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Yoshida, Takahiko ; Yamauchi, Hiroshi ; Fan Sun, Gui

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Takahiko Yoshida[a*], Hiroshi Yamauchi[b] and Gui Fan Sun[c]

[a]Department of Health Science, Asahikawa Medical College, Asahikawa, Hokkaido 078-8510, Japan,

[b]Department of Preventive Medicine, St. Marianna Medical College, Kawasaki, Kanagawa 216-8511, Japan,

[c]School of Public Health, China Medical University, Shengyang 110001, China

Corresponding author.

Department of Health Science, Asahikawa Medical College, 2-1-1-1 Midorigaoka Higashi, Asahikawa, Hokkaido 078-8510, Japan

FAX: +81-166-68-2409.

E-mail address: tyoshida@asahikawa-med.ac.jp (T. Yoshida).

ABSTRACT

Chronic arsenic (As) poisoning has become a world wide public health issue. Most human As exposure occurs from consumption of drinking water containing high amounts of inorganic As (iAs). In this paper, epidemiological studies conducted on the dose-response relationships between iAs exposure via the drinking water and related adverse health effects are reviewed. Before the review, the methods for evaluation of the individual As exposure are summarized and classified into two types, i.e. the methods depending on As concentration of the drinking water and the methods depending on biological monitoring for As exposure; certain methods may be applied as optimum As exposure indexes to study dose-response relationship based on various As exposure situation. Chronic effects of iAs exposure via drinking water include skin lesions, neurological effects, hypertension, peripheral vascular disease, cardiovascular disease, respiratory disease, diabetes mellitus, and malignancies including skin cancer. The skin is quiet sensitive to arsenic and skin lesions are some of the most common and earliest non-malignant effects related to chronic As exposure. The increase of prevalence in the skin lesions has been observed even at the exposure levels in the range of 0.005-0.01 mg/L As in drinking waters. Skin, lung, bladder, kidney, liver and uterus are considered as sites As-induced malignancies, and the skin is though to be perhaps the most sensitive site. Prospective studies in large area of endemic As poisoning, like Bangladesh or China, where the rate of malignancies is expected to increase within the next several decades, will help to clarify the dose-response relationship between As exposure levels and adverse health effects with enhanced accuracy.

Keywords: chronic arsenic poisoning; epidemiological field research; dose-response; drinking water; adverse health effects; skin lesions; skin cancer; internal malignancies

INTRODUCTION

Arsenic (As) is a common elements and there are several chances in which people are exposed to As in daily life. Occupational As exposures are observed frequently in smelter workers from the inhalation of As fumes, since As is found as sulfide compounds in various ores as ubiquitous contaminant. Lung cancer is well known to result from As exposure in occupational settings. In recent times, As has become an essential component in the production of semiconductor chips. In occupational settings, workers are often monitored for As exposure level by measuring As contents in biological samples, such as hair, urine or blood, to help reduce exposure before the onset of the overt clinical manifestations of As poisoning (Yamauchi et al., 1989, Peyster et al., 1995). Pre-clinical manifestations of As exposure can be combined with biological monitoring for As exposure, as with workers engaged in semiconductor industries where hair level of As have been evaluated alone with immunological alternations induced by As exposure (Yoshida et al., 1987). The target population of occupational exposure to As differs from that of general population, since occupational exposure subjects are typically healthy adults with a disproportional distribution of males. In addition there is often co-existing exposures in occupational settings. So it can be difficult to relate the adverse health effects observed in occupationally exposed workers exclusively to As. Inorganic As has been used pharmacologically for the treatment of malaria, syphilis, leukemia or psoriasis under the name of Fowler's solution, etc. Skin lesions, including dermal malignancies, were observed in the patients who were prescribed arsenical medicines. The prevalence of malignancy was correlated with As intake (Cuzick et al., 1992). These various patient populations are similarly not representative of the general population.

Chronic As poisoning in the general population has been widely reported in many areas of the world today. In these situations, As exposure occurs by consumption of drinking water that naturally contains high amount of inorganic forms of As (Smith et al., 2000a). The outbreak of As poisoning in many areas was triggered by the desire to obtain microorganism free safety drinking water, and often surface water was replaced by underground water obtained by tube wells. Arsenic poisoning via the drinking water affects all the residents who are living in the contaminated field. Thus accurate evaluation on dose-response relations between As exposure and adverse health effects in a general population could be assessed in the endemic area of high As

exposure. The knowledge of dose-response relationships between As exposure and adverse health effects will help in estimation of health risk and prevention of As poisoning in the future among the resident in areas of endemic As poisoning and also among the workers occupationally exposed to As. In this paper, researches conducted on the dose-response relationships between inorganic As (iAs) exposure via the drinking water and adverse health effects are reviewed.

INDEX of ARSENIC EXPOSURE

Before discussing of dose-response relationship, the methods for evaluation of individual As exposure need to be described. Two major approaches have been used for evaluation of As exposure, as summarized below. Each method has advantages and disadvantages, so it is necessary to observe the situation and to employ the optimum index based on the target symptoms or the health effects.

1. Arsenic in the drinking water as an index of exposure

a) Background

Since this review is focusing on As poisoning after absorption via alimentary tract, all consumed As should be considered to define exposure accurately. Arsenic in the drinking water is most often determined to be in the inorganic form. Although our research reveals that amount of As in crops, like uncooked wheat and corn harvested in the contaminated area is negligible, significant intake of As from foods cooked using contaminated water or foodstuffs made from livestock consuming contaminated drinking water can occur. However, most studies reporting on areas of endemic As poisoning usually only consider the drinking water. It can be difficult to accurately estimate As in foodstuffs. The amount of As from food is typically much less than that from drinking water, although techniques like duplicate meal study are only rarely used (Mohri et al., 1990). In the case of large amount of intake of seaweed, dietary iAs from food should be considered in the total iAs dose because seaweed is relatively rich in iAs beside to arsenosugars (Gallagher et al., 2001). On the other hand, relatively As rich seafood other than seaweed is less concern because arsenobetaine is the main As species in seafood and less toxic than iAs (Mohri et al., 1990).

b) Concentration of As in drinking water as an index of exposure

Some studies simply evaluate the As concentration in the drinking water

locally without considering individual consumption volume. Subjects that show large difference from the average consumption of drinking water may vary widely from this estimated individual As exposure. Furthermore using recently measured drinking water As levels reflects only the present exposure, which may be reasonable for assessing short-term effects, but dose not establish exposure levels over a long duration. If the concentration of As in drinking water was stable for a long period, this index of exposure may have some correlation with As related health effects after chronic exposure. When subjects obtained their drinking water form same well continuously throughout their lives, the mean concentration of As in drinking water can be used instead of a time-weighted average, since both indexes result largely in the same theoretical value. Dose in this case is usually expressed as ppm or mg/L of As in the drinking water.

c) Daily burden of As from drinking water

Improved index of As exposure is obtained by considering individual daily water consumption of As contaminated drinking water. Daily burden of As is thus calculated by multiplying As concentration of drinking water by the daily intake volume. Daily consumption can be estimated from self reporting through interview or questionnaire. Daily individual water consumption is definitely influenced by other factors, e.g. weather (air temperature and humidity) and labor intensity, in addition to body size in subjects. Thus in the existing cases of influencing factors to daily water consumption, daily burden of As from drinking water is better index for estimation of As exposure. Dose is usually expressed as mg/day or mg/kg body weight/day.

d) Average As exposure

The average As exposure index has an advantage for assessing the relationship between exposure and chronic adverse health effects appearing after long exposure periods. The average As concentration in the drinking water, which has been continuously consumed for a long duration, is calculated in a time-weighted manner, by using measured As water concentration multiplied by duration of consumption then divided by total duration. Information on individual water consumption history, including drinking water source, has to collect by interview or questionnaire, potentially introducing some recall bias. Water samples from all sources used during whole observed period have to be determined for As concentrations. Observation period should be dictated according to end-point of the health effects. Diseases such as

cancers would need a long observation period and the cumulative As exposure for long period should be considered. In this index the concentration of As in the current drinking water can be substituted for water consumed in the past, assuming that As concentration has been stable, although it is known that there can be seasonal or yearly fluctuations in drinking water As concentration. Dose is usually expressed as ppm or mg/L.

e) Cumulative As exposure

Cumulative As exposure is calculated as the sum of multiplying As concentration of the drinking water by the duration of consumption and usually expressed in units of ppm-year or mg-year/L. In subjects, where drinking water level of As have large variations or where has been a long period of little As exposure years, the index of cumulative As exposure may be suitable. The two parameters concerning the exposure, namely concentration and duration, should be applied appropriately according to the target adverse health effects. Cumulative As exposure index is suitable for evaluation of dose-response relationships of the adverse health effects appearing after a long period of As exposure. However, the method to take the parameter of time into the index of cumulative As exposure for evaluation of human health effects remains unclear. Our preliminary study revealed that the past 5 years exposure played significantly large role on the present benign skin lesions compare than previous 5 years exposure did, although it is not meaning to deny the effects of the later. Further studies are necessary to confirm the methods to take the parameter of time into the index of cumulative As exposure, especially for evaluation of occurrence of malignancies.

2. Biological monitoring as an index of As exposure

Biomarkers used for monitoring of As exposure have been established and applied widely to estimate individual exposure of workers in occupational health management activities. The amounts of As measured in samples from individual subjects reflect relatively recent As exposure. Knowledge of the chemical form of As is important for biological exposure monitoring. Arsenic in the drinking water, such as from wells, is mostly trivalent or pentavalent iAs. Inorganic As is metabolized by a two step of methylation process in humans and the total amount of iAs, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) in the sample should

be used as the biomarker of As exposure. Trimethylarsenic compounds in the samples are considered to be originated from seafood consumption and not biosynthesized in humans (Yamauchi et al., 1994), and would not be considered as part of As accumulated from drinking water.

a) Concentration of As in voided urine

Urine samples are commonly used for evaluation of As exposure levels, owing the ease of sampling and absence of any painful procedure. Calderon et al. (1999) compared As concentrations in spot urine samples and collected urine samples over 24-hr period and found only a small different between them. These authors also showed minimum fluctuations of urinary As concentration from day to day (Calderon et al., 1999). Most researchers prefer to use spot urine samples adjusted with creatinine for an As exposure index, instead of the more troublesome 24-hr urine collection sampling.

b) Amount of As in the blood

Peripheral blood samples have also been used for the evaluation of As exposure. Blood samples are obtained by venipuncture but difficulties remain in using this method for mass screening. Both of blood and urine samples reflect individual As intake and are relatively free from outer contamination.

c) Amount of As in hair

Hair samples are used for a biomarker of As exposure, since iAs and DMA are deposited at hair root and move into hair shafts. The amount of As in longitudinal segments of hair shafts reflect the past As burden at the time when hair was formed. So the total amount of As in a hair sample is a biomarker of the average As exposure over a significant duration of time. Possibilities of external contamination by washing hair using contaminated water, sweating or fixation of dust are an issue, since it is not so easy to remove externally deposited As selectively without losing internal As.

d) Amount of As in nails

Nails of fingers or toes are also used as a biomarker of the average rate of As exposure during a period of time similar to hair samples. Clipped samples of nail reflect As burden from about three (finger) or six (toe) months ago, since As is deposited by binding to sulfhydryl groups of keratin and then shifts to the tips of the nail as it grows. With nail samples there are also possibilities of external contamination. Karagas et al. (2002) have discussed the advantages of toenail As

concentrations as a biomarker for evaluation of As exposure.

3. Optimal application of indexes for individual exposure

The most desirable indexes for evaluating As exposure for a long period may be obtained by multiplication of the biomarkers of As exposure and exposure durations in each period. But in cross sectional study design, such as is commonly used in field research, it is impossible to collect past biological samples to use for biomarker analysis. So a compromise can be introduced for the indexes for As exposure of individual subjects. For the subjects who are living in an area with only small variation of As concentration in the drinking water from all sources, indexes depending on the concentration of As in drinking water or those depending biomarkers could be use with generally equal confidence. On the other hand, for the subjects who are living in an area with large variations of As concentration in the drinking water from all sources, the average or cumulative As exposure, calculated from actual As concentration in drinking water, are the more suitable indexes to apply. Clearly it is important to select a suitable index of As exposure for the objective assessments of adverse health effects according to the variation of As concentration between each water source, and drinking behavior or history of subjects in the target research field.

DOSE-RESPONSE RELATIONSHIP between ARSENIC EXPOSURE and ARSENIC RELATED CHRONIC HEALTH EFFECTS

The chronic health effects of iAs exposure from consumption of As contaminated water include skin lesions, skin cancer, internal malignancies, neurological effects, hypertension, peripheral vascular diseases, cardiovascular disease, respiratory diseases and diabetes mellitus (Smith et al., 2000a). Skin lesions are one of the most common features of chronic As poisoning and these lesions are used as a diagnostic criteria of endemic As poisoning in Inner Mongolia, China (Guo et al., 2001). There are several reports that discuss the relative risk or prevalence rate of chronic health effects in As exposed populations, although few papers attempt to define dose-response relationships between As exposure via the drinking water and chronic toxicity because of the difficulty in estimation of individual exposure.

1. Non-malignant skin lesions

Dose-response relationships between As exposure and the skin lesions related to chronic As poisoning, excluding skin malignancies, are summarized in Table 1. Borgono et al. (1977) reported a major difference in the level of As in hair form residents in Antofagasta (an endemic arsenism area) compared to a control non-exposed group in a study of populations in Chile, 1969. The mean As content in hair was 0.32 and 0.61 mg As/100g hair for the residents with normal skin and the residents with abnormal pigmentation, respectively, in Antofagasta, whereas it was 0.08 mg As/100g hair for control group, all of whom had no abnormal dermal pigmentation. The residents at Antofagasta consumed As contaminated drinking water containing level between 0.6 and 0.8 mg/L. Follow up research six years after mitigation of drinking water contamination by a water treatment plant revealed that previous As exposed children age of 13-14 years old showed skin lesions at a 65.5% and 78.3% rate in males and females, respectively. They also found high amount of As still remained in hair even after mitigation. In this regard 40.1 % of residents still had levels that exceeded 0.10 mg As/100g hair in 1976, 6 years after mitigation, compared to 82.6% prior to mitigation in 1969. A similar tendency was observed for nail (Borgono et al., 1997).

Tsuda et al. (1995) discussed the dose-response relation between drinking water concentration of As and skin lesions of chronic As exposure in residents who had been exposed to As for at least 5 years in Niigata prefecture of Japan. Prevalence rates of skin lesions were 10.0, 10.8 and 63.6% for groups consuming drinking water with As concentration less than 0.05, 0.05-0.99 and over than 1.00 mg/L, respectively (Tsuda et al., 1995).

Several studies on relationship between As exposure from drinking water and skin lesions have been reported from the areas of endemic As poisoning in Bangladesh and West Bengal. A relatively large population study in West Bengal, India revealed the dose-response relationship between As concentration in drinking water and the prevalence of skin lesions (Mazumder et al., 1998). Age-adjusted keratosis prevalence per 100 subjects was 1.5 in males and 0.4 in females exposed to 0.05-0.10 mg As /L but increased to 10.7 in males and 8.3 in females exposed to higher than 0.80 mg/L As. Age-adjusted skin hyperpigmentation rate per 100 subjects was 3.2 in males and 0.8 in females exposed to 0.05-0.10 mg As/L in the drinking water but increases to 22.7 in males and 11.5 in females in group exposed to higher than 0.80 mg As/L.
Age-adjusted rate of skin lesions examined using daily As dose per body weight showed

same tendency of increasing with increasing As exposure (Mazumder et al., 1998). Tondel et al. (1999) reported a clear dose-response relationship between the As level in drinking water and the rate of skin lesions in typical villages from the area of As poisoning in Bangladesh. Rates of skin lesions per 100 subjects adjusted by age in male rose 18.6 in group where As level in the drinking water less than 0.15 mg As/L to 37.0 in males consuming water with higher than 1.00 mg As/L. Though rates in females subjects were lower than that in males, they also showed same tendency with increased As exposure. The age adjusted log linear regression showed a significant trend for males and females at a relative risk of 1.55 and 1.42 per mg As/L, respectively.

Male subjects from one village in Bangladesh, when divided into 3 groups based on creatinine adjusted urinary As concentration, showed a significant positive correlation between As exposure and dermatologic score (classified by severity of skin lesions as defined by authors), although no such correlation was found in female subjects from this villages or in subjects of either gender from other village (Watanabe et al., 2001). The authors explained this lack of consistency as possibly due to several factors including: recent As exposure from occasional-use water sources; some undefined environmental, nutritional or genetic factors including potentially As metabolism.

Guo et al. (2001) reported a dose-response relationship between As exposure and skin lesions in areas of Inner Mongolia. Rates of As induced skin lesions were 44.8% or 37.1%, respectively, in two As contaminated areas where 96.2% or 69.3% wells were detected with As over 0.05 mg/L in water. The prevalence of skin lesions was higher in older residents over 40 years old and showed no gender differences (Guo et al., 2001).

We conducted field research study at a farm village near the middle stream of the Yellow River in Inner Mongolia. There were about 300 wells in the village and these contained As levels with a wide variation, from 0.0007-1.79 mg As/L. It was possible to estimate As exposure just from drinking water, since the residents did not consume any seafood because of the location far from a seashore. Some residents with sever skin lesions were found to obtain drinking water various neighborhood wells. Often this was from the wells of neighbors with no skin lesions. These subjects had recorded of usage of drinking water from as many as five wells in their life time. So it was necessary to evaluate individual As exposure based on an interview of past history

of drinking water source and to measure all of various water samples that subjects used. The odds ratio of either skin lesions, hyperkeratosis or dyspigmentation verses average As concentration of the drinking water for past 5 years showed a moderate, but significant, dose-response relationship among subject over 20 years old of age (Figure 1).

There are also several negative reports on skin lesions relating to As exposure. Valentine et al. (1992) compared the incidence of skin lesions and other chronic health effects of As exposure, such as gastrointestinal, neurological, musculoskeletal or circulatory, between an As exposure group that consumed between 0.1-0.39 mg As/L of drinking water in Nevada or California and a control group consuming 0.001 mg/L in Wyoming, and they found no difference between them. Authors explained their negative results from reports of positive association by differing socio-economical status and/or nutritional inadequacies of the control and target subjects in the reports where positive relationship was found on the subjects outside the U.S. They collected the information on included skin lesions by self report from residents. Furthermore they included skin lesions that were characteristic to not only for chronic As poisoning but also for acute or sub-acute As poisoning including skin darkening and rashes. So there is some possibility that they missed the typical skin lesions of chronic As poisoning, especially hyperkeratosis. In addition, nutritional status dose not appear to modify As-induced skin lesions, since Smith et al. described such lesions even in the subjects with good nutritional status in a study in Northern Chile (Smith et al., 2000b).

Skin malignancy

Dose-response relationships between As exposure and skin malignancy are summarized in Table 2. Age-adjusted mortality rate of skin cancer was significantly related to increasing As concentration of drinking well water among residents aged 20 years old or more in Taiwan (Wu et al., 1989). Age-adjusted mortality rates per 100,000 of the group drinking water contained As at concentration at less than 0.30, 0.30-0.59 and more than 0.06 mg/L were 2.03, 14.01 and 32.41 for male, and 1.73, 14.75 and 18.66 for female, respectively.

A study in south west Taiwan during 1960s revealed that subjects those As concentration in drinking water for lifetime was 0.00-0.29, 0.30-0.59 and over 0.60 mg/L had, by age 60, developed skin cancer at prevalence rate 27.1, 106.2 and 192.0

per 1,000, respectively (Tseng et al., 1968). Prevalence rate of male was 5.2 to 2.3 times higher than female in low to high exposure groups, respectively.

The villagers in our field study in Inner Mongolia had a relatively short history of As exposure. At our first observation in July 1999, only 1 villager began to drink first As contaminated well water exceed 0.05 mg/L before 20 years ago, and 17 villagers began to be exposed to As before 10 years ago among a total of 116 subjects. There was no occurrence of skin cancer in our follow up research in 2000 and no report by 2002 from the local public health center. It is thought that development of cancer in humans takes a period of 20-30 years. The subjects in this study had received the pipe line water service (concentration of As at 0.036 mg/l) from September 1999. It will be necessary to periodically follow-up these subjects to evaluate dose-response relationship between As exposure and the risk of skin cancer among subjects where reduction in As has occurred to evaluate the long-term effects of mitigation efforts.

Internal malignancies

Dose-response relationships between As exposure and internal malignancies are summarized in Table 3. Age-adjusted mortality rates in Taiwanese subjects from all site malignancy per 100,000 among groups drinking As contaminated water at less than 0.03, 0.30-0.59 and more than 0.06 mg/L were 224.56, 405.12 and 534.61 for male subjects, and 162.22, 277.20 and 487.20 for female subjects, respectively (Wu et al., 1989). Age-adjusted mortality ratios of several internal malignancies including bladder, kidney, lung, liver and prostate, were significantly related to increasing As concentration of drinking well water among residents 20 years old or older (Wu et al., 1989). Prominent and significant sites of cancer were the lung, bladder, skin and kidney.

Bates et al. (1995) analyzed the data from Utah in the National Bladder Cancer Study conducted in 1978 to evaluate the relationship between As exposure and bladder cancer using two As exposure indexes, average As concentration and cumulative As dose (Bates et al., 1995). They found a positive trend in the risk of bladder cancer with As exposure for various exposure durations, especially for 30-39 years prior to diagnosis, among ever smoked subjects but not among never smoked subjects. Representative adjusted odds ratios among ever smoked subjects exposed to As at concentrations less than 8, 8-10, 10-13 and over 13 mg/L-years were 1.00, 1.86, 1.48

and 8.70, respectively.

Tsuda et al. (1995) reported a standardized mortality ratios (SMR) of a group consuming water containing As at concentration over than 1 mg/L was 3.63 for all cancers, 15.69 for lung cancer, and 31.18 for urinary tract cancer. They mentioned the same tendency for liver and uterine cancer.

Study on the SMR with As exposure from ground water in Argentina revealed dose-related association between As exposure and risk of kidney and lung cancers (Hopenhayn-Rich et al., 1998). The classification for exposure groups was based on estimated As concentration in drinking water such that less than 0.04 mg/L was designated the low group and over than 0.178 mg/L the high group. Dose-response relations in SMR from low to high exposure groups were observed for kidney cancer as 0.87 to 1.57 for male, 1.00 to 1.81 for female, and for lung cancer 0.92 to 1.77 for male, 1.24 to 2.16 for female.

A cohort study on bladder and kidney cancers relating to As exposure in Finland found a significant elevation of bladder cancer risk among the subjects that were exposed over 0.5 μg As/L in the drinking water or to a daily dose of 1.0 μg for from 3 to 9 years before diagnosis (Kurttio et al., 1999). There was no association between kidney cancer and As exposure (Kurttio et al., 1999). This research showed relatively low As doses can lead to internal cancers.

Vascular diseases

Age-adjusted mortality rates of peripheral vascular diseases and cardiovascular disease have been related to consumption of well water with increasing As concentration in residents 20 years old or older in Taiwan (Wu, et al., 1989). Cerebrovascular disease was not associated with As exposure in the study. Age-adjusted mortality rates per 100,000 of peripheral vascular diseases were increased to 22.5, 57.8 and 60.4, and 18.2, 48.0 and 35.8 for As concentration in the drinking water of less than 0.3, 0.3-0.59 and over than 0.6 mg/L in male and female subjects, respectively. Those of cardiovascular diseases were also increased to 125.9, 154.0 and 259.5, and 91.1, 153.1 and 144.7 for the same As level in male and female, respectively. Pi et al. (2000) reported a decrease in NO concentration in serum from the residents exposed to As via drinking contaminated well-water in Inner Mongolia. Serum NO reflects the activity of endothelial nitric oxide synthetase (eNOS) and helps dilate

peripheral blood vessels. The ratio of concentrations of nitrite/nitrate (stable NO metabolites which indirectly quantify NO concentration) were negatively correlated with As exposure as evaluated by serum As level (Pi, et al., 2000). The possible role of As on peripheral blood circulation was discussed.

Other symptoms

A significant dose-response relationship was observed between the prevalence of hypertension and As exposure, using either drinking water As level or cumulative As exposure, among the residents living in an As contaminated area in Bangladesh (Rahman et al., 1999). Age, gender and body mass index adjusted prevalence ratios of hypertension were increased to 1.2, 2.2 and 2.5 for exposure groups less than 0.5, 0.5 to 1.0 and over than 1.0 mg/L or to 0.8, 1.5, 2.2, and 3.0 for groups less than 1.0, 1.0 to 5.0, 5.0 to 10.0 and over than 10.0 mg-year/L, respectively (Rahman et al., 1999).

There are several reports on dose-dependent relationship between As exposure and respiratory disease. Mazumder et al. (2000) mentioned that the prevalence of cough, shortness of breath and chest sounds in the lungs rose with increasing As concentration in drinking water. Representatively age-adjusted prevalence of cough per 100 in groups exposed to an As level less than 0.05, 0.05-0.19, 0.20-0.49, 0.50-0.79 and over 0.80 mg/L were 5.1, 4.1, 5.5, 5.4 and 11.9 for male subjects and 2.2, 1.3, 2.6, 4.9 and 5.5 for female subjects, respectively. Field research in Bangladesh by Milton et al. (2002) revealed that unadjusted prevalence ratios for chronic bronchitis rose with increasing As exposure, 1.0, 1.6, 2.7 and 2.6 for As exposure groups of 0.0, less than 0.60, 0.61-0.70 and 0.71-1.0 mg/L, respectively, with a dose-response trend of $p<0.1$. Both of these reports showed a critical concentration of around 0.7 mg/L for appearance of respiratory effects induced by As exposure.

Age and gender adjusted prevalence rate of glucosuria was related to increasing As exposure, using either an average As concentration from well water ranging from non-detectable to 2.04 mg/L, or a cumulative As exposure index among residents 30 years old or older in Bangladesh (Rahman, et al., 1999).

DISCUSSION

Many epidemiological studies on As poisoning due to consumption of As contaminated water have been reported world wide. On the other hand, there are

relatively few reports concerning dose-response relationships between As exposure and As related adverse health effects, since it is often difficult to evaluate individual As exposure. It is critical to evaluate As exposure in studies on the chronic toxic effects of As, especially with regard to the estimation of cancer risk.

Arsenic poisoning from drinking As contaminated underground water was often triggered by the introduction of deep tube-pump wells to replace surface water usage in many areas in Bangladesh or China. Changing the water source for drinking was an attempt to improve water safety and prevent morbidity from gastrointestinal diseases. Unfortunately for the residents of these areas, many of these wells tapped water that was naturally contaminated by As and long-term consumption of this contaminated water became the trigger of As poisoning. The knowledge of when these wells started to be first used is helpful to researchers to identify the beginning of As exposure in the target population. Because of this, there are some highly reliable reports on the correlation between As exposure and non malignant diseases. Majority of subjects in Bangladesh or China began to be exposed to As through drinking water at late 1970s. The duration of exposure within these areas of endemic As poisoning within Bangladesh or China is relatively short particularly with regard to the latency period of human cancer. In fact, only recently small numbers of skin cancer cases started to appear in Bangladesh (Smith et al., 2000a). Therefore, at present, the results of the dose-response relationship between As exposure and external and internal cancers have had to depend on the studies in the areas with a long exposure history like Taiwan, the USA, or Chile.

Assessment of past individual exposure to As has some limitations. For instance one must substitute the current As concentration as representative for past As concentrations, since it is impossible to obtain past water samples. Several methods are used to estimate individual As exposure. All these methods have advantages and disadvantages, and the optimal method is dictated by the As exposure situation in the target field. For example, since waters from wells in our research field in Inner Mongolia shows a wide variation in As concentration, even within the same village, it is necessary to determine individual As exposure by a record of both duration and location of water consumption together with the measurement of As concentration of all well waters which are involved.

Majority of reports linking As exposure and As-related chronic toxicity indicate

a positive dose-response relationship, although the threshold for toxicity, the lowest As exposure level with observation of adverse health effects by As exposure, varies widely. This variation may be due to several factors including a difference in the index of As exposure, a difference in the control group, a racial difference and confounding factors that may influence to modify As-induced diseases. Confounding factor could include coexisting elements in the drinking water, sun exposure, occupations with heavy duty hand work, smoking, and essential rare elements in take. These factors make it difficult to perform a meta-analysis on As-induced diseases. On the other hand, with the same report it is appropriate to compare the specificity or sensitivity of each As related adverse health effect. However very few reports mentioned multiple adverse health effects with dose-response analysis, and the number of subject is often small.

It appears that skin is very sensitive to As and As-induced skin lesions are the earliest non-malignant health effects related to chronic As exposure. We found an increase in the prevalence of skin lesions even at 0.005-0.01 mg As/L in the drinking water, a level lower than the drinking water quality standard of WHO. Skin lesions consisted of two types, dyspigmentation and hyperkeratosis. Mazumder et al. (2000) reported that hyperpigmentation is a more sensitive sign of As exposure than hyperkeratosis in Bangladesh. We also observed the same tendency occurred in some, but not all areas studied in Inner Mongolia, China. So the appearance of dyspigmentation or hyperkeratosis may be different in studies according to unknown confounding factors. A few studies on dose-response effect of As exposure on vascular diseases, respiratory symptoms, hypertension and glucosuria are available and these show lower prevalence rates than for that of skin lesions.

Skin, lung, bladder, kidney, liver and uterus are thought to be major sites of cancer induced by chronic As exposure, since prevalence rates, mortality rates or odds ratios of incidence for cancers of these sites have been shown to increased dose dependently. Cancers of the lung and urinary bladder appear to be the most common in chronic As exposed populations and showed relatively high mortality rates even at relatively low As exposure levels. Wu et al.(1989) observed and compared the mortality rates among malignancies of skin, lung, bladder and kidney, and obtained the highest elevation of odds ratio in skin cancer as 5.31 for male or 12.01 for female in the group of exposure level over than 0.60 mg/L of drinking water against 0.00 to 0.29 mg/L group. The report by Tseng et al. (1968) is one of few reports described the

dose-response between the prevalence rate of skin cancer and three categorized As exposure levels. They appeared to show a dose-dependent correlation between skin cancer and As level. Because they classified the lowest As exposure level as 0.00 to 0.29 mg/L, which is too wide range to accept as control, it is difficult to evaluate the dose-dependency of the data. More precise relationship between As exposure level and prevalence of skin cancer will require further study.

Many reports indicate that non-malignant skin lesions induced by As occur more in male subjects than female, although some reports described no difference between genders. We have noticed that gender-related differences in skin lesions depended on the site in Inner Mongolia (preliminary observation). Watanabe et al. (2001) also pointed out the same observation in Bangladesh. The incidence of As-induced peripheral vascular diseases, cough or skin cancer appear to occur in male, while malignancies of kidney and lung are dominant in the female. Clarify of the basis of these gender-related differences may be helpful in understanding the mechanism of As poisoning and countermeasures for prevention and treatment. Further studies are needed to clarify the basis of these gender-related differences.

There is the possibility that, because of the latency period for cancer development in human, As-induced malignancies may have not yet peaked in Bangladesh or China. Tsuda et al. (1995) discussed that As exposure level when combined with the presence of skin lesions could be used to estimate the future development of malignancy. Prospective study in large endemic areas of chronic As poisoning will help to clarify the dose-response relationship between As exposure and cancer, and potentially help us understand the factors that influence cancer development after As exposure. This should also help to provide data to evaluate the As standard for drinking water quality. Such results are needed to institute countermeasures to reduce the occurrence of malignant diseases from As exposure. Large populations are now exposed to high level of As in many areas, especially Bangladesh and China, with the potential of the occurrence of malignant diseases in the future. Careful observation of these areas of endemic As poisoning needs to continue to help prevent this potential tragedy.

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Table 1 Dose-response relationships between As exposure and skin lesions [a]

Skin lesion	Parameter for As exposure	Exposure Level	Prevalence rate	Country	References
Abnormal pigmentation	Mean value of As in hair	0.32 mg As/100g	Presence (100%)	Chile	Borgono et al., 1977
		0.61 mg As/100g	Absence (0%)		
Darkening of skin	As Conc. of drinking water	0.001 mg/L	3.2%	USA	Valentine et al., 1992
		0.1–0.39 mg/L	6.6%		
Unexplained skin rashes	As Conc. of drinking water	0.001 mg/L	10.8%	USA	Valentine et al., 1992
		0.1–0.39 mg/L	7.7%		
Skin signs [b]	As Conc. of drinking water	<0.05 mg/L	10.0%	Japan	Tsuda et al., 1995
		0.05–0.99 mg/L	10.8%		
		>1.00 mg/L	63.6%		
Keratosis	As Conc. of drinking water	0.05–0.10 mg/L	1.5% male/0.4% female	India	Mazmuder et al., 1998
		0.10–0.149 mg/L	1.6% / 1.2%		
		0.15–0.199 mg/L	4.7% / 2.3%		
		0.200–0.349 mg/L	4.9% / 2.0%		
		0.350–0.499 mg/L	9.0% / 2.7%		
		0.500–0.799 mg/L	8.9% / 3.1%		
		>0.8 mg/L	10.7% / 8.3%		
Hyperpigmentation	As Conc. of drinking water	0.05–0.10 mg/L	3.2% male/0.8% female	India	Mazmuder et al., 1998
		0.10–0.149 mg/L	11.0% / 5.7%		
		0.15–0.199 mg/L	7.8% / 5.1%		
		0.200–0.349 mg/L	13.1% / 6.5%		
		0.350–0.499 mg/L	15.7% / 9.5%		
		0.500–0.799 mg/L	13.8% / 5.3%		
		>0.8 mg/L	22.7% / 11.5%		
Skin lesions [b]	As Conc. of drinking water	<0.15 mg./L	18.6% male/17.9% female	Bangladesh	Tondel et ai., 1999
		0.15–0.35 mg/L	21.9% / 20.5%		
		0.35–0.55 mg/L	32.9% / 32.1%		
		0.55–1.00 mg/L	36.8% / 34.0%		
		>1.00 mg/L	37.0 % / 24.9%		
Skin lesions [b]	% of wells detected As	37.1%	69.3%	China	Guo et al., 2001
	over 0.05 mg/L	44.8%	96.2%		

[a] Skin lesions do not include malignancy.

[b] Either hyperkeratosis and/or hyperpigmentation and depigmentation (hypopigmentation, leukomelanosis)

Table 2 Dose-response relationships between As exposure and skin malignancy

Parameter for As exposure	Exposure Level	Exposure duration		Response	Country	References
As Conc. of drinking water	0.00-0.29 mg/L	by age 60 years old	Prevalence rate	48.1 for male/9.1 for female	Taiwan	Tseng et al., 1968
	0.30-0.59 mg/L	for life time	(per 1,000)	163.4 / 62.0		
	>0.60 mg/L			255.3 / 110.1		
As Conc. of drinking water	<0.30 mg/L	at least 20 years and more	Mortality rate	2.03 for male/1.73 for female	Taiwan	Wu et al., 1989
	0.30-0.59 mg/L		(per 100,000)	14.01 / 14.75		
	>0.60 mg/L			32.41 / 18.66		

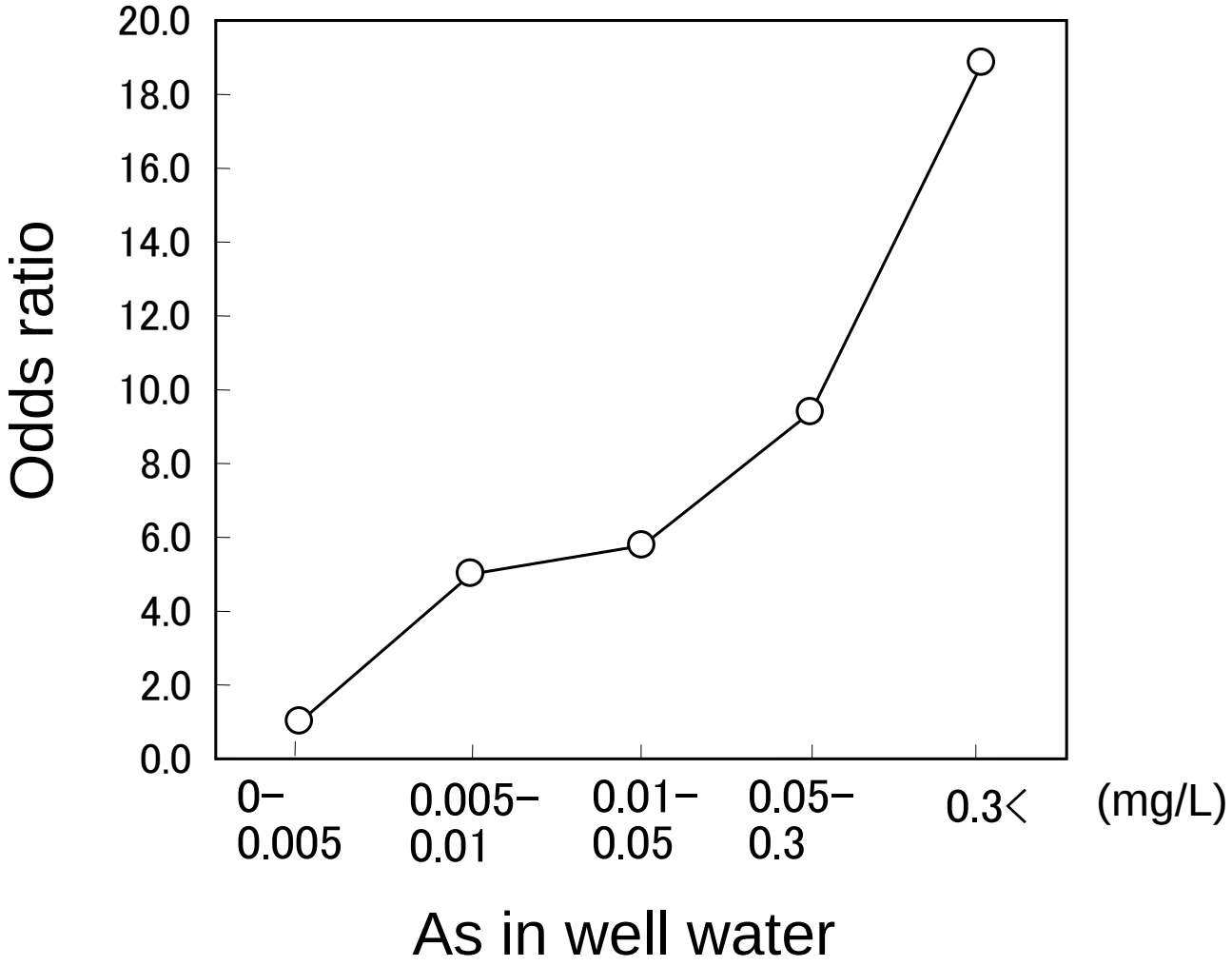
Table 3 Dose-response relationships between As exposure and internal malignancies

Site	Parameter for As exposure	Exposure Level	Response		Country	References
Lung	As Conc. of drinking water	<0.3 mg/L	Mortality rate	49.16 for male/36.71 for female	Taiwan	Wu, 1989
		0.3-0.59 mg/L	(per 100,000)	100.67 / 60.82		
		>0.60 mg/L		104.08 / 122.16		
Bladder	As Conc. of drinking water	<0.3 mg/L	Mortality rate	22.64 for male/25.60 for female		
		0.3-0.59 mg/L	(per 100,000)	61.02 / 57.02		
		>0.60 mg/L		92.71 / 111.30		
Kidney	As Conc. of drinking water	<0.3 mg/L	Mortality rate	8.42 for male/3.42 for female		
		0.3-0.59 mg/L	(per 100,000)	18.90 / 19.42		
		>0.60 mg/L		25.261 / 57.98		
Bladder	Cumlative As dose per year	<19 mg	Odds ratio [2]	1.00 for smoker/ 1.00 for non-smoker	USA	Bates, 1992
		19-33 mg		3.33 / 1.09		
		33-53 mg		1.93 / 0.68		
		>53 mg		3.32 / 0.53		
	Total cumulative As dose	<33 mg/L·years	Odds ratio	1.00 for smoker/ 1.00 for non-smoker		
		33-53 mg/L·years		1.95 / 0.21		
		53-74 mg/L·years		1.21 / 0.25		
		>74 mg/L·years		1.41 / 0.91		
	Total cumulative As dose	<8 mg/L·years	Odds ratio	1.00 for smoker/ 1.00 for non-smoker		
	(30-39 years interval between exposure period and observation)	8-10 mg/L·years		1.11 / 1.86		
		10-13 mg/L·years		0.67 / 1.48		
		>13 mg/L·years		1.03 / 8.70		
Lung	As Conc. of drinking water	<0.05 mg/L	SMR [1]	0.00	Japan	Tsuda, 1994
		0.05-0.99 mg/L		0.02		
		>1.00 mg/L		0.16		
Urinary tract	As Conc. of drinking water	<0.05 mg/L	SMR	0.00		
		0.05-0.99 mg/L		0.00		
		>1.00 mg/L		0.31		
Liver	As Conc. of drinking water	<0.05 mg/L	SMR	0.00		
		0.05-0.99 mg/L		0.00		
		>1.00 mg/L		0.07		
Uterine	As Conc. of drinking water	<0.05 mg/L	SMR	0.00		
		0.05-0.99 mg/L		0.00		
		>1.00 mg/L		0.13		
Kideny	Estimated As Conc. of drinking water	Low: <0.04 mg/L	SMR	0.87 for male/1.00 fo female	Argentina	Hoppenhayn-Rich, 1998
		Middle: 0.04-0.178 mg/L		1.33 / 1.36		
		High: >0.178 mg/L		1.57 / 1.81		
Lung	Estimated As Conc. of drinking water	Low: <0.04 mg/L	SMR	0.92 for male/1.24 fo female		
		Middle: 0.04-0.178 mg/L		1.54 / 1.34		
		High: >0.178 mg/L		1.77 / 2.16		
Bladder	As Conc. of drinking water	<0.1 ug/L	RR [3]	1	Finland	Kurttio, 1999
		0.1-0.5 ug/L		1.53		
		>0.5 mg/L		2.44		
	Daily dose of As	<0.2 ug/day	RR	1		
		0.2-1.0 ug/day		1.34		
		>1.0 ug/day		1.84		

[1] SMR: standardized mortality rate

[2] Odds ratio: adjested for gender, age, baladder infection and high risk occupational history.

[3] RR: age, gende and smorking adjusted risk ratios


Odds ratio
20.0
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0–
0.005
0.005–
0.01
0.01–
0.05
0.05–
0.3
0.3<
(mg/L)
As in well water

Legends

Fig. 1. Odds ratio for the prevalence of skin lesions verses the average As exposure dose over the past five years. N=62 (M;32, F;30) Skin lesions are defined as existence of hyperkeratosis on palm or sole and/or dyspigmentation of significant areas of the skin. Trend test on the dose-response relation with adjusted for age and gender in logarithmic scale by logistic regression model p=0.019.