

Review Paper

Metabolism of inorganic arsenic and non-cancerous health hazards associated with chronic exposure in humans

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Abstract: Humans can be exposed to arsenic from a variety of environmental, occupational and medicinal sources. Exposure from drinking water is the most common source nowadays. Inorganic arsenic is metabolized by two main biochemical reactions: reduction and oxidative methylation. Recent studies have confirmed a reactivation of the toxic effects of arsenic associated with such methylation process, because the methylated metabolites, especially the trivalent forms, are more toxic than the inorganic arsenicals. Chronic exposure to arsenic can cause a variety of cancerous and non-cancerous health hazards in humans. The main non-cancerous health hazards include cardiovascular disease, skin lesions, neurological problems, diabetes mellitus and hypertension.

Key words: Inorganic arsenic, Human exposure, Health hazards, Blackfoot disease, Neuropathy

Introduction

Arsenic is a metalloid element found ubiquitously in nature. It is present in the earth's crust with an average concentration of 2 mg/kg. It can be found in soil, air, water, food, or some medications (Chen *et al.*, 1992, 1999; Tseng, 1999). Inorganic forms of arsenic usually present in well water are much more toxic than organic forms found in crustacean seafood (Ma and Le, 1998). Inorganic arsenic is readily absorbed through the gastrointestinal tract, and mainly metabolized in the liver to organic forms of methylated arsenic, which can be excreted in the urine. However, methylated metabolites of arsenic, especially the trivalent forms, are even more toxic than the inorganic forms (Thomas *et al.*, 2001, 2004; Kitchin, 2001; Styblo *et al.*, 2002). Ingestion of large amount of arsenic can cause acute intoxication presenting with a variety of symptoms and signs involving the gastrointestinal, dermal, nervous, renal, hepatic, hematopoietic, cardiovascular, respiratory and ophthalmic systems (Chen *et al.*, 1992; Tseng, 1999). Chronic exposure with low dose of arsenic from drinking water, coal burning or industrial sources can cause skin lesions, neurological defects, atherosclerosis and cancer (Chen *et al.*, 1992; Tseng, 1999, 2003). Because of the requirement of long gestation time for visible effects to occur, chronic intoxication can cause the occurrence of a variety of endemic diseases once the duration and dosage of exposure to arsenic in a localized population reaches its threshold. In some countries of Asia, the issue of chronic arsenic intoxication seems to be a more important public health problem than other regions of the world (Chen *et al.*, 1999; Tseng, 1999; Smith and Smith, 2004). The most important source of contamination is the drinking

water. The World Health Organization (WHO) established 0.2 mg/l as an allowable concentration in the first version of International Standards for Drinking-Water in 1958 (Yamamura, 1999). In the second version published in 1963, a stricter concentration of 0.05 mg/l was set as a new standard (Yamamura, 1999). A further stricter standard of 0.01 mg/l was suggested as a provisional guideline in the last edition of the WHO Guidelines for Drinking-Water Quality published in 1993 (Yamamura, 1999). In this paper, the potential sources of human arsenic exposure, the current knowledge of the metabolism of inorganic arsenic and the non-cancerous health hazards associated with chronic arsenic intoxication are reviewed.

Human exposure to arsenic:

Human beings can be exposed to arsenic from either natural sources or anthropogenic sources. Natural sources of arsenic include rocks (soil), volcanic emissions, undersea smokers and extra-terrestrial material. Volcanic emission is the most important natural source of arsenic. Arsenic can be found in more than 200 mineral species, of which the most common is arsenopyrite. Anthropogenically, arsenic can be found in products of herbicides, fertilizers, pesticides, leather treatment, cotton desiccants, wood preservation, animal feeds as food additives and pharmaceuticals.

Human beings can be exposed to arsenic through ingestion of arsenic-containing water, food and drugs (such as Fowler's solution containing 1% of potassium arsenite used to treat psoriasis; and arsenic trioxide used to treat leukemia). Air-borne arsenic can be absorbed into the blood stream in

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workers involved in the processing of copper, gold and lead ores, in the production and use of arsenic-containing pesticides, in the manufacturing of glass, semiconductors, and pharmaceutical substances; in using arsenic as pigments and dyes, in burning coal containing high arsenic (e.g., in Guizhou province of China); in smoking high arsenic contaminated tobacco and in chimney sweeping (Chen *et al.*, 1992, 1999; Tseng, 1999).

Water contamination is the most common source of arsenic exposure. Nowadays, Bangladesh and West Bengal-India have the most serious problem of groundwater contamination with arsenic in the world (Mazumder *et al.*, 1998; Milton and Rahman, 2002; Smith and Smith, 2004). Tracing back in history of these areas, surface water was replaced by tubewell water in recent 30 years to fight against infectious diarrheal diseases. These programmes to provide "safe" drinking water from underground unexpectedly bring up another health problem of arsenic hazards. It is estimated that more than 95% of the 120 million people in Bangladesh drink tubewell water and more than one third of the tubewell water contains arsenic above 0.05 mg/l. High arsenic level in drinking water is also reported in countries such as Argentina, Australia, Chile, China, Hungary, Mexico, Peru, Taiwan, Thailand and the United States of America (Chen *et al.*, 1992, 1999; Tseng, 1999).

Metabolism of arsenic:

In drinking water, arsenic is usually found in the form of inorganic arsenate or arsenite depending on the pH and the presence of oxidizing and reducing substances (Andreae, 1977; Shraim *et al.*, 2002). The metabolic pathway of inorganic arsenic involves 2 main steps of chemical reactions: reduction and oxidative methylation (Thompson *et al.*, 1993; Aposhian 1997; Thomas *et al.*, 2001, 2004; Kitchin, 2001; Styblo *et al.*, 2002; Vahter, 2002). Pentavalent arsenate is reduced to trivalent arsenite, probably mainly in the blood, before it can be further metabolized (Vahter, 2002). It is estimated that about 50-70% of a single dose of arsenate is rapidly reduced to arsenite and this reaction seems to be common for most species (Vahter, 1999) and can occur non-enzymatically via glutathione as an electron donor or enzymatically catalyzed by arsenate reductase (Kitchin, 2001). Arsenite is much more rapidly taken up by the hepatocytes than arsenate, because it is present mainly in undissociated form at physiological pH, whereas arsenate is in ionized form (Vahter, 2002). It is also now known that both arsenite and arsenate are actively transported into cells by aquaglyceroporins and by phosphate transporters, respectively (Rosen, 2002). Once inside the cell, arsenite is then oxidatively methylated to monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V) (Vahter, 1999). Although trimethylarsine oxide (TMAO, pentavalent form) can also be formed in small amounts, it is produced mainly in rats and can also be excreted into the urine and reduced to trimethylarsine (TMA^{III}, trivalent form) bearing a garlic odor (Thompson, 1993; Kitchin, 2001; Lu *et al.*, 2003).

The methylation process of arsenic takes place in the

cytosol and is catalyzed by a 42-kDa protein (the methyltransferase) encoded by the *cyt19* genes of mouse and human genomes and the methyl donor has been identified as S-adenosylmethionine (Thomas *et al.*, 2004), although vitamin B₁₂, coenzyme B₁₂ and methyl B₁₂ can also act as methyl donors (Vahter, 1999). Testes have the highest specific activity for methyltransferase in mouse, followed by kidney, liver and lung (Healy *et al.*, 1998). But it is believed that liver is the major site for the methylation of arsenic because of its mass and the first pass effect of ingested arsenic to the liver (Thomas *et al.*, 2001; Vahter, 2002). Previously, methylation of inorganic arsenic has always been regarded as a detoxification mechanism because MMA^V and DMA^V have relatively low toxicity (Yamauchi and Fowler, 1994) and are rapidly excreted in the urine (Vahter, 2002; Gebel, 2002). However, recent studies have confirmed the existence of trivalent intermediates and products of monomethylarsonous acid (MMA^{III}) and dimethylarsinous acid (DMA^{III}), which are formed by reduction of MMA^V and DMA^V, respectively, and are more toxic than inorganic arsenite (Thomas *et al.*, 2001; Kitchin, 2001; Styblo *et al.*, 2002). Trivalent arsenic species are stronger protein-binders than the pentavalent species and the methylation processes replace the ionizable hydroxyl groups by uncharged methyl groups, which make the arsenic species less negatively charged and able to interact directly with negatively charged molecules such as DNA at physiological pH (Kitchin, 2001). These biochemical properties of arsenic species probably explain why the trivalent methylated arsenic species are more toxic than trivalent arsenite. Because TMA^{III} contains no ionizable hydroxyl groups to limit its interaction with DNA, it is postulated that this arsenic species could be very toxic and possibly explain why rats are the most responsible animal model for arsenic-induced carcinogenesis (Kitchin, 2001).

The capacity to metabolize inorganic arsenic differs among individuals; and its biologic effects on various organ systems depend not only on the ingested dosage, but also on the capacity of the individuals to metabolize and detoxify the related compounds. To achieve a more accurate assessment of arsenic methylation capacity, it is necessary to determine the specific arsenic species derived from inorganic arsenic, which are excreted in the urine. The proportional levels of urinary arsenic species can be used as indicators for the metabolism of inorganic arsenic. The percentage of inorganic arsenic in urine represents the unchanged proportion of the ingested dosage, while the percentages of MMA^V and DMA^V in urine may represent the activity of the first and second methylation phase, respectively. Because organic arsenicals may also be detected in the urine and they are always regarded as non-toxic, many studies used the summation of urinary arsenite, arsenate, MMA^V and DMA^V as representative for urinary total arsenic for the denominator while calculating the percentages of urinary inorganic arsenic percentage, MMA^V percentage and DMA^V percentage. Urinary DMA^V percentage has been regarded as an indicator of methylation efficiency (Vahter, 1999). Some investigators

calculate the primary methylation index (PMI) defined as the ratio between MMA^V and inorganic arsenic (arsenate + arsenite) level, and secondary methylation index (SMI) as the ratio between DMA^V and MMA^V to assess the arsenic methylation capacity of the first and second methylation step, respectively (Tseng *et al.*, 2005). Others calculate the percentage ratio between MMA^V plus DMA^V and total arsenic for assessing the methylation capacity (Tokunaga *et al.*, 2002).

Studies evaluating the association between various urinary arsenic metabolites and clinical outcomes or diseases are still rare. The importance of a complete second methylation is implicated from the observation that human beings excrete higher MMA^V percentage in the urine and are more susceptible to arsenic-induced health hazards while compared to animals like mice and hamsters that can methylate arsenic very efficiently, resulting in urinary excretion of MMA^V in less than 10% of the urinary arsenic species (Marafante *et al.*, 1987). Since polluted water is the main source of arsenic intoxication nowadays and the water-borne arsenic problems are endemic in many countries reaching public health attention, epidemiologic studies examining the urinary arsenic metabolites and human diseases resulting from drinking arsenic-contaminated water are urgently required to further elucidate the pathogenesis of arsenic-induced health hazards.

Non-cancerous health hazards:

Immediate symptoms on an acute arsenic poisoning typically include vomiting, esophageal and abdominal pain, and bloody "rice water" diarrhea. However, a variety of symptoms and signs involving the gastrointestinal, dermal, nervous, renal, hepatic, hematopoietic, cardiovascular, respiratory and ophthalmic systems can be observed. Treatment with chelating agents such as dimercaprol or dimercaptosuccinic acid during acute intoxication is classical but may have varying effects.

Cancers can be caused by a variety of risk factors and environmental exposure (Chen and Kadlubar, 2004; Wen Cheng and Lee, 2003; Talaska, 2003; Fu *et al.*, 2003; Ahmed, 2003; Li and Yu, 2002; Benigni and Giuliani, 2001). Long-term exposure to arsenic is well known for its link with a variety of cancers involving the skin (squamous cell carcinoma and basal cell carcinoma), lung, bladder, kidney and liver (Chen *et al.*, 1992). But non-cancerous health hazards can also occur in humans after long-term exposure. The non-cancerous health effects have been estimated to be detectable at doses of 1.0 µg/kg/day and higher (Brown and Ross, 2002). Chelating agents may not be effective in chronic poisoning and avoidance of exposure is the best preventive measure.

Previously, a methylation threshold hypothesis for inorganic arsenic has been proposed for arsenic-induced toxicity, suggesting that after a certain threshold of exposure to inorganic arsenic, the methylation capacity is saturated and the toxic effects of inorganic arsenic will increase (Buchet *et al.*, 1981). However, later studies do not support such a threshold hypothesis

(Hopenhayn-Rich *et al.*, 1993, 1996a, 1996b; Kurtio *et al.*, 1998), and dose-responsive patterns have always been shown in the association between arsenic exposure and health hazards. The absorption, distribution and metabolism of arsenic differ significantly across species. Animals are less sensitive to the toxic effect of arsenic and most of the effects of long-term arsenic exposure on human beings are not observed in animals. Genetic factors may play important roles on these metabolic cascades of arsenic, and thus, may also be involved in the development of the clinical effects of arsenic. However, nutritional status (Schoen *et al.*, 2004) and the interactions with other trace elements such as vitamins, b-carotene, zinc and selenium *etc.* (Tseng, 2004) are important in the development of arsenic-induced health hazards.

Dermal effect: Arsenic skin lesions are characterized by the coexistence of hyper and hypo-pigmentation giving rise to a raindrop pattern and hyperkeratosis of the palms and soles. The pigmentation lesions can occur in all parts of the body including the trunk and the hyperkeratosis is not limited to the palms and soles. According to an early study conducted in the BFD area in Taiwan, the prevalence rates of hyperpigmentation, hyperkeratosis and skin cancers were 183.5, 71 and 10.6 per 1,000 population, respectively (Tseng *et al.*, 1968). In West Bengal, India, a study showed that the age-adjusted prevalence rates of hyperpigmentation in women exposed to drinking water containing arsenic in the lowest level (<50 µg/l) and in the highest exposure level (800 µg/l) were 0.3% and 11.5%, respectively; and the respective rates for men were 0.4% and 22.7% (Mazumder *et al.*, 1998). The respective rates of keratosis in the lowest and highest exposure levels were 0% and 8.5% for women, and 0.2% and 10.7% for men (Mazumder *et al.*, 1998). Another study in West Bengal showed that the lowest peak arsenic ingested by a confirmed case was 115 µg/l, and the average latency for skin lesions was estimated to be 23 years from first exposure (Haque *et al.*, 2003). A dose-responsive pattern between arsenic in drinking water and skin lesions was also detected in this study (Haque *et al.*, 2003). Similar dose-responsive relationship between exposure levels and skin lesions was reported in Bangladesh (Tondel *et al.*, 1999; Ahsan *et al.*, 2000). These arsenic-induced skin lesions are typical and can be seen in many other regions characterized by high arsenic concentration in drinking water, such as in regions of Argentina, Bangladesh, Chile, China, Japan and Mexico (Chen and Lin, 1994). Although these skin lesions are always regarded as benign, in rare cases, skin cancer may occur with hyperkeratosis (Col *et al.*, 1999) and co-occurrence with skin cancer is common (Tseng *et al.*, 1968).

Cardiovascular effects and atherosclerosis: Exposure to arsenic from drinking water has been shown to cause a severe peripheral vascular disease (PVD), which might progress from intermittent claudication, ulceration, gangrene and spontaneous or surgical amputation in Taiwan. The disease has been named 'blackfoot disease (BFD)' after its clinical appearance (Tseng,



2002, 2005). This disease was first reported in early twentieth century and was confined to the southwestern coast of Taiwan, where people used artesian well water from as deep as 100-300 meters underground. The prevalence of BFD ranged from 6.51 to 18.85 per 1,000 people in different villages. A series of epidemiologic studies and surveillance of the arsenic concentrations of the artesian wells carried out during the mid-twentieth century revealed the association between BFD and the consumption of high arsenic-containing artesian well water. In an early study, Tseng (1989), showed a dose-responsive relationship between BFD and arsenic concentrations in well water in different age groups of residents. In villages where the arsenic concentrations in well water were <0.30 mg/l, 0.30-0.59 mg/l and more than 0.60 mg/l, the prevalence rates of BFD for residents aged 20-39 years were 0.5%, 1.3% and 1.4%, respectively, for residents aged 40-59 years, 1.1%, 3.2% and 4.7%, respectively and for residents aged over 60 years, 2.0%, 3.2% and 6.1%, respectively (Tseng, 1989).

To further clarify the effect of arsenic exposure on the development of PVD among the residents of the BFD areas, Tseng *et al.* (1996, 1997) carried out a series of studies by using Doppler ultrasound as a diagnostic tool, calculating indices for estimating individual dosage of arsenic exposure, and controlling possible confounders for PVD since 1990s. Dose-responsive patterns between indices of long-term arsenic exposure and PVD were clearly demonstrated. The prevalence rates of PVD for those with a cumulative arsenic exposure (CAE) of 0, 0.1-19.9 and ≥ 20 mg/l-years were 4.4, 11.6 and 19.8%, respectively and the respective odds ratios were 1.00, 2.77 (0.84-9.14) and 4.28 (1.26-14.54) after adjustment for potential confounders (Tseng, 2002). The prevalence of PVD for those living in the endemic areas for ≥ 60 years could be as high as 28.4% and the multivariate-adjusted odds ratio was 10.54 (2.68-41.37) while compared to those living in the endemic areas for less than 40 years (Tseng, 2002). These later studies fortified the link between arsenic exposure and development of PVD in the BFD-endemic areas in Taiwan.

In another study Tseng *et al.* (2003), evaluated the association between long-term arsenic exposure and ischemic heart disease (IHD) in 462 subjects living in the BFD-hyperendemic villages. IHD was diagnosed by coding the resting electrocardiograms with the Minnesota code and arsenic exposure was estimated by CAE. Among the subjects, 78 cases (16.9%) were diagnosed as having ischemic heart disease and the prevalence rates of IHD for the age groups of 30-39, 40-49, 50-59 and ≥ 60 years were 4.9%, 7.5%, 16.8%, and 30.7%, respectively ($p < 0.001$). For those with CAE of 0, 0.1-14.9 and ≥ 15 mg/l-years, the prevalence rates of IHD were 5.2%, 10.9% and 24.1%, respectively ($p < 0.001$). The odds ratios (95% confidence intervals) for IHD were 1.60 (0.48, 5.34) and 3.60 (1.11, 11.65), respectively, for those with CAE of 0.1-14.9 and ≥ 15.0 mg/l-years, when compared to those lacking drinking water exposure to arsenic after multivariate adjustment.

Chiou *et al.* (1997) also demonstrated a dose-responsive relationship between arsenic exposure and cerebral infarction in the northeastern coast of Taiwan. The multivariate-adjusted odds ratios for CAE of <0.1, 0.1-4.9 and > 4.9 mg/l-year were 1.00, 2.66 (1.21-5.83) and 3.39 (1.42-8.11), respectively and for arsenic content in well water of <0.1, 0.1-50, 50.1-299.9 and ≥ 300 $\mu\text{g/l}$ were 1.00, 3.38 (1.57-7.27), 4.47 (2.03-9.87) and 6.90 (2.91-16.38), respectively.

Therefore, the exposure to arsenic can be associated with increased risk of all forms of atherosclerosis including PVD, IHD and stroke. Long-term exposure to arsenic from drinking water has also been found to be highly associated with hypertension (Chen *et al.*, 1995; Rahman *et al.*, 1999), preclinical microcirculatory defects (Tseng *et al.*, 1995) and arterial insufficiency (Tseng *et al.*, 1994).

Although studies in several other countries have demonstrated that arsenic exposure can be associated with some forms of PVD, similar endemic occurrence of severe BFD has not been observed. It is possible that nutritional status, coexistence of other factors and interaction with other trace elements determine the development of the various clinical manifestations.

Metabolic effect: The relationship between arsenic exposure and diabetes mellitus is a relatively novel finding. This link has been observed in people drinking contaminated well water in Taiwan (Lai *et al.*, 1994; Tseng *et al.*, 2000a, 2000b, 2002; Tseng 2004) and Bangladesh (Rahman *et al.*, 1998, 1999b), and in people working in copper smelters (Rahman and Axelson, 1995) and art glass industry (Rahman *et al.*, 1996) in Sweden. In the prospective follow-up study by Tseng *et al.* (2000b), the incidence of diabetes mellitus in residents of the BFD areas was significantly higher than residents of a control area.

Arsenic-induced diabetes mellitus in chronically exposed subjects may not be directly related to the exposed arsenic species and may involve the methylated metabolites of arsenic. Insulin resistance and β cell dysfunction can be induced by chronic arsenic exposure through the activation of reactive oxygen species, nuclear factor- κB and cytokines (tumor necrosis factor α and interleukin-6) and the inhibition of peroxisome proliferator-activated receptor γ . The pathogenic role of direct interferences on glucose metabolic pathways and energy production as always observed in acute intoxication might not be responsible for the development of arsenic-induced diabetes mellitus in chronically exposed subjects (Tseng, 2004). Individual variability in detoxification capability, nutritional status and interactions with other trace elements could influence the susceptibility of arsenic-exposed subjects to develop diabetes mellitus (Tseng, 2004).

In a study that examined the prevalence of goiter in 2,738 school children living in the BFD areas and 1,829 children living in non-endemic areas, the prevalence was significantly higher in

the endemic than in the non-endemic areas (3.44 vs. 2.08%, $p < 0.01$). When the analyses were performed in separate sexes, only the female children living in the endemic areas showed significantly higher prevalence (4.65 vs. 2.69%, $p < 0.02$) (Chang *et al.*, 1991). The children in the endemic areas also had lower T_3 levels than children in the non-endemic areas had in either the subgroup with goiter or the subgroup without goiter, indicating the existence of some substances that might inhibit the synthesis of thyroid hormone (Chang *et al.*, 1991). However, the T_4 and TSH levels were not significantly different between the subgroups. It is not known whether the hormonal changes observed in this study can be ascribed to an effect of arsenic, therefore further confirmation of the findings is necessary.

Neurological effect: Besides the typical clinical manifestation of arsenic skin lesions, children's intelligence was also found to be inversely related to the arsenic levels in the hair of the children after adjusting for confounders (Siripitayakunkit *et al.*, 1999). Arsenic could explain 14% of the variance in children's intelligence in this area (Siripitayakunkit *et al.*, 1999). Similarly, neuropsychological development was poorer in Mexican children exposed to arsenic (Calderon *et al.*, 2001). In a study comparing four neurobehavioral tests including continuous performance test, symbol digit, pattern memory and switching attention in 49 junior school students drinking arsenic-containing well water and 60 controls, the pattern memory and switching attention were significantly affected by long-term cumulative exposure to arsenic after adjusting for education and sex (Tsai *et al.*, 2003). Neurobehavioral changes associated with arsenic exposure can also be observed in animals (Vardhanan *et al.*, 2002).

The clinical onset of peripheral neuropathy associated with chronic exposure to arsenic occurs insidiously and may go unnoticed for years. Sensory nerve fibers are affected before motor nerve fibers, and distal portions are attacked before proximal parts (Jenkins, 1966). Electrophysiological evidence has shown that axonal degeneration is typical in cases of arsenic-induced peripheral neuropathy, which is further supported by histological examination of sural nerve biopsies (LeQuesne and McLeod, 1977; Oh, 1991; Windebank, 1986). However, secondary demyelination may occur after axonal degeneration takes place (Feldman, 1999). The dying back of long axons eventually involves spinal cord pathways and anterior horn cells (Feldman, 1999). Recovery of neurophysiological tests after subacute arsenic intoxication was slow and only partial improvement of the deficits could be seen by serial examination of conduction velocity up to two years after the onset of the illness (Murphy *et al.*, 1981). Abnormal neurological symptoms and signs existed even after 8 years of exposure (LeQuesne and McLeod, 1977). Regeneration of peripheral neuropathy following arsenic intoxication depends greatly on the length of the nerve fibers. Thus, the longer nerve recovers more slowly (Feldman, 1999).

In a recent study, Tseng (2003) evaluated the possible existence of subclinical sensory nerve defects in residents of BFD-

hyperendemic villages in Taiwan characterized by long-term arsenic exposure from drinking water. Eighty-five seemingly normal subjects living in BFD villages and 75 external normal controls without exposure were recruited. All subjects were 30-75 years old, without possible causes of peripheral neuropathy and suffered from no symptoms of peripheral neuropathy. Current perception threshold (CPT) was measured by Neurometer® at the trigeminal, median and superficial peroneal nerves with frequencies of 5, 250 and 2,000 Hz. The three frequencies could be used for testing three major sensory nerve fiber subpopulations, *i.e.*, 5 Hz for small unmyelinated C fiber (temperature and dull pain), 250 Hz for small myelinated δ fiber (vibration) and 2,000 Hz for large myelinated β fiber (touch and pressure). Results showed that residents of the BFD areas had significantly 1.28- to 2.23-fold higher CPT than normal controls for all frequencies at the 3 nerves and 42.4% of the BFD residents had at least one abnormal measurement (normal mean plus 3 standard deviations). Site and frequency preferences were noted, indicating more common involvement of the longer nerves (superficial peroneal and median nerves) and lower frequencies (5 and 250 Hz). The preferential involvement of small unmyelinated C fiber (5 Hz) and small myelinated δ fiber (250 Hz), rather than large myelinated β fiber (2,000 Hz) support the commonly reported symptoms of numbness and paresthesia of the distal extremities associated with arsenic toxicity (Triebig and Buttner, 1983), which indicates involvement of the C fibers.

Arsenic-related neuropathy was also reported by other investigators. In a cross-sectional epidemiologic study evaluating the nervous system in residents of a small town in Georgia, USA, subjects exposed to arsenic from dust and soil had a 5-fold higher risk of peripheral neuropathy than the unexposed subjects. Arsenic exposure was strongly associated with quantitative tests of standing steadiness, vibrotactile threshold and tremor intensity, but not with nerve conduction velocity (NCV) (Gerr *et al.*, 2000). Another study evaluating neurological examination and NCV in 147 persons exposed to arsenic from well water in Alaskan also did not show association between arsenic exposure and NCV (Kreiss *et al.*, 1983). A recent study carried out in West Bengal revealed that only 2 out of 20 patients (10.0%) with arsenicosis and without clinical neuropathy would have abnormal sensory nerve function; and that evoked potential studies were largely normal (Rahman *et al.*, 2001). Taken together, these studies imply that although peripheral neuropathy, especially without clinical symptoms or signs, could be very common, the use of quantitative sensory test is more sensitive and measurement of NCV might not be sensitive enough to detect the subclinical neuropathy in epidemiologic studies and evoked potential would not be helpful.

Other effects: Arsenic can also efficiently pass through the human placenta and may possibly have an effect on early human development (Concha *et al.*, 1998). Developmental arrest can also be observed in animal embryos of Japanese medaka exposed to sublethal concentrations of arsenic (Ishaque *et al.*, 2004). A small case-control study in Texas showed that stillbirths



Table - 1: Non-cancerous effects of arsenic on human beings

Organ system	Diseases or symptoms/signs
Dermal	Hypo- and hyper-pigmentation (raindrop pattern), hyperkeratosis of palms and soles, exfoliative dermatitis, Bowen's disease (precancerous lesions), facial edema, non-pitting pedal edema
Cardiovascular	Arrhythmia, pericarditis, ischemic heart disease, peripheral vascular disease, cerebral infarction, hypertension, subclinical arterial insufficiency, microcirculatory defects
Gastrointestinal	Abdominal discomfort, anorexia, malabsorption, body weight loss
Neurological	Peripheral neuropathy involving sensory and motor systems, cranial nerve involvement, hearing loss, mental retardation, encephalopathy
Renal	Proximal tubule degeneration, papillary and cortical necrosis, clinical nephritis and proteinuria
Hepatic	Fatty degeneration, non-cirrhotic portal fibrosis, cirrhosis, hepatomegaly, cholestasis
Hematopoietic	Bone marrow hypoplasia, aplastic anemia, anemia, leukopenia, thrombocytopenia, impaired folate metabolism, karyorrhexis
Respiratory	Rhino-pharyngo-laryngitis, tracheobronchitis, pulmonary insufficiency (emphysematous lesions)
Ophthalmic	Conjunctivitis, cataract
Reproductive	High perinatal mortality, low birth weight, spontaneous abortions, stillbirths, pre-eclampsia, congenital malformation
Metabolic	Diabetes mellitus, goiter

were increased in relation to the proximity of maternal residence to an arsenical pesticide production plant (Ihrig *et al.*, 1998). Hopenhayn-Rich *et al.* (2000) reported an increase in infant mortality in a county in northern Chile where residents were exposed to arsenic-containing drinking water of 90-800 µg/l. A later study comparing the birth weight of liveborn and singleton infants in two Chilean cities, one with moderate arsenic exposure of 40 µg/l (Antofagasta) and the other as control with arsenic in drinking water <1 µg/l (Valparaiso), reported that the birth weight of infants born in Antofagasta was lower [-59 g, 95% confidence interval: -123 to 9] (Hopenhayn *et al.*, 2003). Increased spontaneous abortions, stillbirths and preterm births were observed in a retrospective study in Bangladesh, which compared women exposed to high (mean 240 µg/l) and low (<20 µg/l) arsenic levels in drinking water (Ahmad *et al.*, 2001).

Increased prevalence of cough and chronic bronchitis in residents exposed to increased arsenic level in drinking water have been reported in West Bengal, India and Bangladesh (Mazumder *et al.*, 2000; Milton and Rahman, 2002). An ecological study also revealed that the mortality from "bronchitis" among residents of the BFD areas in Taiwan was significantly higher than nearby reference population and the total population, with respective standardized mortality ratio of 1.53 (1.30-1.80) and 1.95 (1.65-2.29) (Tsai *et al.*, 1999).

Significantly higher serum levels of alkaline phosphatase and total bilirubin were observed in residents of the highest exposure town than the lowest exposure town in a study that evaluated the liver function in individuals from three towns in the Region Lagunera of Mexico (Hernandez-Zavala *et al.*, 1998). But the levels of transaminases and albumin were not different significantly. The findings suggested the presence of cholestasis

in arsenic exposed individuals. However, in another study by Santra *et al.* (1999) conducted in West Bengal, India, increased bilirubin or alkaline phosphatase was not characteristic in 93 patients with firm hepatomegaly attributed to chronic arsenicosis. In that study liver biopsy taken from 69 patients revealed portal fibrosis in 63 (91.3%) cases, cirrhosis in 2 cases (2.9%) and normal histology in 4 (5.8%) cases. The investigators concluded that noncirrhotic portal fibrosis is the predominant hepatic lesion associated with arsenic exposure.

The other effects of chronic arsenic exposure can be seen in previous reviews (Chen and Lin, 1994; Tseng, 1999, Hughes, 2002) and are summarized in Table 1.

Global problems of arsenic contamination are emerging (Berg *et al.*, 2001; Naranjo-Pulido *et al.*, 2002) rather than submerging. The arsenic-related health problems in emerging endemic areas can be critical issues in public health. Drinking water poses the greatest threat from arsenic exposure nowadays. However, exposure from coal burning, working environment, mining and industrial emissions may also be significant in some areas. There is no universal definition of the diseases caused by arsenic and there is no way to differentiate pathologically those vascular or cancerous lesions caused by arsenic from other etiologies. All of these complicate the assessment of the burden of arsenic on human health. However, the use of interventional measures to terminate the hazards associated with arsenic should not wait until all these ambiguities are clarified. Up to now, there is no 'magic bullet' for the treatment of the diseases associated with arsenic intoxication. The best strategy is prevention and avoidance of exposure. New sources of water and coal with low arsenic contents, techniques for arsenic removal from drinking water, decreasing industrial arsenic emissions, improving working environments and promoting health education among the affected people are necessary.

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References

- Ahmad, S.A., M.H. Sayed, S. Barua, M.H. Khan, M.H. Faruquee, A. Jalil, S.A. Hadi and H.K. Talukder: Arsenic in drinking water and pregnancy outcomes. *Environ. Hlth. Perspect.*, **109**(6), 629-631 (2001).
- Ahmed, F.E.: Colon cancer: Prevalence, screening, gene expression and mutation and risk factors and assessment. *J. Environ. Sci. Hlth. C*, **21**, 65-131 (2003).
- Ahsan, H., M. Perrin, A. Rahman, F. Parvez, M. Stute, Y. Zheng, A.H. Milton, P. Brandt Rauf, A. van Geen and J. Graziano: Associations between drinking water and urinary arsenic levels and skin lesions in Bangladesh. *J. Occup. Environ. Med.*, **42**(12), 1195-1201 (2000).
- Andreae, M.O.: Determination of arsenic species in natural waters. *Ann. Chem.*, **49**, 820-823 (1977).
- Aposhian, H.V.: Enzymatic methylation of arsenic species and other new approaches to arsenic toxicity. *Annu. Rev. Pharmacol. Toxicol.*, **37**, 397-419 (1997).
- Benigni, R. and A. Giuliani: Tumor geography of Italy and Europe: Patterns and correlations with socioeconomic variables. *J. Environ. Sci. Hlth. C*, **19**, 325-351 (2001).
- Berg, M., H.C. Tran, T.C. Nguyen, H.V. Pham, R. Schertenleib and W. Giger: Arsenic contamination of groundwater and drinking water in Vietnam: A human health threat. *Environ. Sci. Technol.*, **35**, 2621-2626 (2001).
- Brown, K.G. and G.L. Ross: Arsenic, drinking water and health: A position paper of the American Council on Science and Health. *Reg. Toxicol. Pharmacol.*, **36**, 162-174 (2002).
- Buchet, J.P., R. Lauwerys and H. Roels: Urinary excretion of inorganic arsenic and its metabolites after repeated ingestion of sodium meta-arsenite by volunteers. *Int. Arch. Occup. Environ. Hlth.*, **48**, 111-118 (1981).
- Calderon, J., M.E. Navarro, M.E. Jimenez Capdeville, M.A. Santos-Diaz, A. Golden, I. Rodriguez-Leyva, V. Borja-Aburto and F. Diaz-Barriga: Exposure to arsenic and lead and neuropsychological development in Mexican children. *Environ. Res.*, **85**(2), 69-76 (2001).
- Chang, T.C., M.C. Hong and C.J. Chen: Higher prevalence of goiter in endemic area of blackfoot disease of Taiwan. *J. Formosan Med. Assoc.*, **90**(10), 941-946 (1991).
- Chen, C.J., H.Y. Chiou, W.I. Huang, S.Y. Chen, Y.M. Hsueh and C.H. Tseng: Systemic non-carcinogenic effects and developmental toxicity of inorganic arsenic. In: Arsenic: Exposure and health effects (Eds: C.O. Abernathy, R.L. Calderon and W.R. Chappell). Chapman and Hall Press, pp. 124-34 (1992).
- Chen, C.J., L.I. Hsu, C.H. Tseng, Y.M. Hsueh and H.Y. Chiou: Emerging epidemics of arseniasis in Asia. In: Arsenic exposure and health effects (Eds: W.R. Chappell, C.O. Abernathy and R.L. Calderon). Elsevier Science Ltd., Oxford, U.K. pp. 113-121 (1992).
- Chen, C.J., Y.M. Hsueh, M.S. Lai, M.P. Shyu, S.Y. Chen, M.M. Wu, T.L. Kuo and T.Y. Tai: Increased prevalence of hypertension and long-term arsenic exposure. *Hypertension*, **25**, 53-60 (1995).
- Chen, J.Z. and F.F. Kadlubar: Mitochondrial mutagenesis and oxidative stress in human prostate cancer. *J. Environ. Sci. Hlth. C*, **22**, 1-12 (2004).
- Chen, C.J. and L.J. Lin: Human carcinogenicity and atherogenicity induced by chronic exposure to inorganic arsenic. In: Arsenic in the environment, Part II: Human health and ecosystem effects (Ed: J.O. Nriagu). New York, John Wiley and Sons Inc., pp. 109-131 (1994).
- Chiou, H.Y., W.I. Huang, C.L. Su, S.F. Chang, Y.H. Hsu and C.J. Chen: Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. *Stroke*, **28**, 1717-1723 (1997).
- Col, M., C. Col, A. Soran, B.S. Sayli and S. Ozturk: Arsenic-related Bowen's disease, palmar keratosis and skin cancer. *Environ. Hlth. Perspect.*, **107**(8), 687-689 (1999).
- Concha, G., G. Vogler, D. Lezcano, B. Nermell and M. Vahter: Exposure to inorganic arsenic metabolites during early human development. *Toxicol. Sci.*, **44**, 185-190 (1998).
- Feldman, R.G.: Occupational and Environmental Neurotoxicology. Chapter 5, Arsenic. Lippincott-Raven Publishers, Philadelphia, New York, USA. pp. 69-91 (1999).
- Fu, P.P., S.H. Cheng, L. Coop, Q. Xia, S.J. Culp, W.H. Tolleson, W.G. Wamer and P.C. Howard: Photoreaction, phototoxicity, and photocarcinogenicity of retinoids. *J. Environ. Sci. Hlth. C*, **21**, 165-197 (2003).
- Gebel, T.W.: Arsenic methylation is a process of detoxification through accelerated excretion. *Int. J. Hyg. Environ. Hlth.*, **205**, 505-508 (2002).
- Gerr, F., R. Letz, P.B. Ryan and R.C. Green: Neurological effects of environmental exposure to arsenic in dust and soil among humans. *Neurotoxicology*, **21**, 475-487 (2000).
- Haque, R., D.N. Mazumder, S. Samanta, N. Ghosh, D. Kalman, M.M. Smith, S. Mitra, A. Santra, S. Lahiri, S. Das, B.K. De and A.H. Smith: Arsenic in drinking water and skin lesions: Dose-response data from West Bengal, India. *Epidemiology*, **14**(2), 174-182 (2003).
- Healy, S.M., E.A. Casarez, F. Ayala-Fierro and H. Aposhian: Enzymatic methylation of arsenic compounds. V. Arsenite methyltransferase activity in tissues of mice. *Toxicol. Appl. Pharmacol.*, **148**, 65-70 (1998).
- Hernandez-Zavala, A., L.M. Del Razo, C. Aguilar, G.C. Garcia-Vargas, V.H. Borja and M.E. Cebrian: Alteration in bilirubin excretion in individuals chronically exposed to arsenic in Mexico. *Toxicol. Lett.*, **99**(2), 79-84 (1998).
- Hopenhayn-Rich, C., M.L. Biggs, D.A. Kalman, L.E. Moore and A.H. Smith: Arsenic methylation patterns before and after changing from high to lower concentrations of arsenic in drinking water. *Environ. Hlth. Perspect.*, **104**, 1200-1207 (1996a).
- Hopenhayn-Rich, C., M.L. Biggs, A.H. Smith, D.A. Kalman and L.E. Moore: Methylation study of a population environmentally exposed to arsenic in drinking water. *Environ. Hlth. Perspect.*, **104**, 620-628 (1996b).
- Hopenhayn-Rich, C., S.R. Browning, I. Hertz-Picciotto, C. Ferreccio, C. Peralta and H. Gibb: Chronic arsenic exposure and risk of infant mortality in two areas of Chile. *Environ. Hlth. Perspect.*, **108**(7), 667-673 (2000).
- Hopenhayn, C., C. Ferreccio, S.R. Browning, B. Huang, C. Peralta, H. Gibb and I. Hertz-Picciotto: Arsenic exposure from drinking water and birth weight. *Epidemiology*, **14**(5), 593-602 (2003).
- Hopenhayn-Rich, C., A.H. Smith and H.M. Goeden: Human studies do not support the methylation threshold hypothesis for the toxicity of inorganic arsenic. *Environ. Res.*, **60**, 161-177 (1993).
- Hughes, M.F.: Arsenic toxicity and potential mechanisms of action. *Toxicol. Lett.*, **133**, 1-16 (2002).
- Ihrig, M.M., S.L. Shalat and C. Baynes: A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. *Epidemiology*, **9**(3), 290-294 (1998).
- Ishaque, A.B., P.B. Tchounwou, B.A. Wilson and T. Washington: Developmental arrest in Japanese medaka (*Oryzias latipes*) embryos exposed to sublethal concentrations of atrazine and arsenic trioxide. *J. Environ. Biol.*, **25**, 1-6 (2004).
- Jenkins, R.B.: Inorganic arsenic and the nervous system. *Brain*, **89**, 479-498 (1966).
- Kitchin, K.T.: Recent advances in arsenic carcinogenesis: Modes of action, animal model systems, and methylated arsenic metabolites. *Toxicol. Appl. Pharmacol.*, **172**, 249-261 (2001).
- Kreiss, K., M.M. Zack, P.J. Landrigan, R.G. Feldman, C.A. Niles, J. Chirico-Post, D.S. Sax, M.H. Boyd and D.H. Cox: Neurologic evaluation of a population exposed to arsenic in Alaskan well water. *Arch. Environ. Hlth.*, **38**, 116-121 (1983).
- Kurtio, P., H. Komulainen, E. Hakala, H. Kahelin and J. Pekkanen: Urinary excretion of arsenic species after exposure to arsenic present in drinking water. *Arch. Environ. Contam. Toxicol.*, **34**, 297-305 (1998).



- Lai, M.S., Y.M. Hsueh, C.J. Chen, M.P. Shyu, S.Y. Chen and T.L. Kuo: Ingested inorganic arsenic and prevalence of diabetes mellitus. *Am. J. Epidemiol.*, **139**, 484-492 (1994).
- LeQuesne, P.M. and J.G. McLeod: Peripheral neuropathy following a single exposure to arsenic. Clinical course in four patients with electrophysiological and histological studies. *J. Neurol. Sci.*, **32**, 437-451 (1977).
- Li, K. and S. Yu: Economic status, smoking, occupational exposure to rubber, and lung cancer: A case-cohort study. *J. Environ. Sci. Health. C*, **20**, 21-28 (2002).
- Lu, X., L.L. Arnold, S.M. Cohen, W.R. Cullen and X.C. Le: Speciation of dimethylarsinous acid and trimethylarsine oxide in urine from rats fed with dimethylarsinic acid and dimercaptopropane sulfonate. *Ann. Chem.*, **75**, 6463-6468 (2003).
- Ma, M. and X.C. Le: Effect of arsenosugar ingestion on urinary arsenic speciation. *Clin. Chem.*, **44**, 539-550 (1998).
- Marafante, E., M. Vahter, H. Norin, J. Envall, M. Sandstrom, A. Christakopoulos and R. Ryhage: Biotransformation of dimethylarsinic acid in mouse, hamster and man. *J. Appl. Toxicol.*, **7**, 111-117 (1987).
- Mazumder, D.N., J. Das Gupta, A. Santra, A. Pal, A. Ghose and S. Sarkar: Chronic arsenic toxicity in west Bengal - The worst calamity in the world. *J. Indian Med. Assoc.*, **96(1)**, 4-7 (1998).
- Mazumder, D.N., R. Haque, N. Ghosh, B.K. De, A. Santra, D. Chakraborti and A.H. Smith: Arsenic in drinking water and the prevalence of respiratory effects in West Bengal, India. *Int. J. Epidemiol.*, **29(6)**, 1047-1052 (2000).
- Milton, A.H. and M. Rahman: Respiratory effects and arsenic contaminated well water in Bangladesh. *Int. J. Environ. Health. Res.*, **12(2)**, 175-179 (2002).
- Murphy, M.J., L.W. Lyon and J.W. Taylor: Subacute arsenic neuropathy: clinical and electrophysiological observations. *J. Neurol. Neurosurg Psychiatry*, **44**, 896-900 (1981).
- Naranjo-Pulido, A., H. Romero-Schmidt, L. Mendez-Rodriguez, B. Acosta-Vargas and A. Ortega-Rubio: Soil arsenic contamination in the Cape Region, B.C.S., Mexico. *J. Environ. Biol.*, **23**, 347-352 (2002).
- Oh, J.S.: Electrophysiological profile in arsenic neuropathy. *J. Neurol. Neurosurg Psychiatry*, **54**, 1103-1105 (1991).
- Rahman, M. and O. Axelson: Diabetes mellitus and arsenic exposure: a second look at case-control data from a Swedish copper smelter. *Occup. Environ. Med.*, **52**, 773-774 (1995).
- Rahman, M.M., U.K. Chowdhury, S.C. Mukherjee, B.K. Mondal, K. Paul, D. Lodh, B.K. Biswas, C.R. Chanda, G.K. Basu, K.C. Saha, S. Roy, R. Das, S.K. Palit, Q. Quamruzzaman, D. Chakraborti: Chronic arsenic toxicity in Bangladesh and West Bengal, India-a review and commentary. *J. Toxicol. Clin. Toxicol.*, **39**, 683-700 (2001).
- Rahman, M., M. Tondel, S.A. Ahmad and O. Axelson: Diabetes mellitus associated with arsenic exposure in Bangladesh. *Am. J. Epidemiol.*, **148**, 198-203 (1998).
- Rahman, M., M. Tondel, S.A. Ahmad, I.A. Chowdhury, M.H. Faruquee and O. Axelson: Hypertension and arsenic exposure in Bangladesh. *Hypertension*, **33(1)**, 74-78 (1999a).
- Rahman, M., M. Tondel, I.A. Chowdhury and O. Axelson: Relations between exposure to arsenic, skin lesions and glucosuria. *Occup. Environ. Med.*, **56**, 277-281 (1999b).
- Rahman, M., G. Wingren and O. Axelson: Diabetes mellitus among Swedish art glassworkers - An effect of arsenic exposure? *Scand. J. Work Environ. Health*, **22**, 146-149 (1996).
- Rosen, B.P.: Biochemistry of arsenic detoxification. *FEBS Lett.*, **529**, 86-92 (2002).
- Santra, A., J. Das Gupta, B.K. De, B. Roy and D.N. Guha Mazumder: Hepatic manifestations in chronic arsenic toxicity. *Indian J. Gastroenterol.*, **18(4)**, 152-155 (1999).
- Schoen, A., B. Beck, R. Sharma and E. Dube: Arsenic toxicity at low doses: Epidemiological and mode of action considerations. *Toxicol. Appl. Pharmacol.*, **198**, 253-267 (2004).
- Shraim, A., N.C. Sekaran, C.D. Anuradha and S. Hirano: Speciation of arsenic in tube-well water samples collected from West Bengal, India, by high-performance liquid chromatography-inductively coupled plasma mass spectrometry. *Appl. Organomet. Chem.*, **16**, 1-8 (2002).
- Siripitayakunkit, U., P. Visudhiphan, M. Pradipasen, T. Vorapongsathorn: Association between chronic arsenic exposure and children's intelligence in Thailand. In: *Arsenic Exposure and Health Effects: Proceedings of the Third International Conference on Arsenic Exposure and Health Effects* (Eds: W.R. Chappell, C.O. Abernathy and R.L. Calderon). Elsevier, New York. pp. 141-150 (1999).
- Smith, A.H. and M.M.H. Smith: Arsenic drinking water regulations in developing countries with extensive exposure. *Toxicology*, **198**, 39-44 (2004).
- Styblo, M., Z. Drobna, I. Jaspers, S. Lin and D.J. Thomas: The role of biomethylation in toxicity and carcinogenicity of arsenic: A research update. *Environ. Health. Perspect.*, **110(Suppl 5)**, 767-771 (2002).
- Talaska, G.: Aromatic amines and human urinary bladder cancer: Exposure sources and epidemiology. *J. Environ. Sci. Health. C*, **21**, 29-43 (2003).
- Thomas, D.J., M. Styblo and S. Lin: The cellular metabolism and systemic toxicity of arsenic. *Toxicol. Appl. Pharmacol.*, **176**, 127-144 (2001).
- Thomas, D.J., S.B. Waters and M. Styblo: Elucidating the pathway for arsenic methylation. *Toxicol. Appl. Pharmacol.*, **198**, 319-326 (2004).
- Thompson, D.J.: A chemical hypothesis for arsenic methylation in mammals. *Chem. Biol. Interact.*, **88**, 89-14 (1993).
- Tokunaga, H., T. Roychowdhury, N. Chandraskaran, T. Uchino and M. Ando: Urinary arsenic species in an arsenic-affected area of West Bengal, India. *Appl. Organomet. Chem.*, **16**, 406-414 (2002).
- Tondel, M., M. Rahman, A. Magnuson, I.A. Chowdhury, M.H. Faruquee and S.A. Ahmad: The relationship of arsenic levels in drinking water and the prevalence rate of skin lesions in Bangladesh. *Environ. Health. Perspect.*, **107(9)**, 727-729 (1999).
- Triebig, G. and J. Buttner: Neurotoxic occupational substances: I. Metals and their compounds. A literature review of the years 1970 to 1982 [in German]. *Zentralbl. Bakteriol. Mikrobiol. Hyg. [B]*, **177**, 11-36 (1983).
- Tsai, S.Y., Chou H.Y., H.W. The, C.M. Chen and C.J. Chen: The effects of chronic arsenic exposure from drinking water on the neurobehavioral development in adolescence. *Neurotoxicology*, **24(4-5)**, 747-753 (2003).
- Tsai, S.M., T.N. Wang and Y.C. Ko: Mortality for certain diseases in areas with high levels of arsenic in drinking water. *Arch. Environ. Health*, **54(3)**, 186-193 (1999).
- Tseng, C.H.: Chronic arsenic intoxication in Asia: Current perspectives. *J. Intern. Med. Taiwan*, **10**, 224-229 (1999).
- Tseng, C.H.: An overview on peripheral vascular disease in blackfoot disease-hyperendemic villages in Taiwan. *Angiology*, **53**, 529-537 (2002).
- Tseng, C.H.: Abnormal current perception thresholds measured by Neurometer among residents in blackfoot disease hyperendemic villages in Taiwan. *Toxicol. Lett.*, **146**, 27-36 (2003).
- Tseng, C.H.: The potential biological mechanisms of arsenic-induced diabetes mellitus. *Toxicol. Appl. Pharmacol.*, **197**, 67-83 (2004).
- Tseng, C.H.: Blackfoot disease and arsenic: A never-ending story. *Environ. Carcinog. Ecotoxicol. Rev., J. Environ. Sci. Health. C*, **23**, 55-74 (2005).
- Tseng, C.H., C.J. Chen, B.J. Lin and T.Y. Tai: Abnormal response of ankle pressure after exercise in seemingly normal subjects living in blackfoot disease-hyperendemic villages in Taiwan. *Vasc. Surg.*, **28**, 607-617 (1994).
- Tseng, C.H., C.K. Chong, C.J. Chen and T.Y. Tai: Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. *Atherosclerosis*, **120**, 125-133 (1996).
- Tseng, C.H., C.K. Chong, C.J. Chen and T.Y. Tai: Lipid profile and peripheral vascular disease in arseniasis-hyperendemic villages in Taiwan. *Angiology*, **48**, 321-335 (1997).
- Tseng, C.H., C.K. Chong, L.T. Heng, C.P. Tseng and T.Y. Tai: The incidence of diabetes mellitus in Taiwan. *Diabetes Res. Clin. Pract.*, **50(Suppl 2)**, S61-S64 (2000a).
- Tseng, C.H., C.K. Chong, C.P. Tseng, Y.H. Hsueh, H.Y. Chiou, C.C. Tseng and C.J. Chen: Long-term arsenic exposure and ischemic heart disease in arseniasis-hyperendemic villages in Taiwan. *Toxicol. Lett.*, **137**, 15-21 (2003).
- Tseng, C.H., Y.K. Huang, Y.L. Huang, C.J. Chung, M.H. Yang, C.J. Chen and Y.M. Hsueh: Arsenic exposure, urinary arsenic speciation and peripheral vascular disease in blackfoot disease-hyperendemic villages in Taiwan. *Toxicol. Appl. Pharmacol.*, **206**, 299-308 (2005).
- Tseng, C.H., T.Y. Tai, C.K. Chong, C.P. Tseng, M.S. Lai, B.J. Lin, H.Y. Chiou, Y.M. Hsueh, K.H. Hsu and C.J. Chen: Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: A cohort study in arseniasis-



- hyperendemic villages in Taiwan. *Environ. Health Perspect.*, **108**, 847-851 (2000b).
- Tseng, C.H., T.Y. Tai, B.J. Lin and C.J. Chen: Abnormal peripheral microcirculation in seemingly normal subjects living in blackfoot disease-hyperendemic villages in Taiwan. *Int. J. Microcirc.*, **15**, 21-27 (1995).
- Tseng, C.H., C.P. Tseng, H.Y. Chiou, Y.M. Hsueh, C.K. Chong and C.J. Chen: Epidemiologic evidence of diabetogenic effect of arsenic. *Toxicol. Lett.*, **133**, 69-76 (2002).
- Tseng, W.P.: Blackfoot disease in Taiwan: A 30-year follow-up study. *Angiology*, **40**, 547-558 (1989).
- Tseng, W.P., H.M. Chu, S.W. How, J.M. Fong, C.S. Lin and S. Yeh: Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J. Natl. Cancer Inst.*, **40**, 453-463 (1968).
- Vahter, M.: Methylation of inorganic arsenic in different mammalian species and population groups. *Sci. Prog.*, **82**(Pt 1), 69-88 (1999).
- Vahter, M.: Mechanisms of arsenic biotransformation. *Toxicology*, **181-182**, 211-217 (2002).
- Vardhanan, Y.S. and T. Radhakrishnan: Acute toxicity evaluation of copper, arsenic and HCH to paddy field crab, *Paratelphusa hydrodromus* (Herb.). *J. Environ. Biol.*, **23**, 387-392 (2002).
- Wen Cheng, Y. and H. Lee: Environmental exposure and lung cancer among nonsmokers: An example of Taiwanese female lung cancer. *J. Environ. Sci. Health. C*, **21**, 1-28 (2003).
- Windebank, A.J.: Specific inhibition of myelination by lead *in vitro*; comparison with arsenic, thallium and mercury. *Exp. Neurol.*, **94**, 203-212 (1986).
- Yamamura, S.: Arsenic and fluoride in drinking water; WHO's recent endeavours. WHO, Geneva, Switzerland for the Pan-Asia-Pacific Conference on Fluoride and Arsenic Research, Shenyang, China. pp. 16-20 (1999).