Published in final edited form as:

Rev Environ Health. ; 27(4): 191–195. doi:10.1515/reveh-2012-0021.

ARSENIC AND HUMAN HEALTH: EPIDEMIOLOGIC PROGRESS AND PUBLIC HEALTH IMPLICATIONS

Maria Argos¹, Habibul Ahsan¹, and Joseph H. Graziano²

¹Department of Health Studies, The University of Chicago, Chicago, IL 60637

²Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY 10032

Abstract

Elevated concentrations of arsenic in groundwater pose a public health threat to millions of people worldwide, including severely affected populations in South and Southeast Asia. While arsenic is an established human carcinogen and has been associated with a multitude of health outcomes in epidemiologic studies, a mode of action has yet to be determined for some aspects of arsenic toxicity. Herein, we emphasize the role of recent genetic and molecular epidemiologic investigations of arsenic toxicity. Additionally, we discuss considerations for the public health impacts of arsenic exposure through drinking water with respect to primary and secondary prevention efforts.

Keywords

Arsenic; drinking water; Asia; human health

INTRODUCTION

Arsenic is a naturally occurring metalloid, ubiquitously present in the environment. Through reduction-oxidation reactions, arsenic can be released from soil and rock into the surrounding aquifers. Elevated concentrations of arsenic in groundwater were first realized in West Bengal, India, and Bangladesh in the 1980s and 1990s with the appearance of skin lesion epidemics in villages, which accessed drinking water by tubewells that tap into the arsenic-enriched aquifers (1). The tubewells were installed through governmental and public health initiatives beginning in the 1970s to provide microbially-safe drinking water to the population through the consumption of groundwater. This was an effort to reduce mortality and morbidity from cholera and other waterborne diseases that had plagued the population, and proved to be effective towards this end with the subsequent reduction of infant mortality. Most recently, additional regions of South and Southeast Asia have been

---

CORRESPONDING AUTHOR: Maria Argos, PhD, The University of Chicago, Department of Health Studies, 5841 S. Maryland Avenue, MC2007, Chicago, IL 60637, Telephone: 773-834-8601, argos@uchicago.edu.

This commentary was conceived from the key themes presented and discussed at a session entitled “Arsenic” held at the 2012 Joint International Conference of the Pacific Basin Consortium for Environment and Health and the Society for Environmental Geochemistry and Health.

determined to have elevated concentrations of arsenic in groundwater used for human consumption (2).

In 1993, the World Health Organization revised its guideline for the permissible concentration of arsenic in drinking water from 50 µg/L to 10 µg/L, which was also the maximum permissible concentration of arsenic in drinking water adopted by the United States Environmental Protection Agency in 2001 as well as several other developed countries (3). However, the permissible level of arsenic in drinking water regulated by several developing countries in South and Southeast Asia, including Bangladesh, Cambodia, China, India, Lao People's Democratic Republic, Myanmar, Nepal, and Pakistan, is still 50 µg/L. There has not been reliable data to quantify the global burden of arsenic in drinking water worldwide; however, arsenic in drinking water has been detected at concentrations greater than 10 µg/L or the prevailing national standard in several countries including Argentina, Australia, Bangladesh, Cambodia, Chile, China, Hungary, India, Lao People's Democratic Republic, Mexico, Myanmar, Nepal, Pakistan, Peru, Thailand, United States, and Vietnam (2, 4). Globally, nearly 100 million people are chronically exposed to arsenic through naturally contaminated drinking water (5), with the largest affected population in Bangladesh (6).

ARSENIC AND HUMAN HEALTH

The International Agency for Research on Cancer has classified arsenic as a class I human carcinogen (7). Arsenic in drinking water has been associated with increased risk of a wide range of health outcomes including cancers of the skin, lung, bladder, liver, and kidney (8–12), neurological disease (13), cardiovascular disease (14), as well as other non-malignant diseases (15, 16).

While arsenic is a well-established human carcinogen (17) and has additionally been associated with an array of chronic diseases through epidemiologic investigations (12, 18–30), the underlying mechanism(s) of some aspects of arsenic toxicity has not yet been determined. This is largely due to the absence of a suitable animal model for the evaluation of arsenic toxicity (31, 32). Additionally, while the health effects of arsenic exposure through drinking water have been well established at higher doses (>100 µg/L), evidence on the effects of arsenic at low-to-moderate levels (<100 µg/L) of exposure is not well established. Arsenic exposure at low-to-moderate levels is more prevalent than high-level exposure, and even a small increased risk may translate to a large number of excess cases and be of public health concern. Epidemiologic investigations of health effects at these lower arsenic concentrations are of potentially substantial public health relevance for both developed and developing nations worldwide in providing a better basis for planning population interventions and policy decisions.

While the mechanisms of arsenic toxicity have yet to be established, recent advances have been made in arsenic epidemiology with the use of genetic and molecular techniques to shed light on the underlying mechanisms of arsenic toxicity.

Recent Findings from Genetic and Molecular Epidemiology

Arsenic Metabolism—Arsenic is primarily present in the inorganic form (arsenate and arsenite) in drinking water (33). Once internalized, it goes through a series of reduction and oxidative methylation steps (34). While methylation of an exogenous compound is typically considered to be a detoxification process, there is mounting evidence that the partial methylation of arsenic may increase its toxicity *in vivo* particularly via the trivalent monomethylated arsenic species that is more toxic than the inorganic and pentavalent methylated arsenic species (35–38). Ingested inorganic arsenic is typically excreted as 10–20% inorganic arsenic, 10–15% monomethylated arsenic (MMA), and 60–75% dimethylated arsenic (DMA) (39). However, there is known inter-individual variability in the methylation capacity of arsenic (as reviewed in (40)), which has been hypothesized to partly explain the variability in susceptibility to arsenic toxicity.

Recently, the first genomewide association study (GWAS) of arsenic-related metabolism and toxicity phenotypes was conducted (41), which utilized data on urinary arsenic metabolite concentrations and 259,597 genomewide single nucleotide polymorphisms (SNPs) for 1,313 arsenic-exposed Bangladeshi individuals. Five SNPs (rs4919694, rs9527, rs4290163, rs11191527, and rs11191659) near the AS3MT gene (arsenite methyltransferase; 10q24.32) showed significant independent associations for urinary total MMA percent and total DMA percent. Furthermore, the authors showed that one of the SNPs (rs9527) was associated with skin lesion risk through case-control comparison (41). While the role of AS3MT in arsenic metabolism has been previously described (42), two novel SNPs (rs9527 and rs11191527) not strongly correlated with any previously reported SNPs were identified.

Genetic susceptibility to arsenic-related health outcomes has been evaluated by several candidate gene studies in the last decade (43). Despite this, the limited scope of work that has been done to evaluate genetic susceptibility to arsenic toxicity clearly warrants further investigation. Additional GWAS and replication studies will hopefully overcome obstacles in the existing literature including inconsistencies in case definitions, differences in arsenic exposure distributions across populations as well as other covariates, and under-powered studies to be able to synthesize genetic risk factors of arsenic toxicity from future research.

Biological Responses of Prenatal Arsenic Exposure—The health effects of prenatal arsenic exposure have been recently reviewed by Vahter (44). There is increasing epidemiologic evidence of the association of infant growth and mortality with prenatal arsenic exposure; however, the question still remains regarding later life health effects of prenatal and early life arsenic exposure (45). Few epidemiologic studies have evaluated health outcomes in relation to early life arsenic exposure (46–48), although there is some evidence from research in Chile of increased mortality rates associated with prenatal and early life arsenic exposure (46). Molecular biomarkers of early biological effects have been increasingly studied in arsenic epidemiology to elucidate information on toxicity mechanisms and biological pathways. The examination of cellular and molecular responses associated with prenatal arsenic exposure is a first step in a life course approach to evaluate early childhood exposure with potential later-life health outcomes.

In a recent study of mothers and newborns in Thailand, gene expression signals from babies born to arsenic-exposed and arsenic-unexposed mothers were evaluated (49). The authors identified 11 gene transcripts predictive of prenatal arsenic exposure, including up-regulation of molecular networks related to stress, inflammation, metal exposure, and apoptosis in the newborns. Additionally, NF- κ B and IL-1 β was one of the networks observed to underlie the set of differentially expressed genes between infants from arsenic-exposed and –unexposed mothers, a pathway related to inflammation and apoptosis. Interestingly, the NF- κ B and IL-1 β pathway was previously shown to be differentially expressed in a comparison of Bangladeshi adults with and without arsenical skin lesions (50). Another recent study of newborns in Thailand showed that arsenic-exposed newborns had significantly higher levels of arsenic in cord blood, fingernails, toenails, and hair and a slight increase in promoter methylation of p53 in cord blood lymphocytes compared to the newborns of arsenic-unexposed mothers (51). Additional biological effects should be characterized in infants, children, and adolescents to evaluate the effect of prenatal and early life arsenic exposure, including further and more comprehensive investigation of epigenetic effects, which are potentially modifiable and can be the target of future interventions.

PUBLIC HEALTH IMPLICATIONS

The worldwide prevalence of arsenic in drinking water illustrates the fact that arsenic exposure is a major public health concern deserving attention. There are two major public health considerations with respect to arsenic exposure, which we describe in the context of primary and secondary prevention.

Primary Prevention

Arsenic mitigation is a critical public health need in exposed populations, with progress being made toward eliminating arsenic exposure through drinking water sources in the human population. Mitigation efforts have largely taken two forms in arsenic exposed populations: well-switching and arsenic removal technologies.

One of the approaches to mitigation taken in the Araihaazar region of Bangladesh has focused on taking advantage of the high degree of spatial variability of arsenic in groundwater, the consequence of which is that a majority of residents in the area live within walking distance of a tubewell that is low in arsenic (52). Surveys as well as time-series measurements of urinary arsenic have shown that reporting the results of tubewell testing, along with education on the health risks of arsenic in drinking water, has led a substantial portion of households to switch to a nearby low-arsenic well, markedly reducing exposure to arsenic throughout the geographic study area (53, 54). In areas with little opportunity for sharing existing low arsenic wells, the installation of community wells by a local organization has been facilitated, tapping deeper low-arsenic aquifers (55). However, despite the discovery of arsenic-enriched groundwater in South and Southeast Asia, new wells continue to be installed blindly without regard to possible arsenic contamination. Observations from Bangladesh indicate that a large proportion of new tubewells that are installed are not immediately tested for their arsenic concentration; thus, there is the continuous need for testing of new tubewells which can be reliably achieved through field kits (56).

Arsenic removal technologies are another mitigation strategy employed in arsenic exposed regions of South and Southeast Asia. A comprehensive review of arsenic removal technologies has recently been conducted by Jain and Singh (57). There are complex interactions and logistical considerations that should be considered for the large-scale implementation of arsenic removal technologies in populations including the selection of a technology appropriate for the concentration of arsenic found in the groundwater, the economic condition and feasibility of the technology for the population, the population distribution in the geographic area, the technology and labor skill available for the technology operation and maintenance in the population, and environmental impacts (58). Besides the complication of properly maintaining arsenic removal technologies at the household or community level, there is also concern about the likelihood of microbial contamination of filtration systems in regions where sanitation is still very poor.

Secondary Prevention

The second major public health consideration is preventing or reducing harm after chronic arsenic exposure has occurred. While there is substantial evidence of dose-response associations between arsenic in drinking water and various health outcomes, studies have shown that remediation of arsenic exposure alone does not reduce arsenic-related health risks in the population (59–61). In recent publications using prospective data from the Health Effects of Arsenic Longitudinal Study cohort, it was shown utilizing repeated measures of urinary total arsenic exposure over time that once chronically exposed, a reduction of decreasing exposure for a short amount of time did not reduce one's risk of mortality (59) or skin lesion incidence (62). Furthermore, studies from Taiwan and Chile indicate that elevated cancer risk among arsenic exposed populations persists for at least several decades after cessation of exposure (19, 63, 64). Therefore, evidence from these prior studies suggests that it may be important to consider other health prevention and promotion strategies in conjunction with remediation for arsenic-exposed populations. Evaluation of genetic determinants of arsenic-related health outcomes as well as epigenetic modifications associated with exposure could contribute to a greater understanding of the genetic and molecular pathways that underlie arsenic toxicity and may inform future interventions and secondary prevention strategies of arsenic-exposed populations. In addition to elucidating biological mechanisms of action, investigating genetic susceptibility may help identify individuals with higher risk to arsenic-related toxicity, aiding in secondary prevention and intervention of arsenic-exposed populations.

CONCLUSIONS

Estimation of the future public health burden of arsenic exposure through drinking water has been primarily extrapolated from data from other populations (65–67). While the exact magnitude of these estimates may be uncertain, it is clear that millions of individuals in South and Southeast Asia are at increased risk of arsenic-related diseases and mortality. Future public health research should emphasize arsenic mitigation in the most severely affected regions. Additionally, future molecular and genetic epidemiologic findings may have potential translational implications for prevention and treatment of arsenic-associated toxicities worldwide.

Acknowledgments

The authors would like to especially thank the presenters of the session: Drs. Panida Navasumrit, Koichiro Shiomori, Penradee Chanpiwat and Ms. Le Thai Ha.

REFERENCES

1. Dhar R, Biswas B, Samanta G, Mandal B, Chakraborti D, Roy S, et al. Groundwater arsenic calamity in Bangladesh. *Current Science*. 1997; 73(1):48–59.
2. McCarty KM, Hanh HT, Kim KW. Arsenic geochemistry and human health in South East Asia. *Rev Environ Health*. 2011; 26(1):71–78. [PubMed: 21714384]
3. EPA. [accessed May 11, 2012] Arsenic and Clarifications to Compliance and New Source Monitoring Rule: A Quick Reference Guide. 2001. Internet: http://water.epa.gov/drink/info/arsenic/upload/2005_11_10_arsenic_quickguide.pdf.
4. BGS, DPHE. Arsenic contamination of groundwater in Bangladesh. Keyworth: British Geological Survey; 2001. Report No.: BGS Technical Report WC/00/19, Volume 2.
5. Ng JC, Wang J, Shraim A. A global health problem caused by arsenic from natural sources. *Chemosphere*. 2003; 52(9):1353–1359. [PubMed: 12867164]
6. Smith AH, Lingas EO, Rahman M. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. *Bull World Health Organ*. 2000; 78(9):1093–1103. [PubMed: 11019458]
7. International Agency for Research on Cancer (IARC). IARC monograph on arsenic and arsenic compounds. Lyon, France: IARC; 1987. p. 100
8. Smith AH, Goycolea M, Haque R, Biggs ML. Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. *Am J Epidemiol*. 1998; 147(7):660–669. [PubMed: 9554605]
9. Chen CJ, Chen CW, Wu MM, Kuo TL. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. *Br J Cancer*. 1992; 66(5):888–892. [PubMed: 1419632]
10. Hopenhayn-Rich C, Biggs ML, Fuchs A, Bergoglio R, Tello EE, Nicolli H, et al. Bladder cancer mortality associated with arsenic in drinking water in Argentina. *Epidemiology*. 1996; 7(2):117–124. [PubMed: 8834549]
11. Hopenhayn-Rich C, Biggs ML, Smith AH. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. *Int J Epidemiol*. 1998; 27(4):561–569. [PubMed: 9758107]
12. Tseng WP. Effects and dose--response relationships of skin cancer and blackfoot disease with arsenic. *Environ Health Perspect*. 1977; 19:109–119. [PubMed: 908285]
13. Brouwer OF, Onkenhout W, Edelbroek PM, de Kom JF, de Wolff FA, Peters AC. Increased neurotoxicity of arsenic in methylenetetrahydrofolate reductase deficiency. *Clin Neurol Neurosurg*. 1992; 94(4):307–310. [PubMed: 1335858]
14. Wu MM, Kuo TL, Hwang YH, Chen CJ. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am J Epidemiol*. 1989; 130(6):1123–1132. [PubMed: 2589305]
15. Rahman M, Tondel M, Ahmad SA, Chowdhury IA, Faruquee MH, Axelson O. Hypertension and arsenic exposure in Bangladesh. *Hypertension*. 1999; 33(1):74–78. [PubMed: 9931084]
16. Heck JE, Chen Y, Grann VR, Slavkovich V, Parvez F, Ahsan H. Arsenic exposure and anemia in Bangladesh: a population-based study. *J Occup Environ Med*. 2008; 50(1):80–87. [PubMed: 18188085]
17. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some Drinking-water Disinfectants and Contaminants, including Arsenic. Volume 84. Lyon, France: 2004.
18. Smith AH, Goycolea M, Haque R, Biggs ML. Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. *Am J Epidemiol*. 1998; 147(7):660–669. [PubMed: 9554605]

19. Chen CJ, Chen CW, Wu MM, Kuo TL. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. *Br J Cancer*. 1992; 66(5):888–892. [PubMed: 1419632]
20. Hopenhayn-Rich C, Biggs ML, Fuchs A, Bergoglio R, Tello EE, Nicolli H, et al. Bladder cancer mortality associated with arsenic in drinking water in Argentina. *Epidemiology*. 1996; 7(2):117–124. [PubMed: 8834549]
21. Hopenhayn-Rich C, Biggs ML, Smith AH. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. *Int J Epidemiol*. 1998; 27(4):561–569. [PubMed: 9758107]
22. Brouwer OF, Onkenhout W, Edelbroek PM, de Kom JF, de Wolff FA, Peters AC. Increased neurotoxicity of arsenic in methylenetetrahydrofolate reductase deficiency. *Clin Neurol Neurosurg*. 1992; 94(4):307–310. [PubMed: 1335858]
23. Navas-Acien A, Sharrett AR, Silbergeld EK, Schwartz BS, Nachman KE, Burke TA, et al. Arsenic exposure and cardiovascular disease: a systematic review of the epidemiologic evidence. *Am J Epidemiol*. 2005; 162(11):1037–1049. [PubMed: 16269585]
24. States JC, Srivastava S, Chen Y, Barchowsky A. Arsenic and cardiovascular disease. *Toxicol Sci*. 2009; 107(2):312–323. [PubMed: 19015167]
25. Tseng CH. Cardiovascular disease in arsenic-exposed subjects living in the arseniasis-hyperendemic areas in Taiwan. *Atherosclerosis*. 2008; 199(1):12–18. [PubMed: 18367191]
26. Ahmad SA, Sayed MH, Barua S, Khan MH, Faruquee MH, Jalil A, et al. Arsenic in drinking water and pregnancy outcomes. *Environ Health Perspect*. 2001; 109(6):629–631. [PubMed: 11445518]
27. Milton AH, Smith W, Rahman B, Hasan Z, Kulsum U, Dear K, et al. Chronic arsenic exposure and adverse pregnancy outcomes in bangladesh. *Epidemiology*. 2005; 16(1):82–86. [PubMed: 15613949]
28. von Ehrenstein OS, Guha Mazumder DN, Hira-Smith M, Ghosh N, Yuan Y, Windham G, et al. Pregnancy outcomes, infant mortality, and arsenic in drinking water in West Bengal, India. *Am J Epidemiol*. 2006; 163(7):662–669. [PubMed: 16524957]
29. Milton AH, Rahman M. Respiratory effects and arsenic contaminated well water in Bangladesh. *Int J Environ Health Res*. 2002; 12(2):175–179. [PubMed: 12400554]
30. Parvez F, Chen Y, Brandt-Rauf PW, Bernard A, Dumont X, Slavkovich V, et al. Nonmalignant respiratory effects of chronic arsenic exposure from drinking water among never-smokers in Bangladesh. *Environ Health Perspect*. 2008; 116(2):190–195. [PubMed: 18288317]
31. Rossman TG. Mechanism of arsenic carcinogenesis: an integrated approach. *Mutat Res*. 2003; 533(1–2):37–65. [PubMed: 14643412]
32. Tokar EJ, Benbrahim-Tallaa L, Ward JM, Lunn R, Sams RL 2nd, Waalkes MP. Cancer in experimental animals exposed to arsenic and arsenic compounds. *Crit Rev Toxicol*. 40(10):912–927. [PubMed: 20812815]
33. Andreae MO. Determination of arsenic species in natural waters. *Anal Chem*. 1977; 49(6):820–823. [PubMed: 855924]
34. Aposhian HV. Enzymatic methylation of arsenic species and other new approaches to arsenic toxicity. *Annu Rev Pharmacol Toxicol*. 1997; 37:397–419. [PubMed: 9131259]
35. Le XC, Ma M, Cullen WR, Aposhian HV, Lu X, Zheng B. Determination of monomethylarsonous acid, a key arsenic methylation intermediate, in human urine. *Environ Health Perspect*. 2000; 108(11):1015–1018. [PubMed: 11102289]
36. Del Razo LM, Styblo M, Cullen WR, Thomas DJ. Determination of trivalent methylated arsenicals in biological matrices. *Toxicol Appl Pharmacol*. 2001; 174(3):282–293. [PubMed: 11485389]
37. Ahmad S, Anderson WL, Kitchin KT. Dimethylarsinic acid effects on DNA damage and oxidative stress related biochemical parameters in B6C3F1 mice. *Cancer Lett*. 1999; 139(2):129–135. [PubMed: 10395169]
38. Styblo M, Drobna Z, Jaspers I, Lin S, Thomas DJ. The role of biomethylation in toxicity and carcinogenicity of arsenic: a research update. *Environ Health Perspect*. 2002; 110(Suppl 5):767–771. [PubMed: 12426129]

39. Hopenhayn-Rich C, Smith AH, Goeden HM. Human studies do not support the methylation threshold hypothesis for the toxicity of inorganic arsenic. *Environ Res.* 1993; 60(2):161–177. [PubMed: 8472646]
40. Tseng CH. A review on environmental factors regulating arsenic methylation in humans. *Toxicol Appl Pharmacol.* 2009; 235(3):338–350. [PubMed: 19168087]
41. Pierce BL, Kibriya MG, Tong L, Jasmine F, Argos M, Roy S, et al. Genome-wide association study identifies chromosome 10q24.32 variants associated with arsenic metabolism and toxicity phenotypes in Bangladesh. *PLoS Genet.* 2012; 8(2):e1002522. [PubMed: 22383894]
42. Hernandez A, Xamena N, Surrallés J, Sekaran C, Tokunaga H, Quinteros D, et al. Role of the Met(287)Thr polymorphism in the AS3MT gene on the metabolic arsenic profile. *Mutat Res.* 2008; 637(1–2):80–92. [PubMed: 17850829]
43. Hernandez A, Marcos R. Genetic variations associated with interindividual sensitivity in the response to arsenic exposure. *Pharmacogenomics.* 2008; 9(8):1113–1132. [PubMed: 18681785]
44. Vahter M. Health effects of early life exposure to arsenic. *Basic Clin Pharmacol Toxicol.* 2008; 102(2):204–211. [PubMed: 18226075]
45. Vahter M. Effects of arsenic on maternal and fetal health. *Annu Rev Nutr.* 2009; 29:381–399. [PubMed: 19575603]
46. Liaw J, Marshall G, Yuan Y, Ferreccio C, Steinmaus C, Smith AH. Increased childhood liver cancer mortality and arsenic in drinking water in northern Chile. *Cancer Epidemiol Biomarkers Prev.* 2008; 17(8):1982–1987. [PubMed: 18708388]
47. Lindberg AL, Rahman M, Persson LA, Vahter M. The risk of arsenic induced skin lesions in Bangladeshi men and women is affected by arsenic metabolism and the age at first exposure. *Toxicol Appl Pharmacol.* 2008; 230(1):9–16. [PubMed: 18336856]
48. Rahman M, Vahter M, Sohel N, Yunus M, Wahed MA, Streatfield PK, et al. Arsenic exposure and age and sex-specific risk for skin lesions: a population-based case-referent study in Bangladesh. *Environ Health Perspect.* 2006; 114(12):1847–1852. [PubMed: 17185274]
49. Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, et al. Activation of inflammation/NF-kappaB signaling in infants born to arsenic-exposed mothers. *PLoS Genet.* 2007; 3(11):e207. [PubMed: 18039032]
50. Argos M, Kibriya MG, Parvez F, Jasmine F, Rakibuz-Zaman M, Ahsan H. Gene expression profiles in peripheral lymphocytes by arsenic exposure and skin lesion status in a Bangladeshi population. *Cancer Epidemiol Biomarkers Prev.* 2006; 15(7):1367–1375. [PubMed: 16835338]
51. Intarasunanont P, Navasumrit P, Woraprasit S, Chaisatra K, Suk WA, Mahidol C, et al. Effects of arsenic exposure on DNA methylation in cord blood samples from newborn babies and in a human lymphoblast cell line. *Environ Health.* 2012; 11(1):31. [PubMed: 22551203]
52. Van Geen A, Ahsan H, Horneman AH, Dhar RK, Zheng Y, Hussain I, et al. Promotion of well-switching to mitigate the current arsenic crisis in Bangladesh. *Bull World Health Organ.* 2002; 80(9):732–737. [PubMed: 12378292]
53. Chen Y, van Geen A, Graziano JH, Pfaff A, Madajewicz M, Parvez F, et al. Reduction in urinary arsenic levels in response to arsenic mitigation efforts in Araihaazar, Bangladesh. *Environ Health Perspect.* 2007; 115(6):917–923. [PubMed: 17589600]
54. Madajewicz M, Pfaff A, van Geen A, Graziano J, Hussein I, Momotaj H, et al. Can information alone change behavior? Response to arsenic contamination of groundwater in Bangladesh. *Journal of Development Economics.* 2007; 84:731–754.
55. van Geen A, Ahmed KM, Seddique AA, Shamsudduha M. Community wells to mitigate the arsenic crisis in Bangladesh. *Bull World Health Organ.* 2003; 81(9):632–638. [PubMed: 14710504]
56. George CM, Graziano JH, Mey JL, van Geen A. Impact on arsenic exposure of a growing proportion of untested wells in Bangladesh. *Environ Health.* 2012; 11:7. [PubMed: 22353180]
57. Jain CK, Singh RD. Technological options for the removal of arsenic with special reference to South East Asia. *J Environ Manage.* 2012; 107C:1–18. [PubMed: 22579769]
58. Kim KW, Chanpiwat P, Hanh HT, Phan K, Sthiannopkao S. Arsenic geochemistry of groundwater in Southeast Asia. *Front Med.* 2011; 5(4):420–433. [PubMed: 22198754]

59. Argos M, Kalra T, Rathouz PJ, Chen Y, Pierce B, Parvez F, et al. Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study. *Lancet*. 2010; 376(9737):252–258. [PubMed: 20646756]
60. Chang CC, Ho SC, Tsai SS, Yang CY. Ischemic heart disease mortality reduction in an arseniasis-endemic area in southwestern Taiwan after a switch in the tap-water supply system. *J Toxicol Environ Health A*. 2004; 67(17):1353–1361. [PubMed: 15371236]
61. Yang CY, Chiu HF, Chang CC, Ho SC, Wu TN. Bladder cancer mortality reduction after installation of a tap-water supply system in an arsenious-endemic area in southwestern Taiwan. *Environ Res*. 2005; 98(1):127–132. [PubMed: 15721893]
62. Argos M, Kalra T, Pierce BL, Chen Y, Parvez F, Islam T, et al. A prospective study of arsenic exposure from drinking water and incidence of skin lesions in Bangladesh. *Am J Epidemiol*. 2011; 174(2):185–194. [PubMed: 21576319]
63. Marshall G, Ferreccio C, Yuan Y, Bates MN, Steinmaus C, Selvin S, et al. Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. *J Natl Cancer Inst*. 2007; 99(12):920–928. [PubMed: 17565158]
64. Fernandez MI, Lopez JF, Vivaldi B, Coz F. Long-term impact of arsenic in drinking water on bladder cancer health care and mortality rates 20 years after end of exposure. *J Urol*. 2012; 187(3):856–861. [PubMed: 22248521]
65. Lokuge KM, Smith W, Caldwell B, Dear K, Milton AH. The effect of arsenic mitigation interventions on disease burden in Bangladesh. *Environ Health Perspect*. 2004; 112(11):1172–1177. [PubMed: 15289162]
66. Chen Y, Ahsan H. Cancer burden from arsenic in drinking water in Bangladesh. *Am J Public Health*. 2004; 94(5):741–744. [PubMed: 15117692]
67. Adamson GC, Polya DA. Critical pathway analysis to determine key uncertainties in net impacts on disease burden in Bangladesh of arsenic mitigation involving the substitution of arsenic bearing for groundwater drinking water supplies. *J Environ Sci Health A Tox Hazard Subst Environ Eng*. 2007; 42(12):1909–1917. [PubMed: 17952792]