Intraindividual Variability in Arsenic Methylation in a U.S. Population

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Abstract

Several recent investigations have reported associations between a reduced capacity to fully methylate inorganic arsenic and increased susceptibility to arsenic-caused cancer. In these studies, methylation patterns were based on a single assessment of urinary arsenic metabolites collected at the time of cancer diagnosis. However, the latency of arsenic-caused cancer may be several decades, and the extent to which a recent measurement can be used to estimate a person’s past methylation pattern is unknown. In this investigation, the distribution of urinary inorganic arsenic, monomethylarsonate, and dimethylarsinate was used to assess intraindividual variation in methylation capacity in 81 subjects with low to moderate arsenic exposures. Multiple urine samples were collected from each subject over a 1-year period. Duplicate analyses done on 27 samples were used to assess laboratory measurement imprecision. The intraclass correlation coefficients (ICC) for the proportion of urinary arsenic as inorganic arsenic, monomethylarsionate, and dimethylarsinate in samples taken an average of 258 days apart, were 0.45 [95% confidence interval (95% CI), 0.23-0.63] 0.46 (95% CI, 0.24-0.64), and 0.49 (95% CI, 0.28-0.66). In analyses of duplicate samples, ICCs for the concentration of arsenic species ranged from 0.87 to 0.93, whereas ICCs for species proportions ranged from 0.67 to 0.76. These data suggest that individual methylation patterns remain fairly stable over time, although variability due to measurement imprecision or intraindividual changes over time does occur. This variability could lead to misclassification of methylation patterns and could bias relative risk estimates in studies of methylation and cancer towards the null. (Cancer Epidemiol Biomarkers Prev 2005;14(4):919–24)

Introduction

Inorganic arsenic occurs naturally in the groundwater of many parts of the world, and millions of people worldwide are exposed to drinking water containing this known carcinogen (1-9). Ingested arsenic causes cancers of the skin, bladder, and lung and has been associated with cancers of other organs (10-13). The estimated risks associated with these exposures may be quite high. According to a subcommittee of the National Research Council, the cancer risks associated with lifetime exposures at the past U.S. standard of 50 μg/L may be as high as 1 in 100 (10, 11).

The primary metabolic pathway of ingested inorganic arsenic in humans involves a two-step methylation process (14-16). In the first step, ingested inorganic arsenic is methylated to monomethylarsonic acid (MMA3), which is reduced to monomethylarsonous acid (MMA3). In the second step, MMA3 is methylated to form dimethylarsinic acid (DMA5) which is reduced to form dimethylarsinous acid (DMA3). In humans, this process is not complete, and some arsenic remains as either inorganic arsenic or monomethylarsonate. Typically, ingested inorganic arsenic is excreted as 10% to 20% inorganic arsenic, 10% to 15% monomethylarsonate, and 60% to 75% dimethylarsinate (17). However, large interindividual variations exist (18). For example, in a study in Chile, the proportion of urinary monomethylarsonate (%MMA) in individuals ranged from 1.7% to 30.6%, a roughly 18-fold difference (19, 20).

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of arsenic methylation and cancer. This information may also be helpful in identifying the factors that control arsenic methylation. That is, if within-person arsenic methylation patterns are stable over time, this would suggest that genetics or stable environmental factors exert a predominant effect on arsenic metabolism. However, if arsenic methylation patterns are found to change dramatically over time, this would suggest that those environmental factors that change from day to day may have an important role in this process.

The primary excretory pathway of ingested arsenic is through urination, and the relative distribution of arsenic metabolites in urine is commonly used as a biomarker of arsenic methylation patterns (10). In this study, arsenic metabolic products were measured in multiple urine samples collected over a period of ~1 year from 81 individuals. This investigation is the largest published study of arsenic methylation in a U.S. population to date and the first to quantify long-term intraindividual variability in methylation patterns.

Materials and Methods

Subjects. Subjects were residents of six counties in western Nevada and Kings County in California. These areas contain the cities of Hanford, California and Fallon, Nevada, the largest populations in the United States with historically high water arsenic levels (40). Recently, an arsenic treatment plant has been installed in Fallon to meet the new U.S. arsenic standard of 10 μg/L. Before this, arsenic concentrations in the public water supplies in Fallon were about 90 to 100 μg/L. Arsenic concentrations in public water supplies in Hanford were near 100 μg/L in the past but have decreased over the last 10 years due to the development of new low arsenic wells. Most other cities in the study area have public water supplies with arsenic levels below 20 μg/L. Approximately 20% of the study area residents obtain water from private wells. The majority of private wells that have been measured contain <10 μg/L of arsenic, although some wells near the cities of Fallon and Hanford contain arsenic at levels over 100 μg/L, with a few wells over 1,000 μg/L.

Study subjects were recruited from the participants of a case-control study of bladder cancer and arsenic exposure (40). Subjects with bladder cancer were obtained from the Nevada Central Cancer Registry, the Cancer Registry of Central California, and local hospitals and physicians. Control subjects were selected through random digit dialing and from randomly selected lists provided by the Health Care Financing Administration. Further details on the selection of subjects for the case-control study is described elsewhere (40). All participants who had lived in the cities of Fallon or Hanford or the nearby surrounding areas for at least the last 1 year before recruitment were invited to participate in the methylation study.

Data Collection. Two to three urine samples were collected from each participant. To assess both short-term and long-term variability, the second (sample 2) and third samples (sample 3) were collected ~2 weeks and 8 to 10 months, respectively, after the first sample (sample 1). Subjects were provided screw top polypropylene containers and asked to give a midstream sample of the first morning void. The subjects were asked to then place the sealed container on ice until it could be collected by a licensed medical assistant that morning. A previous study has shown strong correlations in arsenic excretion between single first morning samples and samples collected over 24 hours (41). The time from void to the time of collection by the medical assistant ranged from 1 to 3 hours. Upon collection, samples were frozen by placing them on dry ice. They were then transported to the field laboratory each day where they were kept frozen at ~20°C. It has been shown that urinary arsenic metabolite levels remain stable for several months with refrigeration or freezing (42). Because all samples were refrigerated and frozen soon after collection, variations in arsenic measurements due to differences in the collection process are expected to be small. Socioeconomic variables and lifestyle characteristics were collected using a standard study questionnaire. Urine samples were transported overnight on dry ice to the University of Washington, Seattle for analysis. Urine samples and results were identified only by a code number. This study was approved by the University of California, Berkeley Committee for Protection of Human Subjects.

Laboratory Methods. The urinary concentrations were measured using hydride generation atomic absorption spectrometry (43). Briefly, inorganic arsenic (As3 and As5), monomethylarsonate, and dimethylarsinate were reduced to the corresponding arsine in a batch reactor using sodium borohydride in 5-mL samples. The volatile reduction products (arsine, methyl arsine, and dimethylarsine) were removed by sparging with helium. Entrained arsines were concentrated in a chromosorb-filled cryogenic trap in liquid nitrogen temperatures until all arsines forming arsenic in the sample had reacted. The cryotraps were then allowed to warm, and the collected arsines were separated based on differential volatilization. The detection of the separated volatile arsenic species was done using atomic absorption spectrometry using a hydrogen microburner combustion cell to convert arsines to elemental arsenic. To prevent interference by certain compounds (44), each urine sample was acidified with 2 mol/L HCl and allowed to sit for at least 4 hours. Total arsenic was determined by flow injection analysis/atomic fluorescence spectrometry, and this result was compared with the sum of the species detected. If a significant amount of arsenic remained undetected, additional digestion or assay for arselenobetaine was done. Detection limits for inorganic arsenic, monomethylarsonate, and dimethylarsine were 0.5, 1.0, and 2.0 μg/L, respectively. Concentrations below the detection limit were set at one half the detection limit.

Analyses were done throughout the study period in nine separate batches. To maintain consistency from batch to batch, system blanks were run twice per batch and periodic reanalysis and routine recalibration using a standard reference were done after every 5 to 7 samples, 61 times altogether. Because standard urine containing known amounts of arsenic was not available at the time of this study, aqueous standards were prepared using primary standard materials. Standards contained 15 ng/mL of inorganic arsenic, 15 ng/mL of monomethylarsonate, and 70 ng/mL of dimethylarsinate. The average percent difference from the known standard concentrations were 0.01% for inorganic arsenic, 0.001% for monomethylarsonate, and 0.01% for dimethylarsinate. The coefficients of variation in inorganic arsenic, monomethylarsonate, and dimethylarsinate for the standards throughout the course of the study were 6.5%, 6.8%, and 4.9%.

The monomethylarsonate and dimethylarsinate measured in this study were in the pentavalent forms. The trivalent forms, MMA3 and DMA3, are rapidly oxidized to MMA5 and DMA5 during storage (45). Most samples in this study were frozen for 2 to 6 weeks before analysis. We analyzed a subsample of urine specimens for MMA3 and DMA3 but found no MMA3 and only trace amounts of DMA3.

Statistical Analysis. The relative proportion of each arsenic species [percent inorganic arsenic (%InAs), percent monomethylarsonate (%MMA), and percent dimethylarsinate (%DMA)] was calculated by dividing the concentration of each species by the total arsenic concentration (Tot-As), defined as the sum of inorganic arsenic, monomethylarsonate, and dimethylarsinate. The association of each arsenic species with variables such as age, gender, and smoking history were first assessed using univariate analyses. Student’s t test and the Wilcoxon rank sum test were used to compare category means. ANOVA and
Duncan’s multiple range test was used when three or more means were compared. Separate analyses were done in which the concentrations of arsenic species were adjusted by dividing them (µg/L) by the urine creatinine levels (g/L).

Correlation coefficients were used to assess the intraindividual variability in the concentration and relative proportion of each arsenic species and in the monomethylarsonate/dimethylarsinate ratio. This was done by calculating correlation coefficients between individual results from samples 1 to 2 (short-term variability) and from samples 1 to 3 (longer-term variability). Pearson correlation coefficients were used when variables were approximately normally distributed (%InAs, %MMA, %DMA, and monomethylarsonate/dimethylarsinate); otherwise, Spearman correlation coefficients were used (inorganic arsenic, monomethylarsonate, dimethylarsinate, and Tot-As). Intraclass correlation coefficients (ICC) were calculated for the proportion of each arsenic species and the monomethylarsonate/dimethylarsinate ratio (46). Because the concentrations of the arsenic species were not normally distributed, the logarithms of the concentrations were used for ICC calculations. Initially, all analyses were done separately for cases and controls. However, because no differences between these groups were seen in intraindividual variability, cases and controls were combined for the correlation coefficients presented in this report. To assess variability related to laboratory measurement precision, duplicate analyses were run on 27 randomly selected urine samples from this study (10% of all samples). The analyst was not blind to which samples were duplicates. Two measurements were taken from each sample. The ICCs and coefficients of variation for the concentration and proportion of each arsenic species were seen using results from samples 2 and 3. The relative proportions of inorganic arsenic, monomethylarsonate, and dimethylarsinate were 12.9%, 12.5%, and 74.5%, respectively. Females excreted a lower %InAs and %MMA and a higher %DMA than men. Current smokers excreted a higher %InAs and a lower %DMA than former and never smokers, although these differences were not statistically significant. Increasing age was associated with decreasing %InAs but no association was seen between age and %MMA, %DMA, or monomethylarsonate/dimethylarsinate ratio. The proportion of each arsenic species was similar between cases and controls. In addition, no significant association was seen between Tot-As and the proportion of arsenic species or monomethylarsonate/dimethylarsinate ratio.

Table 2 shows the mean concentrations and proportions of the arsenic species in each of the three samples. The average

### Table 1. Mean (SD) concentrations and proportions of arsenic species in the first urine sample collected from 81 subjects

<table>
<thead>
<tr>
<th></th>
<th>InAs (µg/L)</th>
<th>MMA (µg/L)</th>
<th>DMA (µg/L)</th>
<th>Tot-As (µg/L)</th>
<th>%InAs (%)</th>
<th>%MMA (%)</th>
<th>%DMA (%)</th>
<th>MMA/DMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.1 (3.4)</td>
<td>3.1 (3.5)</td>
<td>18.4 (17.7)</td>
<td>24.6 (24.0)</td>
<td>12.9 (6.4)</td>
<td>12.5 (4.5)</td>
<td>74.5 (8.4)</td>
<td>0.176 (0.084)</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td><strong>Men</strong></td>
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<td></td>
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<tr>
<td><strong>Women</strong></td>
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<td></td>
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<tr>
<td><strong>Age</strong></td>
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</tr>
<tr>
<td>&lt;65</td>
<td>18 (22.2)</td>
<td>3.2 (2.9)</td>
<td>3.3 (2.2)</td>
<td>17.6 (14.2)</td>
<td>22.5 (18.5)</td>
<td>10.3 (3.3)</td>
<td>10.6 (4.2)</td>
<td>0.138 (0.068)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>63 (77.8)</td>
<td>3.3 (3.7)</td>
<td>3.2 (2.8)</td>
<td>18.7 (18.7)</td>
<td>25.2 (25.4)</td>
<td>13.7 (6.8)</td>
<td>13.1 (4.5)</td>
<td>0.187 (0.086)</td>
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<tr>
<td><strong>Smoking</strong></td>
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<tr>
<td><strong>Never</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Former</strong></td>
<td>25 (30.9)</td>
<td>2.9 (3.9)</td>
<td>2.9 (3.3)</td>
<td>17.2 (17.3)</td>
<td>23.0 (24.1)</td>
<td>12.7 (5.6)</td>
<td>12.6 (4.0)</td>
<td>0.175 (0.075)</td>
</tr>
<tr>
<td><strong>Current</strong></td>
<td>15 (18.9)</td>
<td>4.1 (4.0)</td>
<td>4.2 (3.9)</td>
<td>23.6 (26.9)</td>
<td>13.3 (5.3)</td>
<td>13.7 (5.9)</td>
<td>73.0 (8.8)</td>
<td>0.195 (0.130)</td>
</tr>
<tr>
<td><strong>Bladder cancer</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td>23 (28.4)</td>
<td>3.0 (3.3)</td>
<td>3.4 (4.7)</td>
<td>17.3 (19.4)</td>
<td>23.6 (26.9)</td>
<td>13.3 (5.3)</td>
<td>13.7 (5.9)</td>
<td>73.0 (8.8)</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>58 (71.6)</td>
<td>3.1 (3.5)</td>
<td>3.0 (3.1)</td>
<td>18.9 (17.2)</td>
<td>25.0 (23.0)</td>
<td>12.7 (6.8)</td>
<td>12.1 (3.8)</td>
<td>75.1 (8.3)</td>
</tr>
<tr>
<td><strong>Tot-As, µg/L (tertiles)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8.5</td>
<td>27 (33.3)</td>
<td>0.7 (0.4)</td>
<td>0.7 (0.3)</td>
<td>4.2 (1.5)</td>
<td>5.7 (1.9)</td>
<td>13.2 (5.9)</td>
<td>13.2 (5.2)</td>
<td>73.5 (9.3)</td>
</tr>
<tr>
<td>8.5-25.0</td>
<td>27 (33.3)</td>
<td>2.2 (1.8)</td>
<td>1.8 (0.8)</td>
<td>11.3 (3.7)</td>
<td>15.3 (4.7)</td>
<td>14.1 (8.5)</td>
<td>12.0 (4.8)</td>
<td>73.8 (9.9)</td>
</tr>
<tr>
<td>&gt;25</td>
<td>27 (33.3)</td>
<td>6.3 (4.0)</td>
<td>6.7 (4.1)</td>
<td>39.8 (14.7)</td>
<td>52.4 (21.4)</td>
<td>11.3 (3.6)</td>
<td>12.5 (3.4)</td>
<td>76.2 (5.4)</td>
</tr>
</tbody>
</table>

NOTE: Abbreviations: InAs, inorganic arsenic; MMA, monomethylarsonate; DMA, dimethylarsinate.

*P for Wilcoxon rank sum test for comparisons of InAs, MMA, DMA, and Tot-As and Student’s t test for %InAs, %MMA, %DMA and MMA/DMA ratio; *Ps are two sided.

1. P for analysis of variance.

1. Spearman rank correlation coefficient for comparisons of InAs, MMA, DMA, and Tot-As; Pearson correlation coefficients for %InAs, %MMA, %DMA and MMA/DMA ratio.

1. Ps for Spearman and Pearson correlation coefficients.

Results

In total, 81 subjects provided at least two urine samples and 62 of these provided three samples. Table 1 shows the distribution of demographic and lifestyle variables among the study participants. Eighteen subjects were female (22.2%), 11 were current smokers (13.6%), 23 (28.4%) had a history of bladder cancer, and the average age was 68 years (range, 19-98 years).

Table 1 also shows the mean concentration and relative proportions of arsenic species and the results of the univariate analyses using the results from sample 1. Similar findings were seen using results from samples 2 and 3. The relative proportions of inorganic arsenic, monomethylarsonate, and dimethylarsinate were 12.9%, 12.5%, and 74.5%, respectively. Females excreted a lower %InAs and %MMA and a higher %DMA than men. Current smokers excreted a higher %InAs and a lower %DMA than former and never smokers, although these differences were not statistically significant. Increasing age was associated with decreasing %InAs but no association was seen between age and %MMA, %DMA, or monomethylarsonate/dimethylarsinate ratio. The proportion of each arsenic species was similar between cases and controls. In addition, no significant association was seen between Tot-As and the proportion of arsenic species or monomethylarsonate/dimethylarsinate ratio.

Table 2 shows the mean concentrations and proportions of the arsenic species in each of the three samples. The average
Table 2. Mean concentrations and proportions of arsenic species in each urine sample collected from each study subject

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sample 1 (n = 81)</th>
<th>Sample 2 (n = 81)</th>
<th>Sample 3 (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean² Mean¹ Range</td>
<td>Mean² Mean¹ Range</td>
<td>Mean² Mean¹ Range</td>
</tr>
<tr>
<td>Time (d)</td>
<td>NA</td>
<td>NA</td>
<td>13</td>
</tr>
<tr>
<td>InAs (µg/L)</td>
<td>3.1</td>
<td>1.8</td>
<td>3.4</td>
</tr>
<tr>
<td>MMA (µg/L)</td>
<td>3.1</td>
<td>1.8</td>
<td>3.4</td>
</tr>
<tr>
<td>DMA (µg/L)</td>
<td>18.4</td>
<td>11.5</td>
<td>21.3</td>
</tr>
<tr>
<td>Tot-As (µg/L)</td>
<td>24.6</td>
<td>15.7</td>
<td>28.6</td>
</tr>
<tr>
<td>Adjusted Tot-As³</td>
<td>40.2</td>
<td>18.2</td>
<td>31.3</td>
</tr>
<tr>
<td>%InAs</td>
<td>12.9</td>
<td>11.6</td>
<td>12.6</td>
</tr>
<tr>
<td>%MMA</td>
<td>12.5</td>
<td>11.7</td>
<td>13.6</td>
</tr>
<tr>
<td>%DMA</td>
<td>74.5</td>
<td>74.0</td>
<td>73.8</td>
</tr>
<tr>
<td>MMA/DMA</td>
<td>0.18</td>
<td>0.16</td>
<td>0.20</td>
</tr>
</tbody>
</table>

NOTE: Abbreviations: InAs, inorganic arsenic; MMA, monomethylarsenate; DMA, dimethylarsinate.

*Arithmetic mean.
¹ Geometric mean.
² No. days between samples 1 and 2 and between samples 1 and 3.
³ Total As in µg/L divided by creatinine concentration in mg/ml.

Table 3. Pearson correlation coefficients (R) and ICCs between the mean concentrations and proportions of arsenic species in urine samples taken from the same individuals at different points in time

<table>
<thead>
<tr>
<th>Measure</th>
<th>Samples 1-2</th>
<th>Samples 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R (95% CI)</td>
<td>ICC (95% CI)</td>
</tr>
<tr>
<td>%InAs</td>
<td>0.68 (0.54-0.78)</td>
<td>0.68 (0.54-0.78)</td>
</tr>
<tr>
<td>%MMA</td>
<td>0.48 (0.29-0.63)</td>
<td>0.45 (0.26-0.61)</td>
</tr>
<tr>
<td>%DMA</td>
<td>0.63 (0.47-0.75)</td>
<td>0.62 (0.47-0.74)</td>
</tr>
<tr>
<td>MMA/DMA</td>
<td>0.56 (0.38-0.69)</td>
<td>0.48 (0.30-0.63)</td>
</tr>
</tbody>
</table>

NOTE: Abbreviations: InAs, inorganic arsenic; MMA, monomethylarsenate; DMA, dimethylarsinate.

Discussion

Several studies have identified links between elevated levels of %MMA and increased risks of arsenic-associated cancer (33-38). These studies have used a single measure of urinary

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arsenic metabolites collected at the time of cancer diagnosis to classify subjects on methylation status. Because the latency of effects for arsenic-caused cancer may be several decades or more (39, 40), the ability of these studies to estimate true relative risk depends on the precision with which a recent measurement of methylation patterns reflects past methylation patterns. In this study, the ICCs for %MMA for samples taken from the same subjects at different points in time was 0.45. This level of correlation was seen both in samples taken ~2 weeks apart and in samples taken ~8 months apart. Because ICCs represent the proportion of the total variance due to between-subject variation, these findings indicate that slightly less than half of the total variance in methylation patterns we identified in this study is due to subject to subject variability. Other than this source of variability, the remaining sources of variance are likely within-person changes over time and imprecision in laboratory analyses. The relatively low ICC of 0.75 we identified for %MMA in our analysis of repeated measurements in duplicate samples suggests that laboratory imprecision made a substantial contribution to the total variance not due to between-subject variability. Based on the ratio of the within-subject mean sums of squares in the analysis of duplicate samples and the analyses of samples taken from the same subjects over time, we estimate that ~45% of the total within-subject variability seen in this study is due to laboratory imprecision. The laboratory precision for measuring monomethylarsonate in this study, in terms of coefficient of variation, is lower than those reported in other arsenic methylation studies. However, this seems related to our inclusion of many subjects with low urinary arsenic concentrations, much lower than those that have typically been used to calculate coefficients of variation in other studies. But, in our analysis confined to those duplicate samples with at least 2 μg/L of monomethylarsonate, the coefficients of variation were 6.2% for monomethylarsonate, 5.1% for %MMA, and 5.6% for Total-As, levels that are consistent with those reported in other studies (35, 38, 47, 48).

All currently published studies linking %MMA to increased cancer risks have involved mean urinary arsenic concentrations above the mean concentration seen in our study. However, in several studies, the urinary arsenic levels in some study subjects overlap with those measured in our investigation. For example, in the Chen et al. study, which reported increased risks of skin cancer in subjects with monomethylarsonate/dimethylarsinate ratios above 0.20, the mean urinary arsenic concentration was 43.0 μg/L of monomethylarsonate, the coefficients of variation were 6.2% for monomethylarsonate, 5.1% for %MMA, and 5.6% for Total-As, levels that are consistent with those reported in other studies (35, 38, 47, 48).

As a whole, these findings suggest that genetic influences play an important role in arsenic methylation. The trivalent form of monomethylarsonate was not measured as part of this study since it is rapidly oxidized to MMA5 in human urine. Although the pentavalent forms of monomethylarsonate and dimethylarsinate seem more readily excreted than inorganic arsenic, several studies have shown that MMA3 is more acutely toxic than dimethylarsinate or inorganic arsenic (25-32). Only a few studies have investigated the presence of MMA3 in nonchelated humans (43-48). In a study of six subjects from an arsenic-exposed region in Mexico, the proportion of urinary MMA3 was 0.9%, whereas the proportions of inorganic arsenic, MMA5, DMA3, and DMA5 were 23.5%, 18.5%, 8.8%, 48.2%, respectively (45). It is unknown whether the measurement of %MMA5 might serve as good surrogate for %MMA3. We used the raw data presented in the Del Razo et al. article to calculate a Pearson correlation coefficient between MMA3 and total monomethylarsionate (MMA3 + MMA5) of 0.48 (P = 0.33). Whereas this coefficient suggests that some correlation exists, this analysis was based on a relatively small number of subjects. In conclusion, the data presented here suggests that individual methylation patterns remain fairly stable over time. However, intraindividual changes in methylation over time and imprecision in laboratory measurement may result in some misclassification of current and past methylation patterns, and these sources of variability could result in some attenuation of true relative risk estimates in studies of methylation patterns and cancer. Future work on the effect of methylation patterns on chronic health effects in populations with low arsenic exposures may benefit from the use of highly precise laboratory measurement techniques. Additional research on
the association between methylation and chronic health effects and further information on the factors that control arsenic methylation may help identify susceptible subpopulations who need additional regulatory protection. Future studies on the specific metabolites of inorganic arsenic, including MMA₃, could add important insights into the carcinogenic mechanisms of this common drinking water contaminant.

References


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