EVIDENCE BASED PUBLIC HEALTH POLICY AND PRACTICE

Mutual interaction between nutritional status and chronic arsenic toxicity due to groundwater contamination in an area of Terai, lowland Nepal

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J Epidemiol Community Health 2007;61:389–394. doi: 10.1136/jech.2005.045062

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Accepted 20 August 2006

Objective: To reveal the inter-relationship between nutritional status and arsenic toxicity.

Design: Cross-sectional study.

Setting: A survey in an area of lowland Nepal, where a high prevalence of both skin manifestation and malnutrition was observed. Daily arsenic intake was estimated by measuring the arsenic concentration and daily consumption of the drinking water.

Participants: Adult villagers (248 men and 291 women). About half were classified as "underweight" (body mass index <18.5), indicating poor nutritional status.

Main results: Arsenic intake was negatively correlated with body mass index and substantially increased the prevalence of underweight individuals, among whom the prevalence of skin manifestations was 1.65-fold higher than normal weight individuals. When exposure level was considered, the prevalence of skin symptoms was consistently higher in the underweight than in the normal group. Although enhanced susceptibility in men was apparent by the increased prevalence of cutaneous symptoms, no sex difference was observed in the prevalence of underweight individuals related with exposure to arsenic.

Conclusions: The present data suggested that exposure to arsenic is associated with an increased prevalence of underweight, a serious health problem in developing countries, which in turn is associated with increased skin manifestation of arsenic poisoning.

Chronic arsenic poisoning associated with groundwater contamination has been reported from many developing countries, where poor nutritional status is concomitantly found. Although it has been suggested that poor nutritional status affects the toxicity and metabolism of arsenic,^{1–3} few systematic reports dealing with this issue exist. A case-control study conducted in Bangladesh showed that malnourished individuals are more often found among patients with arsenicosis than among the non-exposed population⁴; whether the decrease was due to exposure or to clinical manifestations could not be determined. Another case-control study in West Bengal (India) detected some differences between cases and controls in the intake of some nutrients; the difference in the arsenic exposure level between cases and controls and the long interval between the diagnosis and nutritional evaluation made the interpretation of the results difficult.⁵ An extensive study conducted in West Bengal reported heightened susceptibility to arsenic toxicity among individuals with lower body weight⁶; because the groups with different exposure levels were recruited from different areas, the modifying effects (or lack of effects) of nutritional status could have been mediated by other unidentified (environmental) factors such as dietary habit or socioeconomic status. There are some other studies^{7–8} describing the effects of nutrition on arsenic toxicity, with very limited quantitative information.

In 1999, groundwater pollution by arsenic was reported from lowland Nepal. We conducted a community-based, comprehensive survey in a "hot spot" of Terai in 2003 and recently published a summary report⁹ describing the enhanced susceptibility of men relative to women, which we also reported on in a Bangladesh community.¹⁰ Our survey was conducted in three closely located communities sharing similar natural and socioeconomic environments, but with considerable within-community variations in exposure levels, which enabled us to evaluate

the contribution of nutritional factors to the symptoms of chronic arsenic toxicity. We conducted anthropometry to calculate the body mass index (BMI = body weight (kg)/height² (m²)) as an index of nutritional status, and examined the water consumption of the villagers to estimate arsenic intake from water. On the basis of these data, we report the possible modifying effects of nutritional status on arsenic toxicity in terms of skin symptoms. Part of the basic data such as arsenic concentrations in tubewell water and in urine, and the prevalence of skin symptoms have been published elsewhere as a short communication.⁹

MATERIALS AND METHODS

Study sites and population

This study targeted three communities, the same as we reported elsewhere,⁹ located close to each other, in the Nawalparasi district in western Terai. Most of the residents are of Chaudhari ethnicity (caste) and almost all of them were farmers. These communities share a similar environment and lifestyle, hence, they were analysed as a whole in this paper. The field investigations were conducted from December 2002 to February 2003 and in July–August 2003. The population covered was 1705 (893 men and 812 women) in 249 households at the time of the first survey. The subjects of this study had voluntarily visited our health examination site set up in each community for dermatological examination (n = 1343), had been living in the communities for >6 months, were >15 years of age and for whom anthropometrical measurements (n = 539: 248 men and 291 women) were available. Pregnant women and physically handicapped people were excluded.¹¹

Abbreviations: As_{tw}, arsenic concentrations of the tubewells; As_u, arsenic concentrations of the urines; BMI, body mass index; DAI, daily arsenic intake; DWI, daily water intake; WHO, World Health Organization

Informed consent was obtained from each participant before the investigations. The study protocol was approved by the ethics committee of the Graduate School of Medicine, University of Tokyo, Tokyo, Japan, and the local authorities of the Nawalparasi District Headquarters.

Dermatological examination

The presence or absence of arsenic-induced skin symptoms, including melanosis, leucomelanosis and keratosis, was examined by one of us (AA), who is a doctor with ample experience in diagnosing arsenicosis cases in Bangladesh^{12–13} and was blinded to the exposure level and anthropometric data of the participants.

Anthropometric measurements

To assess nutritional status, the height and body weight of the participants were measured with conventional methods.¹⁴ The BMI values were calculated from height and weight, and each individual was classified as “underweight” (BMI <18.5), “normal” (18.5 ≤ BMI <25), “overweight” (25 ≤ BMI <30) or “obese” (BMI ≥ 30) individuals as defined by the World Health Organization (WHO),¹⁵ where the “underweight” category is regarded as chronic energy deficiency.¹⁵

Sampling and determination of arsenic in tubewell water and urine

Details of the sampling and arsenic determination of both tubewell water and urine have been described elsewhere.^{9–16} Water samples from all tubewells in the three communities (n = 146; “age” of tubewells = 10 (8) years; mean (SD)) were collected, immediately acidified with HCl and maintained at 4°C until analysis. Spot urine samples were collected from 106 couples (husbands and wives), frozen, transported to the laboratory at the University of Tokyo, and stored at –80°C until analysis. Arsenic concentrations of the tubewells (As_{tw}) and the urine samples (As_u) were analysed by atomic absorption spectrophotometry coupled with hydride generation (for water samples (SOLAAR 969AA, Thermo Elemental, Cambridge, UK) and for urine samples (ZL-4100, Perkin Elmer, Norwalk, Connecticut, USA)). Before atomic absorption spectrophotometric measurement, the urine samples were wet-ashed by heating with acid mixture. All the samples were found to contain arsenic above the detection limits (1 and 3 µg/l for water and urine, respectively). The accuracy of the assay was confirmed by inclusion of reference materials (for details, see Watanabe *et al*¹⁰). The results fell within the respective certified ranges. The creatinine concentration of the urine samples was determined spectrophotometrically.¹⁷ The chemicals and the reagent kit used were obtained from Wako Pure Chemical Industries (Osaka, Japan).

Water consumption measurement and calculation of daily arsenic dose

The amount of water drunk by the villagers was measured for 24 h in both winter (January) and summer (August) seasons, to take into account seasonal climatic variations. For this purpose, we provided a 1-litre polyethylene terephthalate water bottle to a voluntary subset of participants (total n = 180; n = 45 per sex per season) and requested them to drink water only from the bottle and refill the bottle when empty. The number of refills and the amount of water that remained were checked after 24 h to calculate daily water intake. The details and reliability of this method have been described elsewhere.¹⁶

Using the intake data, sex-specific and season-specific regression lines of the water intake on body weight were calculated, from which two season-specific water intakes were estimated for all participants (n = 539). Then, taking into

account the relative duration of the seasons, annually averaged daily water intake (DWI; per person) was calculated as

$$\text{DWI} = (3 \times (\text{water intake in winter})) + 9 \times (\text{water intake in summer}) / 12.$$

Finally, the daily arsenic intake (DAI) from drinking water (per unit body weight) was computed for each subject as (As_{tw} × DWI)/BW. Although contribution from potential arsenic sources other than water (for example, food) may not be negligible, arsenic concentration of water should be the primary determinant of total arsenic intake.¹⁶

Statistical analysis

Analysis of variance and χ^2 test were used appropriately. For these tests, SPSS V.10.0 statistical software was used. Significance was set at p < 0.05. The statistical difference in the prevalence was evaluated by Poisson distribution and 95% confidence intervals (CI), using CI Analysis V.2.0.0 software.¹⁸ To adjust for the possible confounding effects of age, the prevalence was also analysed by the nominal logistic regression model using JMP software (v.6.0, SAS Institute). In this model, sex, BMI (categorised as 1 for BMI <18.5, others as 0) and age (categorised into five groups: <20, 20–29, 30–39, 40–49, ≥50 years) were included as independent variables.

RESULTS

Arsenic exposure indices

A summary of the arsenic exposure indices has been reported elsewhere.⁹ Briefly, the mean (SD) As_{tw} value was 403 (229) (range 3–1072) µg/l; 97.9% and 87.6% of the tubewells exceeded the WHO and Nepal Interim Standard (NIS) limits (10 and 50 µg/l, respectively) and >30% exceeded 500 µg/l. The mean As_u values were 744 (411) (range 33–1763) and 937 (565) (range 16–2746) µg/g creatinine for men and women, respectively. As_u significantly and positively correlated with As_{tw} both in men (r = 0.74, p < 0.001) and women (r = 0.69, p < 0.001), and As_u values of husbands were significantly correlated with those of wives (p < 0.001; data not shown), suggesting that the main source of arsenic intake was related to the household, presumably tubewell water. In this area, household members rarely used tubewells of other households.

Estimation of arsenic intake from water

For men and women, the means of DWI were 67 (7) and 63 (10) ml/kg/day, respectively, and those of DAI were 31 (17) and 27 (17) µg/kg body weight/day, respectively. Both indices showed a significant sex difference. The DAI far exceeded the provisional tolerable daily intake of 2.1 µg/kg body weight/day (Food and Agriculture Organization/WHO, 1989). The DAI and the As_u were significantly and positively correlated in both sexes (fig 1).

Nutritional status of the participants

Of the 539 participants, approximately half (44% of men and 56% of women) were categorised as underweight (see Materials and methods section for definition). A few overweight (3% of both sexes) and no obese participants were found. The distribution of participants by BMI categories was significantly different between the sexes (χ^2 test; p < 0.05), reflecting the higher prevalence of underweight among women. For further analyses, the participants were dichotomised into underweight and normal (including overweight) groups (table 1).

Underweight men had significantly higher As_{tw} (and As_u) than normal weight men, whereas such a difference was not found among women. In both sexes, the underweight groups had significantly higher DAI than the normal groups. In

Figure 1 Relationship between daily arsenic intake (DAI) from drinking water (abscissa) and urinary arsenic (As_u , ordinate) concentration plotted for 106 married couples. DAI was calculated as the product of water consumption and arsenic concentration of tubewell water. The As_u was adjusted for creatinine (cre; see text). Each dot represents an individual: open circle, husband; closed circle, wife. Regression lines were significant for men ($y = 0.66x + 1.86$, $R^2 = 0.62$) and for women ($y = 0.77x + 1.83$, $R^2 = 0.71$). Note that both variables were converted into logarithm for visual clarity. BW, body weight.

addition, there was a minor but significant age difference in the male groups. The youngest (<20 years) and oldest (>49 years) groups had significantly lower BMIs than other age categories for both sexes.

Effect of nutritional status on arsenic toxicity

The prevalence of arsenicosis among participants was 15% (83/539), being higher in men (23%; 57/248) than in women (9%; 26/291). The prevalence significantly increased with increasing exposure (table 2, upper).

Table 3 shows the effects of nutritional status (BMI) on the prevalence rates for each exposure level. In both sexes, the prevalence ratios were consistently larger than unity (>1) in the middle and higher tertiles, and significant differences were found in the middle tertile groups. The lower tertile groups of either sex did not show an increased prevalence in the underweight group. No significant difference in prevalence among the age categories was found for either sex, although those aged <30 years tended to show lower prevalence. With (nominal) logistic regression analyses on the three exposure level groups, significant regression was achieved only in the mid-tertile ($\chi^2 = 24.4$, $p < 0.001$) and high-tertile groups ($\chi^2 = 14.9$, $p < 0.05$). In the mid-tertile group, the effects of BMI ($p = 0.023$) and sex ($p < 0.001$) were significant, whereas age was not. In the high-tertile group, only the effect of sex ($p = 0.002$) was significant. Thus, the significant effect of nutritional status on prevalence in the mid-tertile groups, as shown in table 3, remained after adjusting for age.

Effect of arsenic exposure on nutritional status

Figure 2 shows that the DAI and BMI were significantly and inversely correlated ($p < 0.001$ for either sex). Significant inverse correlations were also found between As_{tw} and BMI ($r = -0.24$) or between As_u and BMI ($r = -0.29$) in men ($n = 106$) but not in women ($n = 106$). Both in men and in women, an approximately 30% increment in the prevalence of underweight was observed between the high-exposure tertile and the low tertile (table 1, lower).

DISCUSSION

This study examined the mutual interaction between nutritional status and arsenic toxicity in a rural, lowland Nepal population. The high prevalence of skin manifestation (15%) and malnutrition ("underweight"; 50%) in the surveyed population made such analyses of interaction meaningful. The prevalence of skin manifestation was lower in our previous report (7%), which included a younger subpopulation (<15 years) with negligible prevalence (<1%).⁹

The prevalence of malnutrition was in line with previous nationwide surveys exclusively examining women.^{19, 20}

Our results showed that arsenicosis (skin symptoms) was more prevalent among those with lower BMI (low nutritional status) at similar exposure levels and, additionally, that arsenic exposure was associated with a decrease in BMI. This may be the first demonstration of dose-dependent suppression of BMI in a human population chronically exposed to arsenic, although a causal relationship cannot be established because of the cross-sectional nature of this study. Compared with a few preceding studies dealing with the interaction between nutrition and arsenic toxicity in human populations, this study describes the interaction in a well-defined and apparently homogeneous population in a quantitative manner. In the following text, we discuss the significance of malnutrition as a toxic manifestation of arsenic and its relationship with toxicity.

Although body weight reduction by high and acute exposure to arsenic, presumably a non-specific effect, has been reported,²¹ the effect of chronic exposure to arsenic on underweight/BMI has been scarcely reported. Intrapopulation variations in the factors that can influence BMI, such as dietary intake, physical activity, and socioeconomic status including education, should be minimal, because the three communities were closely located, sharing similar environment and lifestyle (see also Sudo *et al*²²). Thus, our results suggest that the lowered BMI could be a toxic manifestation of chronic exposure to arsenic at relatively high exposure levels—that is, at the mean DAI, 30 $\mu\text{g/kg/day}$ for both sexes, 15 times higher than the provisional tolerable daily intake set by WHO/Food and Agriculture Organization.

What is the practical importance of reduced BMI by arsenic? Firstly, in our population, exposure to arsenic substantially (a

Table 1 Anthropometry and exposure to arsenic in the participants as classified by nutritional status

Nutritional status*	n	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)	As_{tw} ($\mu\text{g/l}$)	As_u ($\mu\text{g/g}$ creatinine)	DAI ($\mu\text{g/kg BW/day}$)
Men								
Underweight	110	38.8 (17.4)	45.0 (4.8)	162.0 (6.7)	17.1 (1.1)	494 (240)	877 (379)	36.0 (17.6)
Normal	138	34.4 (11.8)	55.2 (7.0)	162.7 (5.3)	20.8 (2.1)	412 (231)	649 (409)	26.3 (15.2)
p Value		*	***		***	**	**	***
Women								
Underweight	162	37.7 (17.0)	37.4 (4.1)	150.1 (5.4)	16.5 (1.4)	443 (250)	981 (550)	30.7 (17.6)
Normal	129	34.3 (12.1)	47.1 (6.1)	150.4 (5.6)	20.8 (2.2)	406 (242)	889 (581)	22.6 (14.2)
p Value			***		***			***

As_{tw} , arsenic concentration in the tubewell (drinking) water; As_u , arsenic concentration in urine ([adjusted for creatinine]); BMI, body mass index; DAI, daily arsenic intake from drinking water, estimated as the product of daily water consumption and As_{tw} .

*Nutritional status was defined by the BMI. "Underweight": BMI < 18.5; others including "overweight" were categorised as "normal".

Difference between normal and underweight. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ by Student's *t* test.

Table 2 Prevalence of arsenicosis and underweight at different arsenic exposure levels

	Arsenic exposure level* ($\mu\text{g/kg}$ body weight/day)			Overall	χ^2
	Lower	Middle	Higher		
	(0.3–21.6)	(21.7–36.4)	(36.4–92.9)		
Arsenicosis					
Men	2/70† (3%)	22/82 (27%)	33/96 (34%)	57/248 (23%)	23.74***‡
Women	5/110 (5%)	8/97 (8%)	13/84 (16%)	26/291 (9%)	7.08**
Total	7/180 (4%)	30/179 (17%)	46/180 (26%)	83/539 (15%)	
Underweight					
Men	19/70§ (27%)	35/82 (43%)	56/96 (58%)	110/248 (44%)	16.10***‡
Women	45/110 (41%)	54/97 (56%)	63/84 (75%)	162/291 (56%)	22.43***
Total	64/180 (35%)	89/179 (50%)	119/180 (66%)	272/539 (50%)	—

*Defined by the tertiles of the daily arsenic intake (DAI) (see text and the footnote to table 1). Range of the DAI for each tertile is shown in parentheses.

†Number of people with underweight body mass index (BMI < 18.5)/number of people examined.

‡Testing for the difference of prevalence among the different exposure level. χ^2 values are followed by significance (**p < 0.05, ***p < 0.001).

§Number of people diagnosed as arsenicosis/number of people examined.

1.9 and 1.4 times higher prevalence was observed in high and middle exposure tertiles than in the lowest tertile) exaggerated the malnutrition, a serious public health problem in such an area. Secondly, although the increase in the prevalence of skin symptoms by arsenic dose seems to be much larger in men than in women, the increments of underweight were similar in both sexes (table 2). Whether such endpoint dependence is associated with the possible existence of different “receptors” for different end points or is merely reflecting the inherent nature (sex difference) of different symptoms should be important in understanding the toxicology of arsenic. In this connection, it should be noted that either a biochemical or a behavioural explanation might be possible for the decrease in BMI. Arsenic can affect insulin-related sugar metabolism²³ or disturb glucocorticoid function,^{24–25} both of which might compromise the energy metabolism. Alternatively, systemic disease status caused by exposure to arsenic^{26–28} may lead to malnutrition (loss of body weight) through reduced food consumption.

Table 3 Effects of arsenic intake level and nutritional status on the prevalence of arsenicosis

Nutritional status†	Arsenic exposure level* ($\mu\text{g/kg}$ body weight/day)		
	Lower (0.3–21.6)	Middle (21.7–36.4)	Higher (36.4–92.9)
Men			
Total	2/70‡	22/82	33/96
Normal	2/51	9/47	12/40
Underweight	0/19	13/35	21/56
Prevalence ratio§	0.00	1.94	1.25
95% CI	0.00 to 4.92	1.03 to 3.32	0.77 to 1.91
Women			
Total	5/110	8/97	13/84
Normal	4/65	2/43	2/21
Underweight	1/45	6/54	11/63
Prevalence ratio	0.36	2.39	1.83
95% CI	0.01 to 2.01	0.88 to 5.20	0.92 to 3.28

*Defined by the tertiles of the daily arsenic intake (DAI, see text and the footnote to table 1). Range of the DAI for each tertile is shown in parentheses.

†Nutritional status was defined by body mass index (BMI; “underweight” BMI < 18.5; others, including “overweight”, were categorised as “normal”).

‡Number of people diagnosed as arsenicosis/number of people examined.

§Prevalence ratio = (prevalence in “underweight” group)/(prevalence in “normal” group). Italics signify that the prevalence ratio is significantly increased from 1.

On the other hand, skin symptoms of arsenic toxicity were more frequently observed among individuals with a lower BMI. This is in line with two other large-scale studies: one in West Bengal⁶ and another recent one in Bangladesh.²⁹

As BMI and prevalence of skin symptoms showed negative and positive correlations with exposure to arsenic, respectively, it is naturally expected that BMI and prevalence would be negatively correlated. If this is the case, it is expected that the higher the dose, the greater the prevalence ratio (table 2). In fact, the highest prevalence ratios were consistently obtained in the middle exposure tertiles rather than in the higher tertile groups of either sex (although not significant in women). Although this observation should be confirmed with much larger samples, it may be compatible with the view that poor nutritional status shifts the dose–response curve (between arsenic and skin lesions) to the left; if such a leftward shift occurs, the effect should be most evident at the middle range of the ordinal (sigmoid) dose–response curve (see fig 3). With higher dose, the effect of nutrition would be overwhelmed by the toxic effect of arsenic per se. In the West Bengal study,⁶ the effect of malnutrition was observed at their highest dose range, which was similar to that of our middle tertile group. Mitra *et al*⁵ found susceptibility to arsenic was enhanced at relatively low exposure levels (As_{TW} < 500 $\mu\text{g/l}$), by

Figure 2 Relationship between daily arsenic intake (DAI, abscissa) and body mass index (BMI, ordinate) as an index of nutritional status. For the calculation of DAI, refer to fig 1 or text. Each dot represents an individual: open circle, = men; closed circle, = women. The negative regression lines are significant for both men ($y = -0.043x + 20.5$, $r = -0.29$, $n = 248$) and women ($y = -0.050x + 19.8$, $r = -0.30$, $n = 291$).

Figure 3 Schematic representation of the modification of arsenic toxicity by malnutrition. The hypothetical dose-response curve is shifted towards the left in the presence of malnutrition. Such an effect would be observed as the difference in the prevalence of the malnourished group and the normally nourished group (as indicated by the vertical arrows), which would be detected only at a certain (middle) portion of the dose range.

reduced intake of some nutrients although they could not detect any effect of energy intake. Assuming that the water consumption of Mitra's study participants was similar to our participants (approximately 65 ml/kgBW/day), the arsenic intake would be estimated as $<32.5 \mu\text{g/kgBW/day}$, which again coincides with our middle (and lower) exposure tertile. In the recent Bangladesh study,²⁹ the highest exposure group had a median As_{tw} of 255 (ranging from 175 to 864) $\mu\text{g/l}$, which also coincides with our middle exposure tertile. Taken together, there might be an arsenic exposure level at which nutritional status (either energy or specific nutrients) affects the toxic manifestation of arsenic. The prevalence of underweight was higher among those exhibiting skin symptoms than those not exhibiting them, and the prevalence ratio, as similar to table 3, was highest for the middle exposure tertile (data not shown).

The responsible nutrients and their mechanisms for toxicity modification need to be elucidated with further studies. The deficiency of several nutrients such as calcium, animal protein, folate and fibre (but not total energy) might increase the risk of skin lesions.⁵ Earlier experimental studies suggest that poor nutrition results in decreased methylation of arsenic owing to decreased supply of the methylation substrate, eventually leading to enhanced arsenic toxicity.³⁰ This is supported by a recent human study showing that a low dietary intake of protein, iron, zinc or niacin was associated with enhanced accumulation of monomethylarsonic acid in a US population,³¹ although the exposure level was much lower than those found in south Asian countries, including the present one.

In summary, our data showed that BMI reduction was also a quantitative end point of chronic arsenic toxicity, which was essentially devoid of the sex difference that was consistently observed in skin symptoms. The mutual interaction between poor nutrition and arsenic toxicity might create a vicious cycle between nutrition and toxicity, in which arsenic toxicity exaggerates malnutrition and malnutrition in turn exaggerates toxicity. Thus, such a cycle should be interrupted to alleviate the arsenic toxicity and to reduce the prevalence of malnutrition, which would be one of the most concerned public health problems in the rural communities of developing countries. Elucidation of the mechanisms responsible for the interaction might lead to a design of nutritional intervention to alleviate the effects of arsenic.

ACKNOWLEDGEMENTS

We thank all the villagers of Terai for their hospitality and cooperation.

What this paper adds

- Chronic exposure to arsenic due to contaminated groundwater has been mostly found in developing countries, where malnutrition often coexists. Although malnutrition has been considered a modifying factor for arsenic toxicity, quantitative information is very limited. This study was conducted to show the inter-relationship between nutritional status and arsenic toxicity.
- Our data suggests that environmental exposure to arsenic raises the prevalence of underweight, a serious health problem in developing countries, while at the same time, poor nutritional status aggravates the skin manifestation of arsenic. Mutual aggravation of the adverse health effects implied by these results should be interrupted to reduce health risks from exposure to arsenic and from malnutrition.

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Competing interests: None.

Funding: This study was financially supported by the Alliance for Global Sustainability Program and the Ministry of Education, Culture, Sports, Science and Technology in Japan.

REFERENCES

- 1 **National Research Council**. *Arsenic in drinking water*. Washington, DC: Academic Press, 1999.
- 2 **National Research Council**. *Arsenic in drinking water: 2001 update*. Washington, DC: National Academic Press, 2001.
- 3 **Smith AH**, Smith MMH. Arsenic drinking water regulations in developing countries with extensive exposure. *Toxicology* 2004;**198**:39–44.
- 4 **Milton AH**, Hasan Z, Shahidullah SM, et al. Association between nutritional status and arsenicosis due to chronic arsenic exposure in Bangladesh. *Int J Environ Health Res* 2004;**14**:99–108.
- 5 **Mitra SR**, Guha Mazumder DN, Basu A, et al. Nutritional factors and susceptibility to arsenic-caused skin lesions in West Bengal, India. *Environ Health Perspect* 2004;**112**:1104–9.
- 6 **Guha Mazumder DN**, Haque R, Ghosh N, et al. Arsenic levels in drinking water and the prevalence of skin lesions in West Bengal, India. *Int J Epidemiol* 1998;**27**:871–7.
- 7 **Chen CJ**, Wu MM, Lee SS, et al. Atherogenicity and carcinogenicity of high-arsenic artesian well water: multiple risk factors and related malignant neoplasms of blackfoot disease. *Arteriosclerosis* 1988;**8**:452–60.
- 8 **Smith AH**, Arroyo AP, Guha Mazumder DN, et al. Arsenic-induced skin lesions among Atacameno people in Northern Chile despite good nutrition and centuries of exposure. *Environ Health Perspect* 2000;**108**:617–20.
- 9 **Maharjan M**, Watanabe C, Ahmad A, et al. Arsenic contamination in drinking water and skin manifestations in lowland Nepal: the first community-based survey. *Am J Trop Med Hyg* 2005;**73**:477–9.
- 10 **Watanabe C**, Inaoka T, Kadono T, et al. Males in rural Bangladeshi communities are more susceptible to chronic arsenic poisoning than females: analyses based on urinary arsenic. *Environ Health Perspect* 2001;**109**:1265–70.
- 11 **Ahmad SA**, Sayed MHSU, Hadi SA, et al. Arsenicosis in a village in Bangladesh. *Int J Environ Health Res* 1999;**9**:187–95.
- 12 **Tondel M**, Rahman M, Magnusson A, et al. The relationship of arsenic levels in drinking water and the prevalence rate of skin lesions in Bangladesh. *Environ Health Perspect* 1999;**107**:727–9.
- 13 **Ahmad SA**, Maharjan M, Watanabe C, et al. Arsenicosis in two villages in Terai, lowland Nepal. *Environ Sci* 2004;**11**:179–88.
- 14 **Weiner JS**, Lourie JA. *Physical human biology*. London: Academic Press, 1981.
- 15 **World Health Organization**. *Physical status: the use and interpretation of anthropometry*, Technical Report Series Number 854. Geneva: WHO, 1995.
- 16 **Watanabe C**, Kawata A, Sudo N, et al. Water intake in an Asian population living in arsenic contaminated area. *Toxicol Appl Pharmacol* 2004;**198**:272–82.
- 17 **Bonsnes R**, Taussky H. On the colorimetric determination of creatinine by the Jaffe reaction. *J Biol Chem* 1945;**158**:581.

- 18 **Altman DG**, Machin D, Bryant TN, *et al*, eds. *Statistics with confidence*, 2nd edn. London: BMJ Books, 2000.
- 19 **Food**, Agriculture Organization (FAO). *Nutrition country profile–Nepal*. Rome: Food and Agriculture Organization, 1998.
- 20 **Ministry of Health**. *Family Health Survey, Nepal 1996*, Department of Health Services, New ERA and Demographic and Health Surveys. Kathmandu: Macro International, 1997.
- 21 **Hindmarsh JT**, Abernathy CO, Peters GR, *et al*. Environmental aspects of arsenic toxicity. In: Sarkar B, eds. *Heavy metals in the environment*, 1st edn. New York: Marcel Dekker, 2002:217–29.
- 22 **Sudo N**, Sekiyama M, Maharjan M, *et al*. Gender differences in dietary intake among adults of Hindu communities in lowland Nepal: assessment of portion sizes and food consumption frequencies. *Eur J Clin Nutr* 2006;**60**:469–77.
- 23 **Tseng CH**. The potential biological mechanisms of arsenic-induced diabetes mellitus. *Toxicol Appl Pharmacol* 2004;**197**:67–83.
- 24 **Kaltrreider RC**, Davis AM, Lariviere J, *et al*. Arsenic alters the function of the glucocorticoid receptor as a transcription factor. *Environ Health Perspect* 2001;**109**:245–51.
- 25 **Bodwell JE**, Kingsley LA, Hamilton JW. Arsenic at very low concentrations alters glucocorticoid receptor (GR)-mediated gene activation but not GR-mediated gene repression: complex dose–response effects are closely correlated with levels of activated GR and require a functional GR DNA binding domain. *Chem Res Toxicol* 2004;**17**:1064–76.
- 26 **Zierold KM**, Knobelock L, Anderson H. Prevalence of chronic diseases in adults exposed to arsenic-contaminated drinking water. *Am J Publ Health* 2004;**94**:1936–7.
- 27 **Guha Mazumder DN**, Haque R, Ghosh N, *et al*. Arsenic in drinking water and the prevalence of respiratory effects in West Bengal, India. *Intl J Epidemiol* 2000;**29**:1047–52.
- 28 **Yoshida T**, Yamauchi H, Sum GF. Chronic health effects in people exposed to arsenic via the drinking water: dose–response relationship in review. *Toxicol Appl Pharmacol* 2004;**198**:243–52.
- 29 **Ahsan H**, Chen Y, Parvez F, *et al*. Arsenic exposure from drinking water and risk of premalignant skin lesions in Bangladesh: baseline results from the health effects of arsenic longitudinal study. *Am J Epidemiol*. 2006; 163:1138–48).
- 30 **Agency for Toxic Substances and Disease Registry**. *Toxicological profile for arsenic*. Atlanta, GA: ATSDR, US Department of Health and Human Services, Public Health Services, 2000.
- 31 **Steinmaus C**, Carrigan K, Kalman D, *et al*. Dietary intake and arsenic methylation in a US population. *Environ Health Perspect* 2005;**113**:1153–9.

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