To assess the arsenic exposure of a population living in the vicinity of a coal-burning power plant with high arsenic emission in the Prievidza District, Slovakia, 548 spot urine samples were specified for inorganic As (As\textsubscript{inorg}), monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), and their sum (As\textsubscript{sum}). The urine samples were collected from the population of a case–control study on nonmelanoma skin cancer (NMSC). A total of 411 samples with complete As speciations and sufficient urine quality and without fish consumption were used for statistical analysis. Although current environmental As exposure and urinary As concentrations were low (median As in soil within 5 km distance to the power plant, 41 µg/g; median urinary As\textsubscript{sum} 5.8 µg/L), there was a significant but weak association between As in soil and urinary As\textsubscript{sum} (r = 0.21, p < 0.01). We performed a multivariate regression analysis to calculate adjusted regression coefficients for environmental As exposure and other determinants of urinary As. Persons living in the vicinity of the plant had 27% higher As\textsubscript{sum} values (p < 0.01), based on elevated concentrations of the methylated species. A 32% increase of MMA occurred among subjects who consumed homegrown food (p < 0.001). NMSC cases had significantly higher levels of As\textsubscript{sum}, DMA, and As\textsubscript{inorg}. The methylation index (As\textsubscript{inorg}/(MMA + DMA)) was about 20% lower among cases (p < 0.05) and in men (p < 0.05) compared with controls and females, respectively. Key words: arsenic, biomarker, coal combustion, environmental exposure, environmental health, nonmelanoma skin carcinoma. Environ Health Perspect 111:889–894 (2003). doi:10.1289/ehp.5838 available via http://dx.doi.org/ [Online 9 January 2003]

There has been a longstanding scientific interest in the association between environmental arsenic exposure, the As body burden, and carcinogenic effects such as nonmelanoma skin cancer (NMSC) risk, but uncertainties in exposure assessment, metabolism, and mechanism of carcinogenicity still exist (Abernathy et al. 1999). Arsenic occurs in the environment as inorganic As (As\textsubscript{inorg}) in the readily interconvertible valence states arsenite (As\textsuperscript{III}) and arsenate (As\textsuperscript{V}). In oxygenated environments such as surface water and soil, As\textsuperscript{V} is the more stable valence states arsenite (As\textsuperscript{III}) and arsenate (As\textsuperscript{V}). In oxygenated environments such as surface water and soil, As\textsuperscript{V} is the more stable form [U.S. Environmental Protection Agency (EPA) 2001]. In the process of biotransformation, As\textsuperscript{V} is reduced to As\textsuperscript{III}, and As\textsuperscript{III} is sequentially methylated to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). The chemical speciation of As is important for its health effects. There is also growing evidence for carcinogenicity of the methylated As species (Basu et al. 2001; U.S. EPA 2001). Methylation of both DNA and xenobiotics such as As share a common methyl donor (Mato et al. 1997). Besides As exposure from geologic sources, which has been reviewed for health effects associated with As in drinking water (U.S. EPA 2001), smelting activities and coal combustion contribute to an additional environmental As exposure (Farago et al. 1997). In this article we report on the impact of environmental As from coal combustion on urinary As levels in an elderly population in Slovakia. To date, an estimated 3,000 metric tons of As has been emitted since 1953 from a Slovak power plant in the Prievidza District, resulting from a very high As content of the local coal as well as from insufficient emission control in the past. Arsenic emission has been considerably reduced since 1990 because of pollution control measures. The As contents of samples taken from this plant in 1999 were approximately 500 µg/g in coal and up to 1,600 µg/g in fly ash (Keegan et al. 2002; Pesch et al. 2002). In the 1970s, when the annual As emissions were as high as 200 metric tons/year, urinary As was increased in children in the vicinity of the plant (Bencko and Symon 1977). Furthermore, the NMSC incidence of this district has been highest since Slovakia began registering cancer in 1968 [National Cancer Institute of Slovakia (SK NCI) 2000]. Within the district, NMSC cancer incidence has been higher in the vicinity of the plant (Nieuwenhuijsen et al. 2001).

This study was part of the project funded by the European Commission titled Exposure to Arsenic and Cancer Risks in Central and Eastern Europe (EXPASCAN), following a study in this Slovak region by the program funded by the European Commission, titled PHARE, on the impacts of environmental pollution on the health conditions of the population in model spheres (Fabianova and Bencko 1995). In the framework of EXPASCAN and to investigate the NMSC risk of environmental As exposure from the coal-burning power plant in the district of Prievidza, Slovakia, a population-based case–control study was conducted with 264 NMSC cases and 286 controls. The risk estimates for the impact of environmental arsenic on the development of NMSC have been published elsewhere (Pesch et al. 2002). In this biomonitoring study, we investigated potential determinants of the As levels in spontaneous urine samples provided by the subjects of this study and analyzed the association between environmental arsenic exposure from the coal-burning power plant and urinary As concentrations. Data on environmental arsenic exposure were available from the modeling of airborne arsenic pollution by using emission data (Colville et al. 2001) and from the measurement of As levels in soil and dust samples from the households of the study population (Keegan et al. 2002; Pesch et al. 2002).

Materials and Methods

Recruitment of the study population. The study design and exposure assessment of environmental As have been previously reported (Pesch et al. 2002). In brief, from October 1999 through June 2000, this population-based case–control study was conducted in the Slovak district of Prievidza. Cases were eligible if a) they were registered at the department of pathology of Bojnice hospital, which serves as the only reporting center of the district for the Slovak National Cancer Institute, with a histologically confirmed diagnosis of NMSC as a primary, first tumor during 1996–1999; b) they currently resided in this district; and c) they were not older than 80 years. From 374 eligible cases, 328
were contacted and 264 were successfully recruited. Population controls were frequency matched to cases on sex and age (5-year classes) and interviewed within the same period. Controls were ascertained from a random address sample of the mandatory registry of the district. From 396 persons contacted, 286 controls were enrolled. Interviews with a structured questionnaire were conducted in person by trained staff to ascertain demographic characteristics, health status, residential and occupational history, skin type, and dietary and smoking habits, among other data. Informed consent was obtained from the study subjects before the interview.

**Exposure information.** To investigate the association between current As exposure and urinary As, a categorical variable, Res, represents the distance from the subject’s current place of residence to the power plant (≤ 5 km, 6–10 km, > 10 km). The cutoffs for these categories were derived from atmospheric dispersion modeling of the As emission (Calvile et al. 2001). A binary variable (food) of the subject’s As exposure by oral uptake was based on interviewees’ reports of the contribution of homegrown products to their food consumption during the period of the highest arsenic emissions (1970–1989).

The analysis of As in soil and house dust has been reported in detail elsewhere (Keegan et al. 2002; Pesch et al. 2002). In brief, soil and house dust were collected from a random subsample of the study subjects’ households. Each soil sample was a composite of 20 subsamples collected within 5 cm of the surface of the garden, nearby allotment, or entrance to the house of the study subject. House dust was collected with a specific vacuum cleaner from a measured 1-m² area of carpet. Arsenic concentration was analyzed with inductively coupled plasma atomic absorption spectroscopy.

**Arsenic speciation in urine samples.** Study subjects were asked to provide spot urine samples after interview into acid-washed plastic containers to determine the urinary concentrations of As\textsubscript{inorg} (As\textsubscript{III} and As\textsubscript{V}) and the methylated species (As\textsubscript{methyl}) MMA and DMA. As\textsubscript{inorg}/As\textsubscript{methyl} and MMA/DMA were calculated as metabolic indices to measure the stepwise methylation capacity. Detailed information on the urine sampling, storage, and As speciation has been previously reported (Nieuwenhuijsen et al. 2001). In brief, the urine samples were transported to the State Health Institute of Prievidza in a cooling box within the same day. Ninety milliliters of the urine samples were immediately frozen at –18°C to be transported frozen to a nearby specialty laboratory, which was approved by an international quality control study (Crecelius and Yager 1997), once a month for As speciation. In the remaining urine sample, creatinine was determined spectrophotometrically with the Jaffe method (Kasiske and Keane 1996). The limit of detection (LD) was 0.037 g/L. As\textsubscript{inorg}, MMA, and DMA were measured by hydride-cryogenic trap-atomic absorption spectroscopy. Briefly, the As species were online reduced by sodium tetrahydroborate to their arsenic derivatives (As\textsubscript{inorg} to arsine, MMA to methylarsonic, and DMA to dimethylarsonic), which are purged by nitrogen stream and collected in a trap. Then, arsine species were flushed into a quartz cell on an atomic absorption spectrophotometer. Peak areas were used for quantitation. The LD values of this technique, based on baseline noise corresponding to peak area, were 0.4 µg/L for As\textsubscript{inorg}, 0.1 µg/L for MMA, and 0.2 µg/L for DMA. The experimental assembly was calibrated for each batch. Standard reference material 2670 (Toxic Metals in Freeze-Dried Urine, Elevated Level; National Institute of Standards and Technology, Gaithersburg, MD, USA) with a certified value of total As content given with 480 ± 100 µg/L was used for quality control. The recovery results were close to the reference values. Furthermore, urine samples spiked with approximately 25 µg/L of As\textsubscript{inorg}, MMA, and DMA yielded sufficient recovery results.

From the 550 subjects enrolled in the case-control study, 548 subjects provided urine samples. In 544 urine samples, at least one arsenic species could be determined, and 518 samples had all three species, As\textsubscript{inorg}, MMA, and DMA. In 3.8% of the urine samples, the speciation analysis was disturbed by an interfering, mainly in the speciation of MMA and DMA. The sum of these As species (As\textsubscript{sum} = As\textsubscript{inorg} + MMA + DMA) was calculated only if neither of the species was missing. A small percentage of the samples were below the LD for the As speciation (0.0% for As\textsubscript{inorg}, 2.1% for MMA, 5.6% for DMA). Concentrations below the LD were set to two-thirds of the respective LD as expectation of the left-skewed triangle distribution. Although the study participants had been asked not to consume fish within 5 days before urine sampling, several participants admitted recent fish consumption in the interview. Because current fish consumption within 3 days before urine sampling turned out to have a strong influence on the As\textsubscript{methyl} especially on DMA (Table 1), another 80 samples were excluded. Creatinine concentration and the specific gravity were used to control the quality of the spot urine samples. Wehrtrauch et al. (1997) proposed an acceptable range for specific gravity of 1.010–1.024 g/mL, and an acceptable range of creatinine of 0.5–2.5 g/L. Additionally, acceptable creatinine concentrations by sex and age (cutoff, 60 years) were defined according to Boeniger et al. (1993). Twenty-seven urine samples were excluded from further statistical analyses because they did not meet the criteria

**Table 1. Urinary DMA and fish consumption during the last 3 days before urine sampling, EXPASCAN Study, Prievidza District, Slovakia, 1999.**

| Fish during the last 3 days | No. (%) | Minimum | 25th percentile | Median | 75th percentile | Maximum | pValue
|--------------------------|---------|---------|----------------|--------|----------------|---------|-------|
| DMA (µg/L)               |         |         |                |        |                |         |       |
| Yes                      | 80 (100) | < LD    | 2.28           | 5.20   | 10.60          | 41.05   |       |
| No                       | 411 (100)| < LD    | 1.83           | 3.37   | 5.80           | 41.68   | p < 0.0012 |
| Creatinine (µg/g)        |         |         |                |        |                |         |       |
| Yes                      | 80 (0.15)| 2.59    | 4.91           | 11.34  | 41.59          |         |       |
| No                       | 411 (0.10)| 1.89   | 3.15           | 5.19   | 41.41          |         | p < 0.0001 |

*a* For log-transformed variables in t-test. *b* LD = 0.2 µg/L.

**Table 2. Characteristics of the study population with urine samples speciated for urinary arsenic, EXPASCAN Study, Prievidza District, Slovakia, 1999.**

| Characteristic                       | Study subjects with urine samples (No. (%) | Study subjects with eligible urine samples (No. (%)
|-------------------------------------|-------------------------------------------|--------------------------------------------------|
| Sample size                         | 548 (100)                                  | 411 (100)                                        |
| Male sex                            | 270 (49)                                   | 203 (49)                                        |
| NWSC cases                          | 262 (48)                                   | 210 (51)                                        |
| Potential renal disorders<sup>a</sup> | 78 (14)                                    | 53 (23)                                         |
| Current smokers                     | 74 (14)                                    | 53 (13)                                         |
| Potential occupational arsenic exposure | 15 (3)                                     | 3 (11)                                          |
| Place of residence: ≤ 5 km          | 78 (14)                                    | 58 (14)                                         |
| Place of residence: 6–10 km         | 301 (55)                                   | 225 (55)                                        |
| Place of residence: > 10 km         | 169 (22)                                   | 128 (31)                                        |
| Self-supply with homegrown food     | 121 (22)                                   | 88 (21)                                         |
| House dust samples                  | 210 (38)                                   | 162 (39)                                        |
| Soil samples                        | 209 (38)                                   | 159 (39)                                        |
| Age (year) distribution             | Median                                     | 67                                              |
| Range                               | 20–80                                      | 66                                              |
| 25th, 75th percentiles              | 58, 74                                     | 58, 73                                          |

<sup>a</sup> Diabetes, hypertension, glucosis, others.
not pass both criteria of creatinine concentration and specific gravity. In total, 411 urine samples were eligible for the statistical analysis of the impact of environmental As exposure on urinary As concentrations.

**Statistical methods.** Log transformation was applied to all concentration measurements (urinary As and creatinine, As in soil and house dust) to achieve approximately normal distributions for parametric statistics. Groups were compared by *t*-test or analysis of variance. Stepwise multiple linear regression was applied to search for significant determinants of urinary As, with significance levels of 0.1 chosen for inclusion or exclusion. The estimated regression parameters were presented as means ratios. A means ratio was calculated as the ratio of two values of the dependent variable, which are estimated at two different levels of the respective independent variable by the regression model at fixed levels of all other regression variables. Therefore, these estimated means ratios represent quantitatively the influence of the respective independent variables on the dependent variable adjusted for all other independent variables included in the regression model. The multiple *R*² indicates the fraction of variance of the dependent variable explained by the independent variables included in the model. For all statistical computations, we used STATISTICA (Stat Soft Inc. 2002).

**Results**

Demographic and other characteristics of the 548 study subjects who provided urine samples and for the 411 subjects whose urine samples were included in statistical analyses are shown in Table 2. Among the 411 subjects analyzed, 203 were male, and 210 subjects had a diagnosis of NMSC. Fifty-eight persons lived within 5 km of the power plant. Eleven persons were considered occupationally exposed to As from a currently held job in power generation, coal mining, or other high-risk industry (Pesch et al. 2002). More than half of the study population was older than 65 years, with a median of 66 years. Fifty-three study subjects, mostly men, were current smokers. Potential renal disorders such as diabetes and hypertension, which may interfere with urinary As levels, were self-assessed from 53 persons. Eighty-six persons reported self-supply with homegrown fruits and vegetables. Considering the low numbers of eligible urine samples for smokers and subjects with potential renal disorders, a two-sided power calculation yields a relative mean concentration difference of about 30%, at least, for As total, between smokers and nonsmokers and between subjects with and without potential renal disorders, respectively, which should be detectable with a power of 80% at a significance level of 5%.

Table 3 shows the descriptive statistics for the urinary As species in the EXPASCAN study population. The quantity of urinary As was calculated both as volume concentration (micrograms per liter) and as mass per mass creatinine (micrograms per gram creatinine). Asorganic was calculated within a range from 1 to 48 µg/L, with a median of 6 µg/L. Asorganic comprised about 30% of As total, with a median of 1.78 µg/L. MMA was the lowest fraction (12%), with a few urine samples below the LD. Also, DMA, despite the largest fraction (56%), was found in a few samples below the LD. The median MMA/DMA was 0.41; we calculated 0.25 as the median for MMA/DMA to measure the stepwise methylation.

Environmental As in garden soil and household dust varied significantly by distance from the power plant (Table 4). Within 5 km from the plant, the median of As in soil was 40.6 µg/g; it was 23.0 µg/g in the 6–10 km region and 19.8 µg/g in the distant part (> 10 km). A similar pattern was found for house dust, with a median of 21.5 µg/g within 5 km, 10.0 µg/g in the 6–10 km region, and 8.8 µg/g in the distant part of the district. The As levels in soil and in house dust correlated significantly (*r* = 0.33; *p* < 0.001). Figures 1 and 2 and Table 5 illustrate a weak but significant association between urinary As and the place of residence and As in soil, respectively.

Table 6 presents the results of the stepwise multiple regression procedure for environmental As exposure and potential covariates as means ratios or standardized regression coefficients for the urine arsenic species as well as on the two metabolic indices. All characteristics listed in Table 2 and, additionally, creatinine were considered as potential determinants of urinary As and, with the exception of occupational exposure because of the small number, were included in the stepwise regression. The environmental factors (i.e., Res and As in soil and house dust) were treated separately because they are causally dependent and covary by distance from the plant, as demonstrated in Table 4; moreover, soil and house dust samples were available only for about 50% of the study group. The three-level factor Res was represented by two binary variables: place of residence within 5 km of the power station versus > 5 km (Res1), and place of residence between 6 and 10 km distance to the plant versus > 10 km away (Res2). Res2, renal disorders, current smoking status, and As in house dust did not pass the stepwise regression analysis as significant determinants of urinary As species and, therefore, were not included in Table 6. Creatinine, age, sex, case–control status, and environmental As accounted for about 30% of the variance of the As species, but not for the metabolic index MMA/DMA. With respect to the methylated species and Asorganic, men had significantly higher concentrations than did women. This gender difference in methylation was also shown with the ratio of inorganic to organic arsenic. Asorganic dropped about 20% with an increase of 30 years of age, but there was no impact of age on the methylation indices. Asorganic was slightly increased by about 10% for subjects with NMSC, in particular with higher DMA and decreased MMA/DMA.

The environmental As exposure turned out to be a significant factor for urinary As for
both the place of residence and As in soil used as environmental exposure measures. \( A_{\text{sum}} \) was about 30% higher for a subject living within 5 km of the plant or with an As soil concentration of 70 µg/g than for a subject living more distant or being exposed to a soil concentration of 20 µg/g. Res1 was associated with a significant increase of the methylated species MMA and DMA but not of \( A_{\text{inorg}} \). Consumption of homegrown fruits and vegetables was associated with significantly elevated MMA levels. Arsenic in soil, despite being estimated in only half of the samples and thus less powerful in revealing effects, was associated with a significant increase in all urinary As species. Res1 and As in soil were found to be inversely correlated with creatinine excretion, while \( A_{\text{inorg}} / A_{\text{methyl}} \), which was found to be inversely correlated with the nary As species. Res1 and As in soil were associated with a significant increase in all urinary As species. Res1 and As in soil were found to be inversely correlated with the metabolic index \( A_{\text{inorg}} / A_{\text{methyl}} \), which was significant only for Res1 (\( p < 0.01 \)).

**Discussion**

**Urinary As as biomarker of environmental As exposure.** Burning of fossil fuels such as coal is a major source of anthropogenic arsenic exposure (International Programme on Chemical Safety 2001). Arsenic occurs in the environment of the power plant as \( A_{5} \). In the process of biotransformation, \( A_{5} \) is reduced to \( A_{3} \), which is methylated to MMA and DMA; S-adenosyl methionine (SAM) and glutathione (GSH) are essential cofactors (Styblo and Thomas 1995). The liver is considered the major organ in \( A_{5} \) reduction and \( A_{3} \) methylation, but also other organs, especially the kidneys, have been shown to exert methylation capacity (Abernathy et al. 1999). Arsenic and its metabolites were excreted in urine, predominantly as methylated species, with a large variation across individuals and populations (Vahter 2000).

To investigate the association of urinary As with environmental As, several factors have to be controlled. Smoking was not a significant determinant of urinary As levels, confirming studies in European populations (Gebel et al. 1998; Kurttio et al. 1998). Because of the high age of our study subjects, occupational exposure was of minor concern as confounder. Dietary As uptake, especially from fish consumption, increased urinary DMA significantly. In the Slovak diet, shellfish is of minor concern. Furthermore, a normal kidney function has to be assumed, for which creatinine filtration rate is considered a crude indicator. The kidneys are prone to nephropathologic end-stage effects of common diseases such as diabetes and hypertension. Arsenic exposure has also been discussed as a risk factor for hypertension and diabetes (Rahman et al. 1998, 1999). After controlling for fish consumption and urine quality, As excretion was found strongly correlated with creatinine excretion, which has been also reported in literature (Telolahy et al. 1995).

In a German population survey, As concentrations were about 40% higher among men than among women (German Federal Health Office 1989). We found \( A_{\text{sum}} \) and \( A_{\text{methyl}} \) increased in men, but not \( A_{\text{inorg}} \). Younger persons showed higher urinary As. A residual confounding from occupational exposure in younger men cannot be excluded. Besides the possible impact of sex- and age-related differences in As exposure and excretion (Buchet et al. 1996; Gebel et al. 1998), differences in the methylation capacity could be of importance. Blood concentrations of SAM were found to be higher in men (Poirier et al. 2001), and GSH levels were found to be decreased in older individuals (van Lieshout and Peters 1998), but the data on age- and sex-related changes of the methylation capacity are still limited.

**Exposure to environmental arsenic and urinary arsenic excretion.** In 1999, the As contents in soil samples of the Prievidza District > 10 km from the power plant were within the range of background levels (2–20 µg/g) for Europe (Gebel et al. 1998) but were still significantly increased, by a factor of about 2, within the vicinity of the power plant. In the 1970s, at the time of highest As emission, urinary As levels in 10-year-old boys living within 7.5 km of the plant were found to be three times higher than for boys living farther away (Bencko and Symon 1977). The concentrations were as high as in occupationally As-exposed boiler cleaners in the 1990s, with concentrations of

![Figure 1](image1.png) **Figure 1.** Urinary arsenic concentrations by distance of places of residence to the power plant, EXPASCAN Study, Prievidza District, Slovakia, 1999: box plot in logarithmic scale. Abbreviations: Max, maximum; min, minimum.

![Figure 2](image2.png) **Figure 2.** Arsenic in urine and soil, sampled at the places of residence of the study subjects, EXPASCAN Study, Prievidza District, Slovakia, 1999. For linear regression and Pearson correlation, variables are log transformed. \( r = 0.21 (p < 0.01), \) \( y = 3.025 \times x^{0.237}, \) \( n = 159. \)
kinetics of the stepwise enzymatic methylation may be of importance. It is not known with certainty if the methylation is saturable (U.S. EPA 2001).

Only a few studies have investigated the impact of low-level arsenic exposure on biomarkers for marker burden in more detail. In a U.S. population exposed to As in drinking water containing up to 66.6 µg/L, environmental As exposure was associated with both urinary As and toenail As (Karagas et al. 2001). The majority of significant associations were found in environmental settings with high As exposure, such as the historical study of urinary As in children of this district (Bencoko and Symon 1977). Also in the vicinity of a former copper smelter in the U.S. state of Montana, urinary As in children was significantly related to the pollution source (Hwang et al. 1997). In a German region with As soil concentrations above the European average, urinary As of the adult study subjects was significantly correlated with As in soil but with a less pronounced association with consumption of homegrown food (Gebel et al. 1998). We found a significant association between self-supply of homegrown food and MMA but not with oral exposure, such as the historical study of urinary As in children of this district (Bencoko and Symon 1977). Also in the vicinity of a former copper smelter in the U.S. state of Montana, urinary As in children was significantly related to the pollution source (Hwang et al. 1997).

Health effects of arsenic. Arsenic binds to sulfhydryl groups and thus accumulates in keratin-rich tissues such as the skin. In the study region, NMSC incidence has been highest in Slovakia, but not lung and bladder cancer incidence (Nieuwenhuijsen et al. 2001; SK NCI 2000). The NMSC cases had significantly elevated urinary levels of Asenviron, MMA, and DMA, after controlling for age, sex, creatinine, and environmental As exposure, even under the current lower exposure levels. For cases, differences in both As exposure and biomethylation should be considered. A significant impact of environmental As exposure on the NMSC risk has been previously reported (Pesch et al. 2002).

| Covariates | R² | Creatinine in urine | Sex | Age | NMSC cases vs. controls | Food | Asenviron |
|------------|----|---------------------|-----|-----|-------------------------|------|-----------|
| Regression model for the place of residence (Res1; n = 411) |
| Asenviron (µg/L) | 0.32 | 0.48 | 1.14 | 1.26 | 1.12 | — | 1.27 |
| p < 0.001 | p = 0.022 | p = 0.003 | p = 0.030 | — | p = 0.002 |
| Asmethyl (µg/L) | 0.32 | 0.49 | 1.15 | 1.17 | 1.32 | — | 1.40 |
| p < 0.001 | p = 0.036 | p = 0.094 | — | p < 0.001 | p < 0.001 |
| MMA (µg/L) | 0.27 | 0.45 | 1.25 | 1.39 | 1.21 | — | 1.36 |
| p < 0.001 | p = 0.028 | p = 0.020 | p = 0.045 | — | p = 0.028 |
| DMA (µg/L) | 0.22 | 0.41 | 0.82 | — | — | — | 0.72 |
| p < 0.001 | p = 0.002 | — | — | — | p = 0.006 |
| MMA/DMA | 0.04 | — | 0.17 | — | 0.83 | — | 0.08 |
| p < 0.001 | — | — | — | — | p = 0.020 |

Regression model for arsenic in soil (Asenviron; n = 159)

| Asenviron (µg/L) | 0.37 | 0.49 | 1.17 | 1.35 | 1.18 | — | 1.36 |
| p < 0.001 | p = 0.079 | p = 0.013 | p = 0.053 | — | p = 0.002 |
| Asmethyl (µg/L) | 0.31 | 0.31 | — | 1.18 | 1.36 | — | 1.18 |
| p < 0.001 | p = 0.001 | p = 0.035 | p < 0.001 | — | p = 0.010 |
| MMA (µg/L) | 0.34 | 0.51 | 1.21 | — | — | — | 1.30 |
| p < 0.001 | p = 0.008 | — | — | — | p = 0.022 |
| DMA (µg/L) | 0.28 | 0.41 | 1.33 | 1.69 | — | — | 1.44 |
| p < 0.001 | p = 0.039 | p = 0.005 | — | — | p = 0.015 |
| Asmethyl/MMA | 0.24 | 0.37 | 0.78 | 0.78 | 1.22 | — | 0.82 |
| p < 0.001 | p = 0.022 | p = 0.085 | p = 0.052 | — | p = 0.094 |
| MMA/DMA | 0.02 | — | — | 0.74 | — | — | 0.073 |

Results are represented as means ratios (sex, age, cases vs. controls, food) or standardized regression coefficients (creatinine) with p-values. —, Exclusion of the respective covariable by stepwise regression.

Younger versus older with an age difference of 30 years. Consumption of homegrown products: yes versus no. Environmental arsenic determined by place of residence (Res1, ≤ 5 km from the power plant versus > 5 km) or by arsenic in soil (Asenviron, 70 µg/g versus 20 µg/g).
The chemical speciation of As is important for its health effects, but the mechanisms responsible for carcinogenesis have not yet been established (Abernathy et al. 1999; Basu et al. 2001). Although the International Agency for Research on Cancer (IARC) has classified As a human carcinogen (IARC 1987), the U.S. EPA has classified only As$_{inorg}$ as carcinogenic (U.S. EPA 1984). Organic As was found less toxic than As$_{inorg}$ and As$_{III}$ but has been considered more toxic than As$_V$ (Quevauviller et al. 1995). New data indicate oxidative stress from chronic arsenic exposure (Pi et al. 2002). There is growing evidence that the methylated species can be involved in the process of carcinogenesis, and DMA was found to be an especially potent agent in genotoxic test systems (Basu et al. 2001; Gebel 2001).

In a U.S. population-based case-control study, NMSC cases were more prevalent above the 97th percentile of toenail As, although this result was not significant (Karagas et al. 2001). In NMSC cases, we found a higher concentration of As$_{sum}$, As$_{inorg}$, and DMA. SAM is the common methyl donor, shared for a variety of methylation processes, including As biotransformation and DNA methylation (Goering et al. 1999; Poiret et al. 2001). Arsenic excretion was strongly correlated with SAM excretion (Telolahy et al. 1995). If SAM was experimentally depleted, urinary As excretion was markedly depleted, urinary As excretion was found to be an especially potent agent in genotoxic test systems (Basu et al. 2001; Gebel 2001).

Conclusions

Although in the Slovak district the recent levels of environmental As exposure were close to the European average, there was a significant variation of As in soil, house dust, and urinary As by distance from the power plant, and there was a significant association between environmental and urinary As. The environmental effect was shown for As$_{sum}$ and the methylated species but not for As$_{inorg}$. The multivariate analysis of the impact of environmental As from soil and dust and future from the last places of the study subjects on As in spot urine samples, if controlled for urine quality and confounders, accounted for about 30% of the variance of urinary As. The NMSC cases had higher As levels than did population controls. The methylation index As$_{inorg}$/MMA + DMA was about 20% lower among cases than controls ($p < 0.05$) and in men than in women ($p < 0.05$). The speciation into As$_{inorg}$, As$_{methyl}$, MMA, and DMA offered additional information on As.