganic As exposure was associated with respiratory health including lung function, symptoms, acute respiratory infections, chronic non-malignant lung diseases, and non-malignant lung disease mortality. Watanabe et al. [26] reported that dermatological manifestations were associated with arsenic exposure among children living in arsenic-contaminated communities in rural Bangladesh. In addition, As can induce health problems and long-term exposure also can cause several diseases especially cardiovascular diseases, diabetes, oxidative stresses, and various types of cancers [27].

The significant association between gender and urinary As concentration was found in this study and it was higher in females. This result was inconsistent with Vahter et al. [28] who reported that As found to be lower in women due to a higher rate of arsenic methylation affected by sex hormones. The possible explanation may be different food and water intake habits in males and females [24]. We found educational level was significantly associated with urinary As concentration. The participants with an educational level of bachelor degree or higher tended to have higher urinary As than those with below or grade 6 to 11. The result disagreed with Vahter et al. [29] who reported that urinary As concentration decreased with increasing level of archived education. Some studies showed that no association between urinary As concentration and educational level [30,31]. As our findings indicated that water from sources

 doi:10.20944/preprints202009.0501.v1

thought to be As-free, such purchased drinking water maybe indeed contaminated, participants with higher education might consume water from these sources according to their prior knowledge.

A major limitation of this study was that total urinary As concentration, instead of metabolites of inorganic arsenic, was measured. This was due to the budget constrain of the project. The main problem of measuring total urinary As is that seafood intake, a source of organic arsenic, before urine sample collection could lead to a high level of total urinary As. Participants were asked to refrain from consuming seafood three days before urine sample collection to mitigate the issue.

5. Conclusions

Three decades after mitigation attempts, exposure to As still remains an environmental health issue in Ron Phibun. According to our findings, contamination of As in sources of water considered safe was observed. Gender and educational level were identified as a significant association of urinary As concentration. Urinary As concentration was shown to be associated with certain diseases (i.e., respiratory diseases, dermatitis, and dyslipidemia). An investigation of As contamination in all sources of water consumed in Ron Phibun should be done to understand current exposure.

Author Contributions: U.S. conceptualized, collected data, analyzed data, wrote and approved manuscript. S.V. assessed urinary As and urinary creatinine, and approved manuscript. S.Y. assessed urinary As, and approved manuscript. A. W. collected data, and approved manuscript. S.T. conceptualized, and approved manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by Thai Government Budget Grant (contract no. WU60116).

Acknowledgments: We would like to thank Ron Phibun Community Hospital staff and health volunteers for their support in sample selection and data collection. We would also like to thank heads of villages of study area for their insight and contribution on field visit protocol.

Conflicts of Interest: None declared.

References

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2020 doi:10.20944/preprints202009.0501.v1

1. Hoonjan, M.; Jadhav, V.; Bhatt, P. Arsenic trioxide: insights into its evolution to an anticancer agent. *JBIC J. Biol. Inorg. Chem.* **2018**, *23*, 313–329, doi:10.1007/s00775-018-1537-9.
2. Pigna, M.; Violante, A.; Caporale, A.G. A Comparison among Synthetic Layered Double Hydroxides (LDHs) as Effective Adsorbents of Inorganic Arsenic from Contaminated Soil–Water Systems. *Soil Syst.* **2020**, *4*, 37, doi:10.3390/soilsystems4020037.
3. Wang, P.; Sun, G.; Jia, Y.; Meharg, A.A.; Zhu, Y. A review on completing arsenic biogeochemical cycle: Microbial volatilization of arsines in environment. *J. Environ. Sci.* **2014**, *26*, 371–381, doi:10.1016/S1001-0742(13)60432-5.
4. Brammer, H.; Ravenscroft, P. Arsenic in groundwater: A threat to sustainable agriculture in South and South-east Asia. *Environ. Int.* **2009**, *35*, 647–654, doi:10.1016/j.envint.2008.10.004.
5. Dummer, T.J.B.; Yu, Z.M.; Nauta, L.; Murimboh, J.D.; Parker, L. Geostatistical modelling of arsenic in drinking water wells and related toenail arsenic concentrations across Nova Scotia, Canada. *Sci. Total Environ.* **2015**, *505*, 1248–1258, doi:10.1016/j.scitotenv.2014.02.055.
6. Tabassum, R.A.; Shahid, M.; Dumat, C.; Niazi, N.K.; Khalid, S.; Shah, N.S.; Imran, M.; Khalid, S. Health risk assessment of drinking arsenic-containing groundwater in Hasilpur, Pakistan: effect of sampling area, depth, and source. *Environ. Sci. Pollut. Res.* **2019**, *26*, 20018–20029, doi:10.1007/s11356-018-1276-z.
7. Qy, C.; S, S.; H, S.; F, W.; T, K.; Mg, K.; Y, C.; H, A.; M, C. PBMC gene expression profiles of female Bangladeshi adults chronically exposed to arsenic-

contaminated drinking water Available online: https://pubmed.ncbi.nlm.nih.gov/31918125/ (accessed on Aug 20, 2020).

8. Uppal, J.S.; Zheng, Q.; Le, X.C. Arsenic in drinking water—recent examples and updates from Southeast Asia. *Curr. Opin. Environ. Sci. Health* **2019**, *7*, 126–135, doi:10.1016/j.coesh.2019.01.004.
9. Phetliap, W.; Geater, A.; Rozek, L.S.; Oshikawa, S.; Helmick, K.; Rentschler, K.; Kojo, Y.; Thaicharoen, S. Global DNA methylation (LINE-1) associated with exposure to arsenic-contaminated environment and with type of arsenical skin lesions in Thailand. *Hum. Ecol. Risk Assess. Int. J.* **2018**.
10. Siripitayakunkit, U.; Visudhiphan, P.; Pradipasen, M.; Vorapongsathron, T. Association between Chronic Arsenic Exposure and Children's Intelligence in Thailand. In *Arsenic Exposure and Health Effects III*; Chappell, W.R., Abernathy, C.O., Calderon, R.L., Eds.; Elsevier Science Ltd: Oxford, 1999; pp. 141–149 ISBN 978-0-08-043648-7.
11. Williams, T.M.; Rawlins, B.G.; Smith, B.; Breward, M. In-Vitro Determination of Arsenic Bioavailability in Contaminated Soil and Mineral Beneficiation Waste from Ron Phibun, Southern Thailand: A Basis for Improved Human Risk Assessment. *Environ. Geochem. Health* **1998**, *20*, 169–177, doi:10.1023/A:1006545817478.
12. Williams, M.; Fordyce, F.; Paijitprapapon, A.; Charoenchaisri, P. Arsenic contamination in surface drainage and groundwater in part of the southeast Asian tin belt, Nakhon Si Thammarat Province, southern Thailand. *Environ. Geol.* **1996**, *27*, 16–33, doi:10.1007/BF00770599.
13. Choprapawon, C.; Ajjimangkul, S. Major Interventions on Chronic Arsenic Poisoning in Ronpibool District, Thailand—Review and Long-Term Follow Up.

In *Arsenic Exposure and Health Effects III*; Chappell, W.R., Abernathy, C.O., Calderon, R.L., Eds.; Elsevier Science Ltd: Oxford, 1999; pp. 355–362 ISBN 978-0-08-043648-7.

14. Jones, H.; Visoottiviseth, P.; Khoda Bux, M.; Földényi, R.; Kováts, N.; Borbély, G.; Galbács, Z. Case Reports: Arsenic Pollution in Thailand, Bangladesh, and Hungary. In *Reviews of Environmental Contamination Volume 197: International Perspectives on Arsenic Pollution and Remediation*; Reviews of Environmental Contamination and Toxicology; Springer: New York, NY, 2008; pp. 163–187 ISBN 978-0-387-79284-2.
15. Oshikawa, S.; Geater, A.; Chongsuvivatwong, V.; Chakraborti, D. Arsenic contamination of Ronphibun residents associated with uses of arsenic-contaminated shallow-well water other than drinking. *J. Environ. Sci. Health Part A* **2007**, *42*, 1753–1761, doi:10.1080/10934520701564251.
16. Pavittranon, S.; Sripaoraya, K.; Ramchuen, S.; Kachamatch, S.; Puttaprug, W.; Pamornpusirikul, N.; Thaicharuen, S.; Rujiwanitchkul, S.; Walueng, W. Laboratory Case Identification of Arsenic in Ronpibul Village, Thailand (2000–2002). *J. Environ. Sci. Health Part A* **2003**, *38*, 213–221, doi:10.1081/ESE-120016890.
17. R Core Team, Rf. *R: A language and environment for statistical computing*; R foundation for statistical computing Vienna, Austria, 2013;
18. Chongsuvivatwong, V. epicalc: Epidemiological calculator. R package version 2.15. 1.0. *Thail. Epidemiol. Unit Prince Songkla Univ. Sch.* **2012**.
19. Lai, V.W.-M.; Sun, Y.; Ting, E.; Cullen, W.R.; Reimer, K.J. Arsenic speciation in human urine: are we all the same? *Toxicol. Appl. Pharmacol.* **2004**, *198*, 297–306, doi:10.1016/j.taap.2003.10.033.

20. NHANES 2011-2012: Arsenics - Total & Speciated - Urine Data Documentation, Codebook, and Frequencies Available online: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/UAS_G.htm (accessed on Sep 8, 2020).
21. Scheer, J.; Findenig, S.; Goessler, W.; Francesconi, K.A.; Howard, B.; Umans, J.G.; Pollak, J.; Tellez-Plaza, M.; Silbergeld, E.K.; Guallar, E.; et al. Arsenic species and selected metals in human urine: validation of HPLC/ICPMS and ICPMS procedures for a long-term population-based epidemiological study. *Anal. Methods* **2012**, *4*, 406–413, doi:10.1039/C2AY05638K.
22. Wang, D.; Shimoda, Y.; Wang, S.; Wang, Z.; Liu, J.; Liu, X.; Jin, H.; Gao, F.; Tong, J.; Yamanaka, K.; et al. Total arsenic and speciation analysis of saliva and urine samples from individuals living in a chronic arsenicosis area in China. *Environ. Health Prev. Med.* **2017**, *22*, doi:10.1186/s12199-017-0652-5.
23. Agusa, T.; Trang, P.T.K.; Lan, V.M.; Anh, D.H.; Tanabe, S.; Viet, P.H.; Berg, M. Human exposure to arsenic from drinking water in Vietnam. *Sci. Total Environ.* **2014**, *488–489*, 562–569, doi:10.1016/j.scitotenv.2013.10.039.
24. Biswas, A.; Das, A.; Roychowdhury, T.; Mazumder, D.N.G. Low Arsenic Exposure Risk in Endemic Population, Cohort Study for Consecutive Years. *Expo. Health* **2018**, *10*, 273–286, doi:10.1007/s12403-017-0260-z.
25. Sanchez, T.R.; Perzanowski, M.; Graziano, J.H. Inorganic arsenic and respiratory health, from early life exposure to sex-specific effects: A systematic review. *Environ. Res.* **2016**, *147*, 537–555, doi:10.1016/j.envres.2016.02.009.
26. Watanabe, C.; Matsui, T.; Inaoka, T.; Kadono, T.; Miyazaki, K.; Bae, M.-J.; Ono, T.; Ohtsuka, R.; Bokul, A.T.M.M.H. Dermatological and nutritional/growth effects among children living in arsenic-contaminated communities in rural

Bangladesh. *J. Environ. Sci. Health Part A* **2007**, *42*, 1835–1841, doi:10.1080/10934520701566850.

27. Hussain, S.; Rengel, Z.; Qaswar, M.; Amir, M.; Zafar-ul-Hye, M. Arsenic and Heavy Metal (Cadmium, Lead, Mercury and Nickel) Contamination in Plant-Based Foods. In *Plant and Human Health, Volume 2: Phytochemistry and Molecular Aspects*; Ozturk, M., Hakeem, K.R., Eds.; Springer International Publishing: Cham, 2019; pp. 447–490 ISBN 978-3-030-03344-6.
28. Vahter, M.; Åkesson, A.; Lidén, C.; Ceccatelli, S.; Berglund, M. Gender differences in the disposition and toxicity of metals. *Environ. Res.* **2007**, *104*, 85–95, doi:10.1016/j.envres.2006.08.003.
29. Vahter, M.E.; Li, L.; Nermell, B.; Rahman, A.; Arifeen, S.E.; Rahman, M.; Persson, L.Å.; Ekström, E.-C. Arsenic Exposure in Pregnancy: A Population-based Study in Matlab, Bangladesh. *J. Health Popul. Nutr.* **2006**, *24*, 236–245.
30. Roswall, N.; Hvidtfeldt, U.A.; Harrington, J.; Levine, K.E.; Sørensen, M.; Tjønneland, A.; Meliker, J.R.; Raaschou-Nielsen, O. Predictors of Urinary Arsenic Levels among Postmenopausal Danish Women. *Int. J. Environ. Res. Public. Health* **2018**, *15*, 1340, doi:10.3390/ijerph15071340.
31. Vimercati, L.; Carrus, A.; Sciannamblo, G.; Caputo, F.; Minunni, V.; Nichilo, G. de; Bellotta, M.R.; Gagliardi, T.; Bisceglia, L.; Assennato, G. A study of factors influencing urinary arsenic excretion in exposed workers. *Int. J. Environ. Health Res.* **2009**, *19*, 369–377, doi:10.1080/09603120903079349.