The adverse health effects of exposure to high arsenic levels, including a deterioration of skin on the hands (Dibner 1958), were recognized as early as 1556. The effects of exposure to As were reported four centuries later by Hutchison, who described skin cancer lesions in patients treated with arsenical-based compounds (Hunter 1957).

Subsequently, inhalation of inorganic As was found to produce lung cancer [International Agency for Research on Cancer (IARC) 1980], and studies in the 20th century have shown increased risks of skin, liver, lung, bladder, and kidney cancers in Taiwanese, Mexican, Indian, German, Argentinean, and Chilean populations [Agency for Toxic Substances and Disease Registry (ATSDR) 1989; Bergoglio 1964; Biagini et al. 1978; Cebrian et al. 1983; Chakraborty and Saha 1987; Chen et al. 1985, 1986, 1988a, 1994; Chen and Wang 1990; Chiang et al. 1988; Dang et al. 1983; U.S. Environmental Protection Agency (EPA) 1988; Science Applications International Corporation (SAIC) 1987; Tseng et al. 1968; Tsuda et al. 1990; Wu et al. 1989; Yamauchi and Yamamura 1983; Zaldivar 1974; Zaldivar et al. 1981] and skin lesions in Bangladesh subjects (Rahman and Axelson 2001; Yu et al. 2003) who ingested As-contaminated drinking water.

The occurrence of total As in drinking water and in food has been reported (Branch et al. 1994; Hwang and Jiang 1994; SAIC 1987; Thomas and Sniatecki 1995). Both organic and inorganic forms of As are present in varying amounts. Fish and shellfish contain relatively high concentrations of total As, with levels reaching into the parts per million range. However, most of the As is in the organic form as arsenobetaine (AsB) (Velez et al. 1995).

Drinking water surveys have reported that most major supplies contain < 5 ppb of total As, but levels > 50 ppb do occur in some areas of the United States (SAIC 1987). Inorganic As can be present in drinking water as either arsenate [As(V)] or arsenite [As(III)].

Total As has been reported in soil and house dust at 0.2–40 ppm and 0.2–400 ppm, respectively (Fernando et al., unpublished data). Because urban air levels for As occur at about 20 ng/m³, inhalation is not considered a significant route of environmental exposure (IARC 1980).

Of the three possible routes of exposure (inhalation, ingestion, and dermal) to As, ingestion is potentially the greatest contributor to exposure, with drinking water and food the two primary ingestion pathways. However, there is a paucity of population-based exposure data that describes the total ingestion (also referred to as intake) of the different forms of As from the combination of drinking water and food. The extent of population exposure occurring from a combination of these pathways is not well understood. Understanding such relationships may improve future exposure and risk assessments for As.

Based on the current knowledge of As levels in the environment, the primary exposure to As is potentially through ingestion; however, a probability-based exposure distribution of arsenical species from ingesting drinking water and food has not been previously reported for the population in the Great Lakes (USA) area. Both pathways are the focus of this study. In this article we report the contribution of total As and its species from dietary sources to exposure of a general population.
Methods

Study design and populations for collected U.S. EPA Region 5 and Children's Study samples. The NHEXAS conducted in R5 and the Minnesota Children’s Pesticide Exposure Study (CS), a module of the NHEXAS that focused on children 3–12 years of age, are probability-based surveys of noninstitutionalized persons that provided multimedia environmental concentration data, exposure data, and biomarker data. The R5 study was conducted in 1995–1996 and involved the monitoring of approximately 250 participants residing in the six states surrounding the Great Lakes. The CS, conducted in the summer of 1997, involved similar monitoring for 102 children living in Minneapolis/St. Paul, Minnesota, and in two rural Minnesota counties. These NHEXAS studies have been described in previous papers, including papers on design and measurement issues (Pellizzari et al. 1995; Quackenboss et al. 2000) and on survey design, weighting, and response rates (Whitmore et al. 1999).

Samples collected for arsenic analysis. Table 1 lists the samples available from the studies and the data derived from these samples for total As and its forms.

Food samples. Four-day composite food samples collected from 1995 to 1997 in R5 and in 1997 in the CS were extracted and analyzed for total and As species (Table 1). Sample collection methods have been previously described (Pellizzari et al. 1995; Thomas et al. 1999). The samples were collected, homogenized, and stored in 50-mL polypropylene tubes at −20°C until analysis.

Drinking water sample. Drinking water samples collected from 102 homes in the CS were available for measuring total and speciated As (Table 1). Sample collection methods have been previously described (Pellizzari et al. 1995; Thomas et al. 1999). Briefly, the samples were collected in 50-mL polypropylene tubes and stored at −20°C. As part of the quality control (QC) assessment, field controls (FCs) were prepared in the laboratory by spiking As(V), As(III), dimethyl arsenic acid (DMA), and monomethyl arsenic acid (MMA) in deionized water at 50 ng/mL. They were taken to the field, kept with the samples, and stored frozen along with the samples. Laboratory controls (LCs), which were prepared and stored frozen but not taken to the field, were intended to show that As species were preserved by freezing over time (samples were collected in 1997 and analyzed in 1999).

Urine samples. Urine samples collected from subjects on days 3, 5, and 7 of the monitoring period in the CS in 1997 were made available for measuring total and speciated As (Table 1). The samples were collected and stored in 50-mL polypropylene tubes at −20°C until analysis in 2000 (Pellizzari et al. 1995; Quackenboss et al. 2000).

All food, water, and urine samples with total As levels below the detection limit were not analyzed for individual As species. For these cases, a zero value was imputed for statistical analysis.

House dust and hair samples. House dust and hair samples collected in the CS were available for measuring total As levels. The samples had been stored in polypropylene bags at −20°C until analysis in 2000 (Pellizzari et al. 1995).

Sample analysis. Drinking water, food, and urine samples were analyzed for total and As species using previously reported methods (Milstein et al. 2002, 2003a, 2003b). At the beginning of sample analysis, an eight-point calibration curve was prepared covering the range from 0.05 to 50 ppb As. Every batch of samples analyzed included a calibration check (1 and 10 ppb), a calibration blank (0 ppb), and 10 field samples, a control sample (a standard reference material (SRM) or LC for drinking water, and a method control (MC) or certified reference material (CRM) for food and hair), and an independent check standard (10 ppb). The calibration check standard was used to assess sensitivity as judged by the total area counts for As and the bias of the calibration curve prior to the analysis of samples. The calibration blank served to assess any background carryover in the ion chromatographic system. The independent check standard at the end of the batch of samples was used to assess ion chromatograph inductively coupled plasma-mass spectrometer (ICP-MS) stability or drift from the original calibration curve. In addition, duplicate samples (DS) were analyzed to assess reproducibility. Table 2 summarizes the types of QC samples used.

Available arsenic data. For both R5 and the CS, the As food measurements were for composite (duplicate diet) samples of solid foods consumed over a 4-day period (days 4–7 of a participant’s monitoring period); both As concentrations (micrograms per kilogram) and intakes (micrograms per day) were determined for the food samples. We calculated intakes from the amount of food consumed per day times the concentration in the food composite. For the CS, As data were also available from three urine samples (nanograms per milliliter) obtained on days 3, 5, and 7 of the participant’s monitoring period, from drinking water, and from house dust and hair samples (total As only). The basic unit of observation that represents the integrated exposure period measured is a person-period for the food (4 days), urine (first morning void), and hair (1.5 months) data, and a household-period for the drinking water and dust data. Thus, distributional estimates

Table 1. Samples and available data.

| Study | Media | No. | Total | As(V) | As(III) | DMA | MMA | AsB | AsC |
|-------|-------|-----|-------|-------|---------|-----|-----|-----|-----|
| R-5   | Food  | 159 | Y     | Y     | Y       | Y   | Y   | Y   | Y   |
| CS    | Food  | 99  | Y     | Y     | Y       | Y   | Y   | Y   | Y   |
|       | Water | 102 | Y     | Y     | Y       | Y   | Y   | N   | N   |
| Urine, day 3 | 79 | Y | Y | Y | Y | Y | Y | Y |
| Urine, day 5 | 83 | Y | Y | Y | Y | Y | Y | Y |
| Urine, day 7 | 83 | Y | Y | Y | Y | Y | Y | Y |
| Dust  | 101  | Y   | N    | N    | N       | N   | N   | N   | N   |
| Hair  | 79   | Y   | N    | N    | N       | N   | N   | N   | N   |

Abbreviations: N, no; Y, yes. *Number of observations.

Table 2. QC samples available.

| Sample type | Media | Total | As(V) | As(III) | DMA | MMA | AsB | AsC |
|-------------|-------|-------|-------|---------|-----|-----|-----|-----|
| Blanks      | Food  | Y     | N     | N       | N   | N   | N   | N   |
| Water       | Y     | N     | N     | N       | N   | N   | N   | N   |
| Urine       | Y     | Y     | Y     | Y       | Y   | Y   | Y   | Y   |
| Dust        | Y     | N     | N     | N       | N   | N   | N   | N   |
| Hair        | Y     | N     | N     | N       | N   | N   | N   | N   |
| Controls    | Food  | Y     | N     | N       | N   | N   | N   | N   |
| Water       | Y     | Y     | Y     | Y       | N   | N   | N   | N   |
| Urine       | Y     | Y     | Y     | Y       | N   | N   | N   | N   |
| Duplicate analysis | Food | Y  | Y | Y | Y | Y | Y | Y |
| Water       | Y     | Y     | Y     | Y       | Y   | N   | N   | N   |
| Urine       | Y     | Y     | Y     | Y       | Y   | N   | N   | N   |
| Dust        | Y     | N     | N     | N       | N   | N   | N   | N   |

Abbreviations: N, no; Y, yes.
determined for these various media are for distributions over those respective units.

Statistical methods for analysis of quality control data. We computed summary statistics for the blank, control, and DS and duplicate analyses. Analytical bias was assessed by determining the amount of background contribution in blanks and by the percent As recovered in control samples, i.e., a comparison of the measured to a certified or known amount. This was quantitatively judged by the mean recoveries and coefficient of variation (CV) for paired observations.

We first assessed analytical precision by calculating standard deviations (SDs) and relative standard deviations (RSDs) of the duplicate analyses; similar measures were determined for the replicate aliquots. We computed these statistics when both observations of a pair had measurable values above the detection limit. The duplicate extract/digest analysis SDs and RSDs include only the instrumental analytical error, whereas replicate-aliquot measures include variability associated with preparation of aliquots, extraction in the case of food, as well as the instrumental analysis. The various aspects of precision were judged by summarizing the distributions of the SDs and RSDs over various cases. The sample size, the minimum, median, mean, and maximum were determined.

Statistical methods for analysis of field samples. Proper analysis of data collected for members of a probability sample requires that all observations be weighted inversely to their probabilities of selection. These sampling weights enable design-unbiased estimation of linear population parameters such as population totals. Initial sampling weights were developed as a part of the sample design activities of the R5 and CS; after data collection, these sampling weights are adjusted to compensate (at least partially) for the potential bias resulting from survey nonresponse. We used weighting class adjustment procedures in those studies to make the adjustments. The paragraphs below indicate how the adjusted sampling weights were employed in making estimates of various population parameters.

A common example requiring weighted data analysis is the estimation of a population proportion. For instance, for estimating a proportion \( p \), the general form of the estimate is

\[
\hat{p} = \frac{\sum w_i X_i}{\sum w_i},
\]

where the summations are over all sample participants, \( w_i \) denotes the sampling weight associated with participant-period (or household-period) \( i \), and \( X_i \) is an indicator variable with a value of 1 if participant-period \( i \) has the characteristic of interest and a value of 0 otherwise. The numerator is an estimate of the total number of participant-periods (or household-periods) in the population having the characteristic, and the denominator is an estimate of the total number of participant-periods (or household-periods) in the population. This type of estimate is used, for instance, to produce a weighted estimate of the percent measurable (e.g., the estimated percent of the population of person-periods with detectable levels of a given As species) by setting \( X = 1 \) for all observations with a detectable level, and setting \( X = 0 \) for all nondetects.

If \( Y_i \) denotes a continuously measured quantity for observation \( i \) (e.g., the As total concentration in food), then a similar expression is used to estimate the mean of the target population:

\[
\hat{\mu} = \frac{\sum w_i Y_i}{\sum w_i}.
\]

The numerator estimates the total of the \( Y \) variable that would have been obtained if all members of the target population had been observed; as before, the denominator estimates the total size of the target population.

In addition to estimating such population parameters (e.g., proportions, means), it is important to estimate the precision of the estimate, which is usually expressed in terms of its variance or standard error. The estimation of sampling variances and standard errors for statistics calculated from probability sampling data should be based on the randomization distribution induced by the sampling design (i.e., they should account for all features of the sampling design, such as stratification and multistage sampling). Such an approach is robust because it makes no assumptions regarding the distribution of occurrence (e.g., normality) of the survey items. Hence, analyses based on the design-induced distribution provide the most defensible basis for making inferences from the sample to the target population.

The classic approach to estimating standard errors for nonlinear statistics such as means and proportions from complex probability sampling designs is a first-order Taylor Series linearization method, which was the method employed in this study. Alternative variance estimation techniques for such designs include jackknifing and balanced repeated replication. RTI used its special purpose survey data analysis (SUDAAN) software to analyze complex survey data (RTI International, Research Triangle Park, NC). SUDAAN estimated the standard errors using the classical Taylor Series method because such estimates are both computationally and statistically efficient. This software includes procedures for survey based estimation of standard errors of population totals, means, proportions, and ratios, as well as linear and logistic regression relationships. For means, proportions, differences in means, or differences in proportions, the precision is generally reported as an approximate 95% confidence interval calculated as the estimate \( \pm \) two times the standard error of the estimate.

The method for calculating measures of precision for percentiles was somewhat different. First, the percentile estimate (e.g., for the \( p \)th percentile) was determined by forming a weighted cumulative empirical distribution and determining the point (e.g., \( X_p \)) at which the sum of the weights was 100\% of the total sum of the weights. A domain consisting of all observations with observed values less than \( X_p \) was then formed, and the proportion of the population falling into this domain (approximately equal to \( p \)) was estimated as \( \hat{p} \). The standard error of this estimate was formed via the Taylor’s Series method, and a confidence interval for \( p \) was formed as \( [\hat{p} - t_a SE(\hat{p}) \leq p \leq \hat{p} + t_a SE(\hat{p})] \), where \( t_a \) is an appropriate tabulated \( t \) value. An inverse interpolation of the empirical cumulative distribution was then used to translate this interval into one for the percentile.

That is, the lower confidence limit was that point \( L_p \) at which 100\% of the weights occurs, and the upper confidence limit was that point \( U_p \) at which 100\% of the weights occurs. This interval, \([L_p, U_p]\), forms an interval estimate for the \( p \)th percentile; it is typically asymmetric about \( X_p \). The interval was translated into a standard error by dividing the interval length \((U_p - L_p)\) by \( 2t_a \). Although such a standard error statistic cannot be used along with the estimated percentile to directly construct a confidence interval, it can be used to indicate the precision of one estimated percentile relative to another.

Because some media and chemicals exhibited a low percent measurable, the above types of weighted summary statistics (e.g., means and percentiles) and associated confidence intervals were generated only for those media/chemicals with \( \geq 10\% \) measurable; those weighted statistics employed half the detection limit for all nondetects.

In addition to the weighted statistics, we generated various Spearman (rank) correlations and weighted Pearson correlations; the latter were performed for logarithms of the concentrations, because the log-scaled data tended to be more symmetrically (and normally) distributed.

Results and Discussion

Quality control data. The QC results for the calibration blanks indicated that the background was less than the lowest calibration standard (0.05 ppb) for all days of analysis for As species. The bias between the nominal As level in the standard and that calculated was
determined for each As form in each batch of samples analyzed. In most cases, this bias was < 10%. Percent recovery was used to evaluate how well the instrumental analysis system performed on the check standards. The percent recovery for the 1-ppb and 10-ppb check standards were generally excellent, ranging from 86 to 107.

The results for total As measurement in field blanks indicated that no major contamination was associated with the vessels used to collect, store, and process the food, drinking water, hair, and dust samples. These results for total As were also applicable to As speciation.

We used CRM (food, hair), MCs (food), LCs and FCS, and SRMs (drinking water) to assess bias of the analysis methods. The results for these samples were expressed as a percent recovery (ratio of measured to known values). A summary is given in Table 3, which provides the number of QC samples of each type, the mean of the percent recoveries, and the CV of the percent recoveries. The percent recoveries were excellent in most cases for each of the As forms across the media.

We used duplicate injection (DI) of the same sample extract, duplicate analysis of an aliquot of the same sample (DA), and analysis of DS to assess precision of the instrumental method, the analysis method, and the overall collection and analysis methods, respectively, for selected As forms. Percent RSDs were determined for each pair, and the distributions of these RSDs were then summarized in terms of a mean, median, and maximum. These results for DI and DA pairs are given in Table 4 for food, drinking water, and urine. Except for drinking water, the DI and DA median percent RSDs were < 26%. For As(V) in drinking water, one pair had a large SD, but the reason for this could not be determined.

Table 5 presents the results of analysis for DS for dust and drinking water. In general, the precision associated with processing and extracting As of the sample was less than the precision for DA.

\[ \text{NHexas field data.} \] Table 6 lists the number of samples specified for As and the number of samples in which total As was measured. It also provides statistically weighted estimates of the percentage of samples with measurable values above the detection limits. These percentages represent estimates of those expected if the entire target populations were subjected to the data collection and analysis methodologies used in the R5 and the CS. The analytical methods used for measuring As species were sensitive to < 1 ppb.

The highest percent measurable values occurred for total As across all samples (> 90%, Table 6). This was expected because the detection limit was lower for total As than for any of the forms measured. AsB had the highest percent of measurable values in food. In a few samples, As(V) was also detected in food.

The most prevalent As form in water was As(V), whereas As(III) was measurable in a few samples. This compared with DMA in urine, which was measurable in up to 73% of the samples. Arsenocholine (AsC) was essentially not found any of the samples. In food, the most prevalent form was AsB.

During the analysis of food and drinking water samples by ion chromatograph ICP-MS, chromatographic peaks appeared that contained As, but they did not correspond to those being quantified. Thus, in some samples, the sum of the individual As species levels was less than the total As level measured, because the unknown forms of As were not quantified. In addition to the measured As forms reported here, there are as many as 18 other forms that have been identified in environmental and biological systems (Francesconi et al. 1999; Le et al. 1999, 2004; Migunes-Rodriguez et al. 2002; Montilla et al., unpublished data; Sanchez-Rodas et al. 2002; Schmeisser et al. 2004; Soerres et al. 2005). These forms include dimethylarsiniolethanol, several arsenosugars, and thioarsenosugars found in shrimp, oysters, and seaweed.

Table 7 furnishes estimates of the population distributions for selected media and As species (or total). Inestimable percentiles

### Table 3. Percent As recoveries from control samples used in CS.

| Media | Type | As form | No. | Mean | CV(%) |
|-------|------|---------|-----|------|-------|
| Food  | CRM  | Total   | 8   | 100  | 34    |
| MC    | Total | 8       | 100 | 8.2  |
| Hair  | CRM  | Total   | 11  | 98   | 12    |
| Water | FC   | As(V)   | 11  | 101  | 34    |
|       | As(III) | 11  | 103 | 37   |
|       | DMA   | 11     | 105 | 14   |
|       | MIA   | 11     | 104 | 14   |
| Water | LC   | As(V)   | 5   | 122  | 17    |
|       | DMA   | 5      | 97  | 21   |
|       | MIA   | 5      | 113 | 20   |
|       | Total | 10     | 83  | 33   |
| Water | SRM  | As(V)   | 2   | 86   | 4.5   |
|       | Total | 12     | 103 | 3.1  |

*Number of observations.

### Table 4. Arsenic results for duplicate analyses of food, drinking water, and urine samples in the NHexas.

| Study   | Media | Type | As form | No. | Mean | Median | Maximum | Percent RSD |
|---------|-------|------|---------|-----|------|--------|---------|-------------|
| R5 and CS | Food  | DA   | AsB     | 8   | 30   | 26     | 128     | 104         |
| R5 and CS | Food  | Di   | AsB     | 4   | 10   | 9.5    | 19      |
| CS      | Water | Di   | As(V)   | 6   | 76   | 74     | 108     |
|         | Total | 1    | 11     | 11   | 11   |        |         |
| Urine   | DA    | DMA  | 1       | 14  | 14   | 14     |         |
|         |       | MMA  | 1       | 23  | 23   | 23     |         |
|         | Total | 18   | 13     | 9.4 | 34   |         |         |
| Urine   | Di    | As(V)| 2       | 26  | 26   | 26     | 43      |
|         |       | As(III)| 1    | 3.2 | 3.2  | 3.2    |         |
|         |       | DMA  | 16      | 5.8 | 5.8  | 5.8    | 23      |
|         |       | MMA  | 3       | 15  | 17   | 17     | 18      |
|         |       | AsB  | 8       | 9.0 | 9.0  | 9.0    | 25      |
| Total   | 4     | 6.8   | 6.9    | 11  |      |        |         |

*Number of pairs.

### Table 5. Arsenic results for DS of surface dust and drinking water in CS.

| Media      | As form | Units | No. | Mean | Median | Maximum | Percent RSD |
|------------|---------|-------|-----|------|--------|---------|-------------|
| Dust       | Total   | ng/cm²| 6   | 32   | 32     | 64      |
| Dust       | Total   | µg/g  | 6   | 14   | 5.1    | 36      |
| Water      | As(V)   | ng/mL | 5   | 26   | 28     | 42      |
| Total      |         |       | 10  | 6.3  | 6.0    | 11      |

*Number of observations.

### Table 6. Weighted percent measurable estimates.

| Study   | Media | As form specified | As(V) | As(III) | DMA | MMA | AsB | AsC | Total |
|---------|-------|-------------------|-------|---------|-----|-----|-----|-----|-------|
| R5      | Food  | 159               | 2.2   | 0.0     | 0.4 | 0.0 | 12.9| 0.0 | 99.7  |
| CS      | Food  | 101               | 3.3   | 0.0     | 0.0 | 0.0 | 15.2| 0.0 | 100.0 |
| Dust    |       |                   |       |         |     |     |     |     |       |
| Hair    |       |                   |       |         |     |     |     |     |       |
| Water   | day 3 | 82                | 1.7   | 1.3     | 70.5| 9.9 | 14.4| 0.0 | 100.0 |
| Urine   | day 5 | 86                | 17.0  | 2.7     | 65.2| 17.2| 17.6| 0.0 | 100.0 |
| Urine   | day 7 | 83                | 8.7   | 1.4     | 72.8| 19.7| 19.7| 1.8 | 100.0 |

*No data.

...
drinking water correlated with DMA and MMA in urine (day 3). More statistically significant Pearson (log-scale) correlations of total As and its species (Table 9) were found than were found via the Spearman method, but the general trend of food and urine relationships were similar (Table 9). Total As levels in dust did not show a relationship with urine or hair. We observed no relationships for food, drinking water, or dust with hair.

Urine samples, as previously noted, were collected on days 3, 5, and 7 of participants’ monitoring periods. Correlations among these data are presented in Table 10. Total As levels in urine were significantly associated across the three pairwise combinations, for example, day 3 versus day 5. Because the half-life of As in the body is approximately 3 days, this suggests that some exposure continually occurred from day to day. This trend was also observed for AsB, which suggests that food is responsible for the continual exposure. DMA and MMA in urine were also significantly correlated but not in all combinations.

The combination of ingestion and metabolism of inorganic and organic As yields a complex array of As forms in human urine (Aposhian et al. 2004; Donohue and Abernathy 2001; Hansen et al. 2004; Styblo et al. 2001; Thomas et al. 2001; Vahter 1999), which accounts for the combination of correlations observed between the various As forms ingested and DMA and MMA in urine from NHEXAS subjects. Most studies indicate, on average, 10–30% inorganic As, 10–20% MMA, and 60–70% DMA in urine, but the methylation of As is governed by its absorption, dose level, route of exposure, and age (Vahter 1999). The relative levels measured in urine for NHEXAS (Tables 6 and 7) are consistent with these reported observations.

**Summary**

**Data quality.** Before interpreting results derived in this study, the QC data from chemical analyses were thoroughly analyzed to establish the level of quality that was achieved. In general, data quality was considered excellent, very good, or acceptable if the precision or bias was < 10%, < 20%, or < 30%, respectively. A summary for each facet of the study follows.

**Drinking water sample analysis. Total arsenic.** The QC results derived from calibration blanks indicated that the background was less than the lowest calibration standard (0.05 ppb) for all days of analysis. The bias between the As level in the 1-ppb calibration

---

**Table 7. Population-weighted estimates.**

| Study | Media | As Form | Units | No. | Population size (1,000s) | Percentiles | 10th | 25th | Median | 75th | 90th | 95% confidence limits |
|-------|-------|---------|-------|-----|------------------------|-------------|------|------|--------|------|------|----------------------|
|       |       |         |       |     |                        |             |      |      |        |      |      | Mean | 10th | 25th | Median | 75th | 90th |
| Rs    |       |         |       |     |                        |             |      |      |        |      |      |       |      |      |        |      |      |
| Food  | Total | µg/kg   | 159   | 47,548 | 99.7 | 17.18 | 3.57 | 4.87 | 7.72  | 17.74 | 43.05 |       | 12.35  | 2.74 | 3.97 | 6.06  | 12.08 | 23.66 |
|       |       | µg/day  | 158   | 47,403 | 99.7 | 12.67 | 1.65 | 2.53 | 5.04  | 13.82 | 31.65 |       | 8.63   | 1.02 | 2.09 | 3.52  | 8.03  | 18.86 |
| CS    |       |         |       |     |                        |             |      |      |        |      |      |       |      |      |        |      |      |
| Food  | Total | µg/kg   | 99    | 88    | 100.0 | 32.41 | 9.79 | 13.09| 17.50 | 25.99 | 46.58 |       | 13.50  | 8.57 | 11.33 | 15.05 | 19.90 | 28.50 |
|       |       | µg/day  | 99    | 85    | 100.0 | 16.46 | 4.23 | 5.46 | 8.71  | 13.33 | 28.58 |       | 5.13   | 11.62 | 15.15 | 20.17 | 34.15 | 92.25 |
| Dust  | Total | ng/cm² | 102   | 47    | 99.4  | 0.88  | 0.51 | 0.61 | 0.80  | 1.01  | 1.31  |       | 0.78   | 0.48  | 0.53 | 0.75  | 0.84  | 1.13  |
| Hair  | Total | µg/g    | 99    | 83    | 100.0 | 7.48  | 5.48 | 8.06 | 9.79  | 12.70 | 25.98 |       | 0.98   | 0.55  | 0.75 | 0.84  | 1.19  | 1.50  |
| DW    | As(V) | ng/mL   | 102   | 47    | 99.7  | 0.98  | 0.51 | 0.61 | 0.80  | 1.01  | 1.31  |       | 0.98   | 0.55  | 0.75 | 0.84  | 1.19  | 1.50  |
| Urine,|       |         |       |     |                        |             |      |      |        |      |      |       |      |      |        |      |      |
| day 3 | DMA   | ng/mL   | 82    | 83    | 70.5  | 0.17  | 0.06 | 0.12 | 0.23  | 0.33  |       | 0.14   | 0.05  | 0.07 | 0.09  | 0.19  | 0.24  |
|       |       |         |       |     |                        |             |      |      |        |      |      |       |      |      |        |      |      |
|       |       |         |       |     |                        |             |      |      |        |      |      |       |      |      |        |      |      |
|       |       |         |       |     |                        |             |      |      |        |      |      |       |      |      |        |      |      |

-meas., measurable. 10th, 25th, 75th, and 90th are percentiles.

*a* 0.5 times the detection limit was substituted for nondetectable values.

*b* Number of observations. *c* Low confidence limit. *d* High confidence limit.
standard and that determined from a standard curve was in most cases < 10%. Percent recovery for 1-ppb and 10-ppb check standards was used to evaluate how well the instrumental analysis system performed. In general it was very good, ranging from 86 to 107%.

The inclusion of SRMs during the analysis of water samples permitted the assessment of precision and bias. The precision was ≤4% across all batches of samples analyzed, and the bias was ≤6%.

Field blanks were included in the NHEXAS study, and results indicated that no major contamination was associated with the vessels used to collect, store, and process the samples. These results for total As were also applicable to As speciation.

Results for urine sample analysis. Total arsenic. Except for a few cases, the percent bias for total As quantification was ≤10% across the calibration standards and QC check standards. In cases where the bias was large, the analysis of the set of samples was repeated. The calibration blank contained negligible traces of As.

Duplicate analysis of sample extracts for total As permitted an evaluation of instrumental precision. The instrumental precision was excellent (mean percent RSD < 10%). The results for individual DS pairs, a measure of method precision, were very good (mean percent RSD 13%).

Arsenic species. The RSD between the initial calibration standard and the QC check standard was ≤30% across the six As species and in many cases was < 10%. In cases where measurable values for As species were observed in both DS, reproducibility, as expressed as the RSD for each pair, was acceptable.

A summary of the results for paired RSDs across the few DSs and samples available with measurable values for As species found in the urine and the observed precision for the method yielded acceptable results.

Table 8. Spearman correlations of As and As species: biomarkers versus environmental and exposure measures.

| Biomarker concentration | Food AsB (µg/kg) | Food Total (µg/kg) | Water AsB (µg/L) | Water Total (µg/L) | Dust AsB (µg/g) | Dust Total (µg/g) | Hair Total (µg/g) |
|-------------------------|----------------|-------------------|-----------------|------------------|----------------|------------------|-----------------|
| Day 3 Urine             | 0.268          | 0.273             | 0.212           | 0.119            | 0.094          | 0.143            |
| Day 5 Urine             | 0.314*         | 0.295*            | 0.280           | 0.222*           | 0.249          | 0.238*           |
| Day 7 Urine             | 0.314*         | 0.295*            | 0.280           | 0.222*           | 0.249          | 0.238*           |
| Day 3 ASB               | 0.069          | 0.094             | 0.113           | 0.053            | 0.043          | 0.023            |
| Day 5 ASB               | 0.043          | 0.094             | 0.113           | 0.053            | 0.043          | 0.023            |
| Day 7 ASB               | 0.043          | 0.094             | 0.113           | 0.053            | 0.043          | 0.023            |
| Hair Total              | -0.003         | 0.050             | 0.028           | 0.050            | 0.028          |

*Statistically significant at the 0.01 level. **Statistically significant at the 0.05 level.

Table 9. Pearson log-scale correlations of As and As species: biomarkers versus environmental and exposure measures.

| Biomarker concentration | Food AsB (µg/kg) | Food Total (µg/kg) | Water AsB (µg/L) | Water Total (µg/L) | Dust AsB (µg/g) | Dust Total (µg/g) | Hair Total (µg/g) |
|-------------------------|----------------|-------------------|-----------------|------------------|----------------|------------------|-----------------|
| Day 3 Urine             | 0.206          | 0.124             | 0.273           | 0.217            | 0.186          | 0.017            |
| Day 5 Urine             | 0.314*         | 0.295*            | 0.280           | 0.222*           | 0.249          | 0.238*           |
| Day 7 Urine             | 0.314*         | 0.295*            | 0.280           | 0.222*           | 0.249          | 0.238*           |
| Day 3 ASB               | 0.069          | 0.094             | 0.113           | 0.053            | 0.043          | 0.023            |
| Day 5 ASB               | 0.043          | 0.094             | 0.113           | 0.053            | 0.043          | 0.023            |
| Day 7 ASB               | 0.043          | 0.094             | 0.113           | 0.053            | 0.043          | 0.023            |
| Hair Total              | -0.003         | 0.050             | 0.028           | 0.050            | 0.028          |

*Statistically significant at the 0.01 level. **Statistically significant at the 0.05 level.

Table 10. Spearman and log-scale Pearson correlations between urine samples.

| As form | Day 3 vs. day 5 | Day 3 vs. day 7 | Day 5 vs. day 7 | Day 3 vs. day 5 | Day 3 vs. day 7 | Day 3 vs. day 7 |
|---------|----------------|----------------|----------------|----------------|----------------|----------------|
| Total   | 0.245**        | 0.269**        | 0.412**        | 0.311**        | 0.449**        | 0.472**        |
| As(V)   | 0.060          | 0.052          | -0.074         | -0.061         | 0.096          | -0.069         |
| AsB     | 0.390*         | 0.443*         | 0.403*         | 0.262**        | 0.521*         | 0.280**        |
| DMA     | 0.191          | 0.238**        | 0.216          | 0.225**        | 0.305*         | 0.249**        |
| MMA     | 0.094          | 0.300**        | 0.199          | 0.079          | 0.317*         | 0.143          |

*Statistically significant at the 0.01 level. **Statistically significant at the 0.05 level.
percent RSD was generally very good for the six species (< 20%). From DA, results were available only for AsB. These results were used to assess instrumental precision of analysis. For four analysis pairs, the precision was very good. DS results permitted a measure of the precision of com- postive food aliquoting and method of analysis. As expected, the instrumental precision was better than the method precision. The vari- ability was due partly to the variation in AsB between samples, i.e., at lower levels, the per- cent RSD was larger. The mean percent RSD for AsB was 10% and 30% for instrumental and method analyses, respectively.

**NHEXAS field samples.** Raw data from the analysis of As in drinking water, hair, dust, food [duplicate plate, composited 4-day food samples (days 4–7) from the participants], and urine (days 3, 5, and 7) were available for statistical evaluation. Except for AsB and As(V), the levels for As species measured in the sam- ples were very low or nonexistent in food and drinking water. (The analytical methods used for measuring As species were sensitive to <1 ppb.) During the analysis of food and drinking water samples, chromatographic peaks appeared that indicated As, but these did not correspond to the As species being quantified. Thus, in several samples there was underre- porting of As species concentrations, because some forms of As were not quantified. On the other hand, total As was detectable in almost all samples (> 90%) except for hair (47%), indicating that the analytical method was suf- ficiently sensitive.

It was evident from the distributional results (Figure 1) that the exposure of chil- dren to total As in food was about twice as high as the general R5 population (e.g., medians of 17.5 and 7.7 ppb for the CS and R5, respectively). AsB was the most frequently detected species in food eaten by the parti- cipants, whereas the more toxic As(V) was only rarely detected (i.e., the predominant dietary exposure was from an organic form of As.)

Both Pearson (log-scale) and Spearman (rank) correlations between the biomarkers (urine, hair) and the other measures (food, drinking water, dust) and urine versus hair were performed. In the CS, total As and AsB in food were significantly correlated with their levels in urine. Levels of As(V) in drinking water exhibited significant correlations with DMA and MMA in urine. Arsenic levels in dust did not show relationships with urine or hair. We observed no relationships for food, drinking water, and dust with hair.

The major findings of the study included a) acceptable to excellent data quality in As exposure and biomarker measurements; b) con- firmation of the presence of the As species expected in water ([As(V)], in food, (AsB), and in urine (MMA and DMA)); c) some significant associations between exposure and biomarker levels of As and its species; and d) the low level of personal exposure to toxic forms of As in R5.

The lack of some other associations is likely due to the various times of measurement and the transformations and half-lives that As species undergo within the body.

**Figure 1.** Distribution of arsenic species in environ- mental and human biological samples. AsT, total As.

**References**

Aposhian VH, Zakaryan RA, Avram MD, Sampayo-Reyes A, Wollenberg ML. 2004. A review of the enzymology of arsenic metabolism and a new potential role of hydrogen peroxide in the detoxification of the trivalent arsenic species. Toxicol Appl Pharmacol 198:327–333.

ATSDR. 1989. Toxicological Profile for Arsenic. ATSDR/TP- 88/02. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Bergoglio RM. 1964. Mortality from cancer in regions of arsenical waters of the Province of Cordoba, Argentina. Prensa Med Argent 51:9954–10008.

Bingini R, Rivera M, Salvador M, Cordoba S. 1978. Chronic arsenism and lung cancer. Arch Dermatog 28:151–158.

Branch S, Ebdon L, O’Neill P. 1994. Determination of arsenic species in fish by directly coupled high-performance liquid chromatography-inductively coupled plasma mass spectrometry. J Anal At Spectrom 9:33–36.

Cebrian ME, Albores A, Aquilar M, Blakely E. 1983. Chronic arsenic poisoning in the north of Mexico. Hum Toxicol. 2:121–133.

Chakraborty AK, Saha KC. 1987. Arsenical dermatosis from tube- well water in West Bengal. Indian J Med Res 85:328–334.

Chen CJ, Chuang YC, Lin TM, Wu HY. 1985. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic arsensiasis and high cancer. Cancer Res 55:1150–1152.

Chen CJ, Chuang YC, Yeu SL, Lin HY. 1988. A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. Br J Cancer 53:399–405.

Chen CJ, Kuo TL, Wu MM. 1988a. Arsenic and cancers [Letter]. Lancet 1(8582):414–415.

Chen CJ, Wang CJ. 1990. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. Cancer 50:5470–5475.

Chen CJ, Wu MM, Lee SS, Wang JD, Cheng SH, Wu HY. 1988b. Atherogenicity and carcinogenicity of high-arsenic arsenic well water; multiple risk factors and related malignant neo- plasms of blackfoot disease. Arterioscler 8:452–460.

Chen S, Zheng SR, Yang M. 1994. Arsenic species in groundwater of the blackfoot disease area, Taiwan. Environ Sci Technol 28:877–881.

Chiang H, Hong C, Guo H, Lee E, Chen T. 1988. Comparative study on the high prevalence of bladder cancer in the blackfoot disease endemic area in Taiwan. J Formos Med Assoc 87:1074–1080.

Deng HS, Jaiswal DD, Somasundaram S. 1983. Distribution of arsenic in human tissues and milk. Sci Total Environ 29:171–175.

Dibner B. 1959. Arscila on Metals. Norwich, CT: Burndy Library.

Donohue DM, Abenhamty CD. 2001. Arsenic methylation and the S-adenosylmethione-mediated transmethylation/transul- furation pathway. In: Arsenic Exposure and Health Effects (Abenhamty CD, Calderon RL, Chappell WR, eds). London: Elsevier Science Ltd., 367–379.

Francesconi KA, Hunter DA, Bachmann B, Bager G, Goessler W. 1999. Uptake and transformation of arsenosugars in the shrimp Crangon crangon. Appl Organomet Chem 13699–679.

Hansen RR, Raab A, Jaspers M, Mine BF, Feldmann J. 2004. Chem Res Toxicol 17:1086–1091.

Hunter D. 1957. The Diseases of Occupations. London: English Universities Press.

Hwang C, Jiang S. 1994. Determination of arsenic compounds in water samples by liquid chromatography-inductively coupled plasma mass spectrometry with an in situ nebulizer-hydrinlyzer generator. Anal Chim Acta 289:205–213.

IARC. 1980. Some metals and metal compounds. IARC Monogr Eval Carcinog Risks Hum. 23.

Le XC, Lu X, Li X-F. 2004. Arsenic speciation. Anal Chem 76:264–275.

Le XC, Ma M, Lui V. 1999. Exposure to arsenosugars from seafood ingestion and speciation of urinary arsenic metabolites. In: Arsenic: Exposure and Health Effects (Abenhamty CD, Calderon RL, Chappell WR, eds). London:Elsevier Science Ltd., 69–79.

Migues-Rodriguez M, Pickford R, Thomas-Dates JE, Pergantis SA. 2002. Arsenosugar identification in seaweed extracts using high-performance liquid chromatography/electro- spray ion trap mass spectrometry. Rapid Commun Mass Spectrom 16:322–331.

Mistleis LS, Essader A, Murrell C, Pellizzari ED, Fernando RA, Raymer Jr, M. 2003a. Sample preparation, extraction efficiency, and determination of six arsenic species present in food composites. J Agric Food Chem 51:4180–4184.

Mistleis LS, Essader A, Pellizzari ED, Fernando RA, Akino D. 2002. Selection of a suitable mobile phase for the speciation of four arsenic compounds in drinking water samples using ion exchange chromatography coupled to inductively coupled plasma mass spectrometry. Environ Int 27:277–283.

Mistleis LS, Essader A, Pellizzari ED, Fernando RA, Raymer Jr, Levine KE, Milstein LS, et al. 2003b. Development and application of a robust speciation method for determination of six arsenic compounds present in human urine. Environ Health Perspect 111:293–299.

Pellizzari ED, Liy P, Quackenboss J, Whitemore R, Clayton A, Freeman N, et al. 1995. Population-based exposure measures in EPA Region 5: a phase I field study in support of the National Human Exposure Assessment Survey. J Expo Environ Epidemiol 5:237–250.

Quackenboss JJ, Pellizzari ED, Shubit P, Whitemore RW, Adgate J, Thomas KG, et al. 2000. Design strategy for assessing multi-pathway exposure for children: the Minnesota Children’s Pesticide Exposure Study (MNCPES). J Expo Environ Epidemiol 10:145–158.

Rahman M, Axelson O. 2001. Arsenic ingestion and health effects in Bangladesh: epidemiological observations. In: Arsenic Exposure and Health Effects (Abenhamty CD, Calderon RL, Chappell WR, eds). London:Elsevier Science Ltd., 367–379.

Sanchez-Rodas D, Geisinger A, Gomez-Ariza JL, Francesconi KA. 2002. Determination of an arsenosugar in oyster extracts using high-performance liquid chromatography/electro- spray ion trap mass spectrometry. J Chromatogr A 970:251–258.

Schmeisser E, Raml R, Francesconi KA, Kuehnelt D, Lindberg A-L, Soeres C, Goessler W, Francesconi KA, Milstein LS, et al. 2004. Thio arsenosugars in freshwater
mussels from the Danube in Hungary. J Environ Monit 7:688–689.

Styblo M, Lin S, Del Razo LM, Thomas DJ. 2001. Trivalent methylated arsenicals: toxic products of the metabolism of inorganic arsenic. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). London: Elsevier Science Ltd., 325–337.

Thomas KW, Pellizzari ED, Berry MR. 1999. Population-based dietary intakes and tap water concentrations for selected elements in the EPA Region V National Human Exposure Assessment Survey (NHEXAS). J Expo Anal Environ Epidemiol 9:402–413.

Thomas P, Sniatecki K. 1995. Determination of trace amounts of arsenic species in natural waters by high-performance liquid chromatography-inductively coupled plasma mass spectrometry. J Anal Atom Spectrom 10:615–618.

Thomas DJ, Styblo M, Lin S. 2001. The cellular metabolism and systemic toxicity of arsenic. Toxicol Appl Pharmacol 176:127–144.

Tseng WP, Chu HM, How CW, Fong JM, Lin CS, Yeh S. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst 40:453–463.

Tsuda T, Nagira T, Yamamoto M, Kume Y. 1990. An epidemiological study on cancer in certified arsenic poisoning patients in Toroku. Ind Health 28:53–62.

U.S. EPA. 1988. Special Report on Ingested Inorganic Arsenic: Skin Cancer; Nutritional Essentiality. EPA/625/3-87/013. Washington, D.C.: U.S. Environmental Protection Agency.

Vahter M. 1999. Variation in human metabolism of arsenic. In: Arsenic Exposure and Health Effects (Abernathy CO, Calderon RL, Chappell WR, eds). London: Elsevier Science Ltd., 267–279.

Velez D, Ybanez N, Montoro R. 1995. Percentages of total arsenic represented by arsenobetaine levels of manufactured seafood products. J Agric Food Chem 43:1289–1294.

Whitmore RW, Byran MZ, Clayton CA, Thomas KW, Zelon HS, Pellizzari ED. 1999. Sampling design, response rates, and nonresponse compensation for the National Human Exposure Assessment Survey (NHEXAS) in EPA Region 5. J Expo Anal Environ Epidemiol 9:369–380.

Wu MM, Kuo TL, Hwang YH, Chen CJ. 1989. Dose-response relation between arsenic well water and mortality from cancer. Am J Epidemiol 130:1123–1132.

Yamauchi H, Yamamura Y. 1983. Concentration and chemical species of arsenic in human tissue. Bull Environ Contam Toxicol 31:267–277.

Yu WH, Harvey CM, Harvey CF. 2003. Arsenic in groundwater in Bangladesh: a geostatistical and epidemiological framework for evaluating health effects and potential remedies. Water Resour Res 39(6):1146.

Zaldivar R. 1974. Arsenic contamination of drinking water and food-stuffs causing endemic chronic poisoning. Beitr Pathol 151:284–400.

Zaldivar R, Prumes L, Ghai GL. 1981. Arsenic dose in patients with cutaneous carcinomata and hepatic haemangioendothelioma after environmental and occupational exposure. Arch Toxicol 47:145–154.