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Exposure, Metabolism, and Effects of Arsenic in Residents from Arsenic-contaminated Groundwater Areas of Southeast Asia

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Abstract—Since 2000, we have investigated the exposure, metabolism, and toxic effect of arsenic (As) in residents from As-contaminated groundwater areas of Southeast Asia. Here, we introduce the recent results of the investigations. Monitoring studies showed that As contamination is ubiquitous in the groundwater from Southeast Asia and also exceeded WHO guidelines in a large number of samples from the Mekong River. The results of As analyses in the human hair and urine indicate that residents in the As-contaminated areas are mostly exposed to As through the uptake of As contaminated groundwater. Studies on genetic polymorphisms of arsenic (+III) methyltransferase and glutathione-*S*-transferase suggested that these enzymes are involved in the metabolism of arsenic in residents who have been exposed to high levels of As. Levels of urinary 8-hydroxy-2′-deoxyguanosine were higher in the subjects with elevated levels of As in the hair and urine, suggesting the induction of oxidative DNA damage by As exposure.

Keywords: arsenic, groundwater, human, genetic polymorphism, oxidative stress

INTRODUCTION

It is well known that inorganic As is carcinogenic. Contamination by naturally derived inorganic As in groundwater is one of the serious health issues on a global scale, especially in developing countries. Skin, lung, kidney, bladder, and liver cancers or skin lesions including keratosis and pigmentation by chronic exposure to As through groundwater consumption were observed in local residents from these areas (Wu *et al*., 1989; Tondel *et al*., 1999). In the Ganges Delta (Bangladesh and West Bengal in India), which is one of the most As affected areas, it is estimated that 36 million people are subjected to the risk of As exposure (Nordstrom, 2002).

Since Berg *et al*. (2001) reported remarkably high As concentration (up to 3,050 μg/l) in groundwater from Vietnam, several studies on As contamination

in groundwater from Southeast Asia has been carried out and reported high concentration of As (e.g., Trang *et al.*, 2005; Berg *et al.*, 2006, 2007; Buschmann *et al.*, 2007, 2008). Therefore, human health risk by As exposure through the consumption of groundwater is of concern in these areas. However, information is still scarce on the exposure, metabolism and toxic effects of inorganic As in residents from As-contaminated groundwater areas in Southeast Asia compared with Bangladesh and West Bengal, India. Since 2000, we have collected the groundwater and biological samples from the local residents in Vietnam, Cambodia, Thailand, Laos, and India. Based on the results of investigations, the geographical distribution of As contamination in groundwater was clarified, and the exposure level, metabolic capacity and effects of As in humans were assessed (Agusa *et al.*, 2002, 2004, 2005, 2006, 2007, 2008, 2009a, 2009b, 2009c, 2010a, 2010b, 2010c, 2011, 2012; Kubota *et al.*, 2006; Iwata *et al.*, 2007). Here, we briefly introduce our recent results of investigations carried out in Vietnam, Cambodia, Thailand, Laos, and India in 2000–2007.

DISTRIBUTION OF AS IN GROUNDWATER

Concentration of As in groundwater is shown in Fig. 1 (Agusa *et al.*, 2002, 2004, 2005, 2006, 2007, 2008, 2009a, 2009b, 2009c, 2010a, 2010b, 2010c, 2011, 2012; Kubota *et al.*, 2006; Iwata *et al.*, 2007). Through our studies, we found that totally 37% of water samples analyzed had over the standard level (10 μg/l) for As in drinking water established by WHO (WHO, 2004). Remarkably, more than 1,000 μg/l of As was observed in several groundwater samples from Kandal, Cambodia (Iwata *et al.*, 2007) and these levels were comparable with Bangladesh or West Bengal in India (Nordstrom, 2002). Hence, As contamination in ground water, which is of great concern on human health risk, is widespread in Southeast Asia and India.

Exposure to As: A Case Study in Northern Vietnam

It is well known that ingested inorganic As is metabolized to methylated species (monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA)) in the liver and then excreted into the urine and hair. Therefore, urine and hair samples are useful indicators to assess exposure status and metabolism of As in human. To assess human As exposure level, we analyzed As concentrations in human hair and urine of residents from As-contaminated groundwater areas in North Vietnam (Agusa *et al.*, 2002, 2005, 2006, 2007, 2008, 2009a, 2009b, 2009c, 2010a, 2010b, 2010c, 2011, 2012; Kubota *et al.*, 2006). For the collection of human samples, the informed consent was obtained from all the participants. Our studies have been approved by the Ethical Committee of Ehime University, Japan and the Center for Environmental Technology and Sustainable Development (CETASD), Hanoi National University, Hanoi, Vietnam.

A significant positive correlation between As concentrations in drinking water and human hair was observed. Urinary arsenite (As[III]) as well as its metabolites, MMA and DMA concentrations in humans were also positively

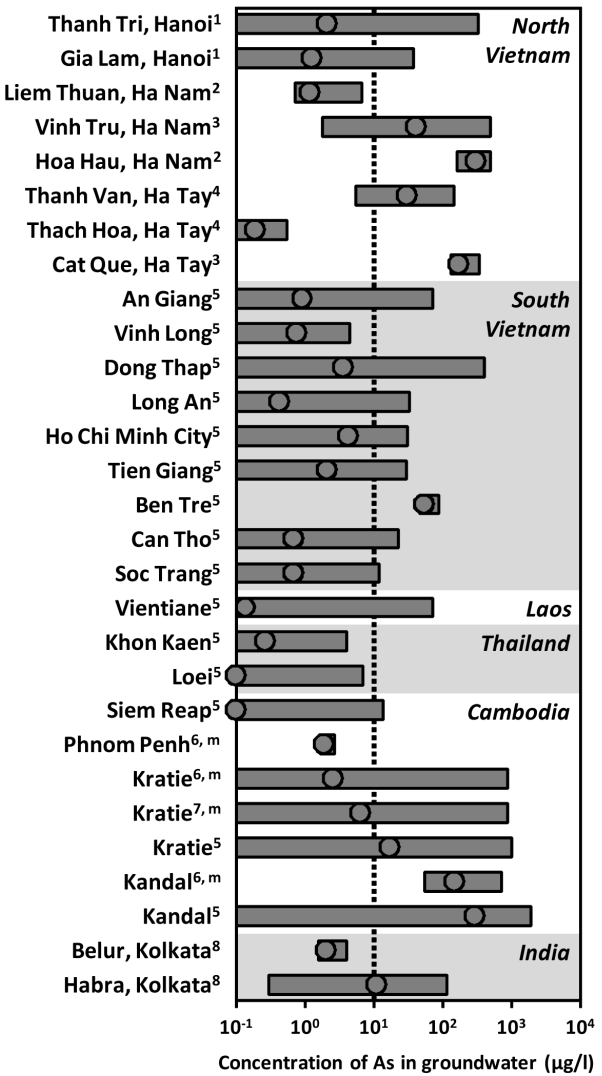

Fig. 1. Concentration (μg/l) of As in groundwater from Vietnam, Laos, Thailand, Cambodia, and India. Bar and circle represent range and geometric mean, respectively. Vertical dotted line indicates WHO drinking water guideline for As (10 μg/l) (WHO, 2004). m, median; 1, Agusa *et al*., 2006; 2, Agusa *et al*., 2009c; 3, Agusa *et al*., 2009a; 4, Agusa *et al*., 2012; 5, Iwata *et al*., 2007; 6, Agusa *et al*., 2002; 7, Kubota *et al*., 2006; 8, Agusa *et al*., unpublished data.

correlated with As concentrations in drinking water. These results suggest that local residents are exposed to As through the drinking water and the ingested inorganic As is metabolized to its methylated compounds.

Metabolism of As: A Case Study in Northern Vietnam

There is a large variation in the susceptibility of inorganic As toxicity among individuals and population. It is suggested that the variation is related to genetic polymorphisms in the metabolism of inorganic As. In general, there are two main reactions on As metabolism in human; reductive reactions of pentavalent to trivalent As, and methylation reactions in which trivalent forms of As are sequentially methylated to form mono-, and dimethylated products. In these pathways, two enzymes, glutathione-*S*-transferase omega (GSTO) (Zakharyan *et al*., 2005) and arsenic (+III) methyltransferase (AS3MT) (Lin *et al*., 2002; Wood *et al*., 2006) play a role in inorganic As metabolism; GSTO has the reductase activity of pentavalent arsenicals to trivalent forms, while AS3MT can catalyzes the methylation of As compound. Significant associations of single nucleotide polymorphisms (SNPs) in *AS3MT* and *GSTO1* with variations in metabolic capacity of inorganic As are reported in several *in vitro* and/or human case studies (Meza *et al*., 2005; Schmuck *et al*., 2005; Wood *et al*., 2006; Schläwicke Engström *et al*., 2007; Lindberg *et al*., 2007; Steinmaus *et al*., 2007).

Our recent study investigated relationships between As metabolic capacity estimated by urinary As profile and genetic polymorphisms in As metabolic enzymes in 199 subjects from the Red River Delta in Vietnam (Agusa *et al*., 2009c, 2010a, 2010b, 2010c, 2011, 2012). Urinary DMA/MMA for the hetero type (Met/Thr) of *AS3MT* Met287Thr in Vietnamese is significantly lower than the wild type (Met/Met). Urinary MMA/inorganic As for the hetero type (Glu/dell) of *GSTO1* Glu155del was high compared with the homo type (Glu/Glu) ($p < 0.05$). For the *GSTM1* polymorphism, the null type had lower As[III]/arsenate (As[V]) and MMA/inorganic As than the wild type. These findings indicate that genetic polymorphisms in *GSTM1*, *GSTO1*, and *AS3MT* may be responsible for inorganic As metabolism in Vietnamese.

Several studies reported significant associations of *GSTO1* and *GSTM1* polymorphisms with increased prevalence of As induced skin lesions or cancers (Ghosh *et al*., 2006; Ahsan *et al*., 2007), while negative results were observed (McCarty *et al*., 2007; De Chaudhuri *et al*., 2008). Study on the relationships among As exposure, metabolic capacity, genetic polymorphisms, and health effects in human is needed in future.

DNA Damage by As: A Case Study in Cambodia

It has been suggested that oxidative stress caused by As exposure is a trigger of carcinogenesis (Kitchin and Ahmad, 2003). Reactive oxygen species such as hydroxyl radical and dimethylarsenic peroxy radical produced by As exposure can directly or indirectly damage cellular DNA (Liu *et al*., 2001). 8-Hydroxy-2′-deoxyguanosine (8-OHdG) is known to be an indicator of oxidative stress due to one of the major forms of damaged DNA. Elevated 8-OHdG concentrations were observed in urine of residents chronically exposed to As through drinking water in Inner Mongolia, China (Fujino *et al*., 2005), As-related skin neoplasms and keratosis of Bowen's diseases (Matsui *et al*., 1999), and As-related human skin

tumors of inhabitants in As polluted area in Gejiu, China (An *et al*., 2004). In the case of our Cambodian study, urinary 8-OHdG level was elevated in higher As exposure group compared with lower As exposure group (Kubota *et al*., 2006). Such a high oxidative DNA damage observed in the subjects from the As affected areas of Cambodia may be due to chronic exposure to As from groundwater.

We noticed no symptoms of As-related diseases in subjects in a line of investigations, probably due to short history of usage of groundwater. The latency period for human carcinogenesis is thought to be 30–50 years (Yamauchi *et al*., 2004). In the regions examined in our studies, the inhabitants started using tube-well water as drinking water in the latter half of 1990s. However, skin disease by chronic As exposure in some people from Southeast Asia have been reported in other studies (Dang *et al*., 2004; Mazumder *et al*., 2009). Further epidemiological studies on human health effects are required.

CONCLUSIONS

Through investigations in 2000–2007, we indicate the following; 1) The elevated As contamination in groundwater are widely distributed in Southeast Asia and India. 2) Local residents are exposed to high level of As, which oxidative stress is considered, through the consumption of groundwater. 3) Genetic polymorphisms of *AS3MT* and *GST* isoforms are significantly associated with As metabolism. The relationships between As exposure and health effects in humans have not yet been fully evaluated in these As-contaminated groundwater areas. A larger and more comprehensive epidemiologic study is needed for the accurate risk assessment of As in local residents of the present study areas.

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