

# Arsenic in Drinking Water and Bladder Cancer Mortality in the United States: An Analysis Based on 133 U.S. Counties and 30 Years of Observation

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*This study analyzes the relationship between arsenic exposure through drinking water and bladder cancer mortality. The county-specific white male bladder cancer mortality data (1950–1979) and county-specific groundwater arsenic concentration data were obtained for 133 U.S. counties known to be exclusively dependent on groundwater for their public drinking water supply. No arsenic-related increase in bladder cancer mortality was found over the exposure range of 3 to 60 µg/L using stratified analysis and regression analyses (both unweighted and weighted by county population and using both mean and median arsenic concentrations). These results, which provide a direct estimate of arsenic-related cancer risk for U.S. residents, exclude the National Research Council's 2001 risk estimate that was based on Southwest Taiwan data and required adjusting for differences between the body mass and water consumption rates of U.S. and Taiwanese residents. (J Occup Environ Med. 2004;46:298–306)*

Arsenic has long been known to be a human carcinogen, primarily on the basis of epidemiologic evidence. The relationship between arsenic exposure and various cancers is most clear with respect to the link between occupational inhalation of arsenic in copper smelters and other metal plants and lung cancer,<sup>1</sup> and the association between ingestion of arsenic by drinking water and skin cancer.<sup>2</sup> More recently, studies from Asia (Taiwan, Japan, and Inner Mongolia) and Latin America (Chile, Argentina, and Mexico) have indicated that ingestion of arsenic in drinking water could also cause bladder, liver, or lung cancer.<sup>3–10</sup>

Three parts of the world are of great interest to practitioners of environmental medicine concerned with the health-related effects of exposure to arsenic in drinking water: Southwest Taiwan, the regions of West Bengal and Bangladesh, and the United States. Current Taiwanese regulations allow a maximum of 10 µg/L arsenic in drinking water, however, between 1920 and the mid-1960s, populations in parts of Southwest Taiwan were exposed to concentrations of hundreds of micrograms per liter arsenic in drinking water from artesian wells. This long exposure period has made Southwest Taiwan the primary place to investigate the long-term effects of arsenic exposure. Studies of those regions have linked Black-Foot Disease (BFD) to the use of water from these

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wells,<sup>11</sup> and further work attributed it to either the arsenic<sup>2</sup> or the humic acids in the water.<sup>12</sup> Other studies have investigated the relationship between arsenic exposure in this area and chronic arsenicism and skin cancer<sup>2</sup>; cancers of the bladder, skin, kidney, lung, liver, and colon<sup>13</sup>; peripheral and cardiovascular diseases<sup>14</sup>; and noninsulin-dependent diabetes mellitus.<sup>15</sup>

In contrast to Southwest Taiwan, West Bengal and Bangladesh face an ongoing problem with widespread exposure to very high concentrations of arsenic in drinking water. Between 35 and 77 million of Bangladesh's 125 million residents are now thought to be exposed to arsenic in drinking water that in some sources exceeds 2000  $\mu\text{g/L}$ .<sup>16</sup> In West Bengal, an estimated 1 million residents are exposed to groundwater containing up to 3900  $\mu\text{g/L}$ .<sup>17</sup> The large populations of these regions, coupled with concentrations of arsenic in drinking water in the hundreds or thousands of micrograms per liter, already constitute what many consider a public health cataclysm. Furthermore, because some cancers have a latency period of 20 to 30 years, and widespread exposure to these very high concentrations of arsenic began only in the 1970s with the drilling of millions of tube wells, it could be that the full effect of arsenic exposure in West Bengal and Bangladesh is yet to be seen.

Southwest Taiwan, West Bengal, and Bangladesh are of interest because of their extremely high concentrations of arsenic. The United States, on the other hand, is of interest because although its arsenic concentrations are quite low in comparison to those other regions, assessments of health risks incurred by U.S. residents from exposure to arsenic in drinking water are made by extrapolating from non-U.S. data. For instance, the National Research Council's (NRC) 2001 risk assessment for arsenic in drinking water<sup>18</sup> and the U.S. Environmental Protection Agency's (EPA) 2001 revision of the U.S. drinking water standard

for arsenic from 50  $\mu\text{g/L}$  (which had been the U.S. standard since 1974) to 10  $\mu\text{g/L}$ <sup>19,20</sup> were based primarily on the Morales et al. analysis of Wu et al.'s data from Southwest Taiwan.<sup>21</sup> Studies from the United States, however, where drinking waters contain arsenic measured up to the 10s of micrograms per liter, have not demonstrated arsenic carcinogenicity.

We have conducted an ecologic study of male bladder cancer mortality in the United States to see whether U.S. populations exposed to U.S. levels of arsenic in drinking water experience the bladder mortality rates predicted from the Southwest Taiwan data. The present study is designed to be analogous to the Wu et al. (1989) Southwest Taiwan study,<sup>21</sup> but has 2 important advantages. First, because it is conducted with U.S. exposure data, extrapolations to the exposure range of interest (3–60  $\mu\text{g/L}$ ) are unnecessary. Second, because it is conducted with a U.S. population, conversions for differences in body size and water consumption rates are not required. Two orders of magnitude greater in size than the Southwest Taiwan study, this study offers potential advantages of statistical power to offset the lower sensitivity inherent in the investigation of low-exposure effects.

## Materials and Methods

This study combined county-specific white male (WM) bladder cancer mortality data for the period 1950 to 1979 from the National Cancer Institute (NCI) and EPA<sup>22</sup> with county-specific arsenic groundwater data from the U.S. Geological Survey (USGS).<sup>23</sup> Population data came from the U.S. Census Bureau, and state departments of health or environment provided the information used to identify those counties that have historically depended exclusively on groundwater as their source of drinking water. Merging these data produced a database for an ecologic study of drinking water arsenic and bladder cancer mortality in the United States that includes over 4500 U.S. WM

bladder cancer deaths and over 75 million person-years (PY) of observation.

The USGS groundwater arsenic data is a publicly available set of county-specific summary statistics (median and mean) of arsenic levels in groundwater well sources. From this dataset, 268 counties in the contiguous United States with median groundwater source arsenic levels of 3  $\mu\text{g/L}$  or greater were identified. Of these, 196 counties also had WM bladder cancer mortality data that included at least one WM bladder cancer death and an annual average age-adjusted death rate for each of the decades 1950–1959, 1960–1969, and 1970–1979. State departments of health or departments of the environment were contacted to determine water source information for each county; of the 196 counties, 133 were found to depend historically and currently exclusively on groundwater for their drinking water. These 133 counties in 26 states served as the study population for these analyses.

The county-specific WM bladder cancer standardized mortality ratios (SMRs) were plotted against the median groundwater arsenic level and analyzed using least-square linear regression, with each county weighted equally in the regression analysis. Inspection of the data showed that the scatter in the data was larger than sampling error alone would contribute. This variation could be due to differences in population (since the study counties varied widely with respect to population and the number of WM bladder cancer deaths observed in each) or to other factors relevant to bladder cancer etiology such as smoking, urbanization, and industrialization for which our analysis does not directly adjust.

Because these factors could affect the validity of the regression analysis (by violating the requirement that the variance of the dependent variable be constant), 2 further analyses were performed to identify their possible effects on the results: 1) the regres-

sion was repeated using only the 98 counties with at least 10 cases, and 2) weighted regression was performed using weights  $w_i = (0.06 + n_i^{-1})^{-1}$ , where  $n_i$  is the number of bladder cancer cases in the  $i^{\text{th}}$  county. Each of these analyses was repeated using the mean as the independent variable; the results were not appreciably different.

The county-specific WM bladder cancer SMR is the ratio of the observed number of WM bladder cancer deaths in a county to the expected number. For each county and each state in the study, the number of WM bladder cancer deaths and the average annual age-adjusted (to U.S. 1970 standard population) death rate per 100,000 were abstracted for each decade. The expected number of deaths for each county was calculated for each decade by dividing the number of observed deaths in that county by the ratio of the decade-specific mortality rate of the county to the decade-specific mortality rate of the state. Thus, the expected numbers are the numbers of deaths that would have been expected if that county's WM population had had the state's mortality rate. The 30-year SMR for each county was calculated by dividing the number of WM bladder cancer deaths observed over the 3 decade period by the number of expected WM bladder cancer deaths over the 3 decades for that county. Least-square linear regression analyses were conducted (as described previously), and the resulting curves were graphed on the plot of county SMRs by median arsenic level.

The same data were investigated stratified by arsenic exposure level. The ratio of the observed to the expected number of WM bladder cancer deaths for the counties in each exposure stratum was calculated, 2-tailed 95% confidence limits of each ratio were determined, and a 2-sided chi-squared test for trend was performed.

County-specific WM bladder cancer lifetime mortality rates per PY were calculated according to the following formula, using 1960 population figures to represent county pop-

ulations between 1950 and 1979 and assuming a 75-year average lifespan:

$$\text{Mortality Rate} = \left( \frac{\text{WM Bladder Cancer Deaths (1950-79)}}{\text{WM 1960 Population}} \right) \times \left( \frac{75 \text{ year lifespan}}{30 \text{ year observation}} \right)$$

Regression analyses (as described previously) were conducted on county-specific WM bladder cancer lifetime mortality rates, and the results were plotted against both the median and mean arsenic levels. The 95% confidence limits of the estimated slope of that regression line provide the range of slopes consistent with the U.S. data.

## Results

The study population was comprised of 2.5 million WMs in 133 counties in 26 states. The observation period was 30 years (1950–1979). Assuming that the 1960 population was representative of the population over the observation period, the study comprised over 75 million PYs of observation and 4537 bladder cancer deaths. The overall

observed bladder cancer mortality rate was 6 per 100,000 PY. The median groundwater arsenic exposure levels in these 133 counties are 3 to 60  $\mu\text{g/L}$ , with 65% of these counties and 82% of the population in the range of 3 to 5  $\mu\text{g/L}$ .

## Relative Rates (SMRs)

County-specific WM bladder cancer SMRs are shown in Figure 1. Linear regression revealed no evidence of an arsenic-dependent rate increase in this 3 to 60  $\mu\text{g/L}$  exposure range (F statistic = 0.69 on 1 and 131 df, significance of F-statistic = 0.41).

The slope estimate of the regression line ( $\beta$ ) is indistinguishable from zero ( $\beta = -0.004$ , 95% CI =  $-0.01$ – $+0.01$ ) and the estimated y-intercept ( $\alpha$ ) is 0.97 (95% CI =  $+0.88$ – $+1.05$ ). The statistical analysis seems to indicate that the WM bladder cancer SMR is not adversely influenced by exposure to arsenic in the groundwater in the concentrations found in these counties. Regression analysis limited to the 3- to 30- $\mu\text{g/L}$  range shows similar results, with a slope estimate indistinguish-

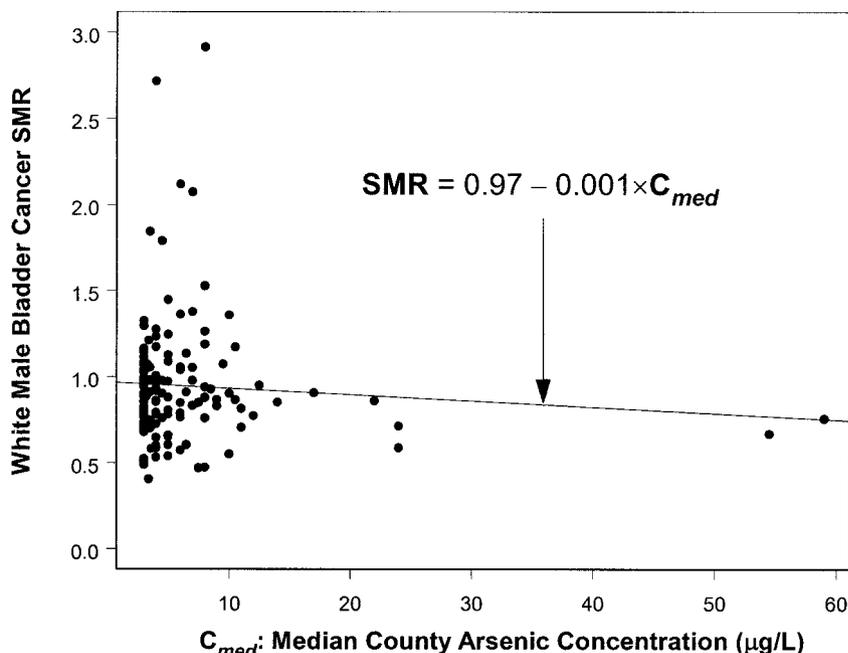


Fig. 1. White male bladder cancer mortality relative rate (1950–1979) (U.S. counties with median arsenic levels of  $\geq 3$   $\mu\text{g/L}$  in drinking water).

able from zero ( $\beta = -0.001$ , 95% CI =  $-0.02$ – $+0.02$ ;  $\alpha = 0.96$ , 95% CI =  $+0.84$ – $+1.07$ ).

Results obtained when the mean arsenic concentration is used as the independent variable are similar: for all 133 counties,  $\beta = -0.001$  (95% CI =  $-0.003$ – $+0.001$ ) and  $\alpha = 0.96$  (95% CI =  $+0.89$ – $+1.05$ ). When the data are restricted to the 98 counties with 10 or more cases,  $\beta = -0.001$  (95% CI =  $-0.03$ – $+0.002$ ) and  $\alpha = 0.99$  (95% CI,  $+0.92$ – $+1.07$ ). Weighted regression ( $w_i = [0.06+n^{-1}]^{-1}$ ) yields estimates of  $\beta = -0.001$  (95% CI =  $-0.004$ – $+0.001$ ) and  $\alpha = 0.94$  (95% CI =  $+0.87$ – $+1.02$ ).

Stratified analysis presented in Table 1 shows that the overall SMR is 0.94 (95% CI = 0.90–0.98). For different exposure levels in the range of 3.0–19.9  $\mu\text{g/L}$ , the exposure-specific SMR values range between 0.89 and 0.97. The counties in the study have lower bladder cancer mortality rates than do their states, suggesting that state data could be more heavily influenced by other bladder cancer mortality risk factors such as urbanity, industrialization, and cigarette smoking. At higher levels of arsenic exposure (20–59.9  $\mu\text{g/L}$ ), the SMRs decrease, although none of these results are statistically significant. A chi-squared test for trend indicates a statistically insignificant decrease in the number of observed WM bladder cancer deaths relative to the

number of expected WM bladder cancer deaths as arsenic concentrations increase ( $P = 0.16$  for 2-sided test; chi-square = 1.99).

### Lifetime Bladder Cancer Mortality Rates

Assuming a lifespan of 75 years for WMs in the United States, the lifetime rate of bladder cancer mortality for WMs exposed to 3 to 60  $\mu\text{g/L}$  is approximately 0.005 (1 in 200). Figure 2 plots the county-specific lifetime WM bladder cancer mortality rate against the county-specific median arsenic concentration for the 133 counties. The figure also includes the NRC 2001 predicted U.S. male (white and non-white) risk of  $4.5 \times 10^{-5}$  deaths per 1  $\mu\text{g/L}$  arsenic for comparison (calculated from Table ES-1 and using the NRC assumption that the mortality rate is 20% of the incidence rate).<sup>18</sup>

When all 133 counties are used, the estimated slope ( $\beta$ ) of this regression line is  $-3.5 \times 10^{-6}$  (95% CI =  $-5.0 \times 10^{-5}$ – $+4.2 \times 10^{-5}$ ) and the estimated y-intercept ( $\alpha$ ) of this line is  $4.9 \times 10^{-3}$  (95% CI =  $+4.5 \times 10^{-3}$ – $+5.3 \times 10^{-3}$ ). When the analysis is limited to the 98 counties with 10 or more deaths, the slope estimate is positive but statistically indistinguishable from zero ( $\beta = +6.7 \times 10^{-6}$ , 95% CI =  $-5.3 \times 10^{-5}$ – $+6.6 \times 10^{-5}$ ). With weighted regres-

sion ( $w_i = [0.06+n^{-1}]^{-1}$ ), the estimates are  $\beta = +1.8 \times 10^{-6}$  (95% CI =  $-4.9 \times 10^{-5}$ – $+5.3 \times 10^{-5}$ ) and  $\alpha = 5.0 \times 10^{-3}$  (95% CI =  $+4.5 \times 10^{-3}$ – $+5.4 \times 10^{-3}$ ).

Figure 3 presents the results of analyses in which the mean arsenic concentration is used as the independent variable (along with the NRC 2001 predicted risk).

When all 133 counties are used, the estimate of  $\beta$  is  $-4.7 \times 10^{-6}$  (95% CI =  $-1.7 \times 10^{-5}$ – $+7.3 \times 10^{-6}$ ) and the estimate of  $\alpha$  is  $4.9 \times 10^{-3}$  (95% CI =  $+4.6 \times 10^{-3}$ – $+5.3 \times 10^{-3}$ ). When the analysis is limited to the 98 counties with at least 10 cases,  $\beta = -4.0 \times 10^{-6}$  (95% CI =  $-1.9 \times 10^{-5}$ – $+1.1 \times 10^{-5}$ ) and  $\alpha = 5.2 \times 10^{-3}$  (95% CI =  $+4.8 \times 10^{-3}$ – $+5.6 \times 10^{-3}$ ). When weighted regression ( $w_i = [0.06+n^{-1}]^{-1}$ ) is used, similar estimates are obtained:  $\beta = -5.1 \times 10^{-6}$  (95% CI =  $-1.9 \times 10^{-5}$ – $+8.5 \times 10^{-6}$ ) and  $\alpha = 5.1 \times 10^{-3}$  (95% CI =  $+4.7 \times 10^{-3}$ – $+5.4 \times 10^{-3}$ ).

These analyses indicate that over the range of arsenic concentrations (median, 3–60  $\mu\text{g/L}$ ; mean, 3–255  $\mu\text{g/L}$ ) considered in this study, no increase in the lifetime mortality rate was found. In addition, the NRC's lifetime mortality estimate falls above the upper 95% confidence limits indicated for WM bladder cancer lifetime mortality ( $4.2 \times 10^{-5}$  for regression on median arsenic con-

TABLE 1

White Male (WM) Bladder Cancer Standardized Mortality Ratios (SMRs) Stratified by Median Arsenic Concentration in Groundwater

$\mu\text{g/L}$	Counties	1960 WM population	Median arsenic exposure	Observed	Expected	SMR	95% CI
3.0–3.9	53	1,108,868	3.00	1962	2065	0.95	0.89–1.01
4.0–4.9	22	833,587	4.00	1519	1604	0.95	0.88–1.02
5.0–7.4	28	246,638	6.00	409	420	0.97	0.85–1.12
7.5–9.9	14	114,459	8.00	231	259	0.89	0.75–1.06
10.0–19.9	11	156,775	11.00	349	386	0.90	0.78–1.04
20.0–49.9	3	24,124	24.00	46	58	0.80	0.54–1.17
50.0–59.9	2	13,734	56.75	21	29	0.73	0.41–1.27
Totals	133	2,498,185		4537	4820	0.94	0.90–0.98

CI, confidence interval.

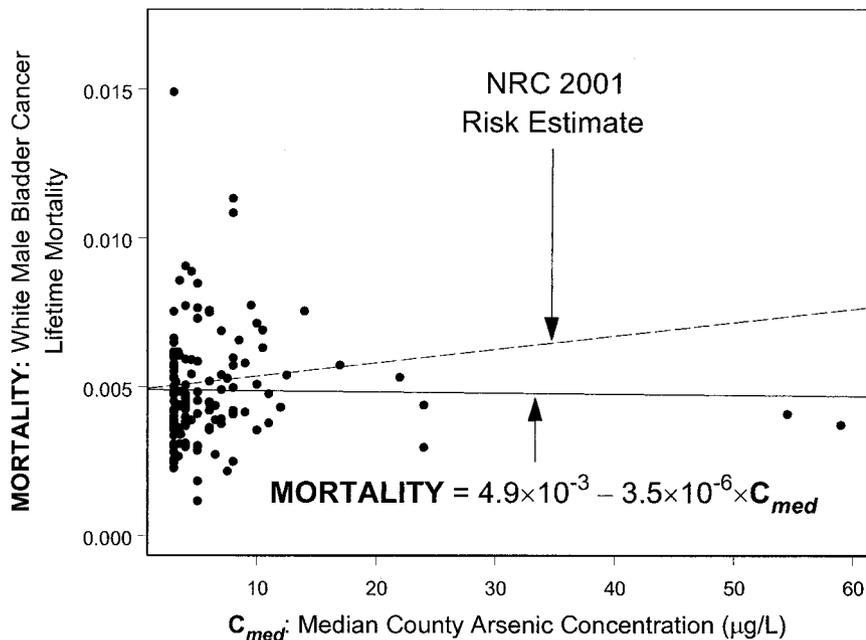


Fig. 2. White male bladder cancer lifetime mortality rate by median arsenic concentration (U.S. counties with median arsenic levels of  $\geq 3 \mu\text{g/L}$  in drinking water).

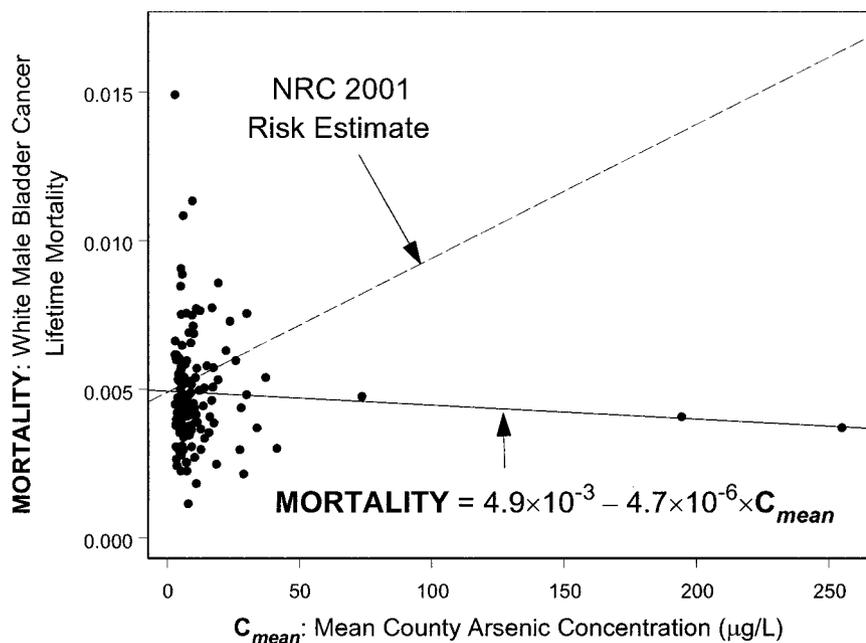


Fig. 3. White male bladder cancer lifetime mortality rate by Mean arsenic concentration (U.S. counties with median arsenic levels of  $\geq 3 \mu\text{g/L}$  in drinking water).

centration;  $8.5 \times 10^{-6}$  for weighted regression on mean concentration). However, the EPA's 2001 slope estimates are lower and *not* excluded by the data.

## Discussion

This is the first nationwide study of the relationship between bladder

cancer mortality and the level of arsenic in U.S. drinking water. It shows no arsenic-related increase in the lifetime WM bladder cancer mortality rate for counties that depend exclusively on groundwater containing median arsenic concentration of 3 to 60  $\mu\text{g/L}$  for their drinking water supplies.

This study is of special importance because it provides an independent evaluation of the estimates of risk that have been the basis for the new U.S. regulations. Furthermore, it is also of general relevance for environmental medicine. The details concerning arsenic's carcinogenicity in humans have been difficult to determine, in part because what we know comes primarily from epidemiologic studies. In particular, there are open questions regarding the proper form of the dose-response curve. Carcinogens that directly alter DNA are appropriately analyzed with a model with a single parameter characterizing the per-unit increase in either incidence or mortality. Arsenic, however, does not appear to alter DNA in this way, and studies have suggested that its carcinogenic effects are more appropriately described with a threshold model.<sup>24</sup> The size of the present study should make it a valuable source of data for determining the health effects of low-level arsenic exposure. Learning at what concentration health outcomes of interest begin to increase will, in turn, be helpful in making decisions about remediation policies in regions of the world where arsenic exposure is most acute.

Because this is an ecologic study, caution should be exercised in using its results to derive a dose-response relationship or rate slope. The data in this study are aggregated at the county level, and because of the "ecologic fallacy," it is possible that the relationship between arsenic exposure and mortality at that level does not represent the relationship at the individual level. Even recognizing the inherent limitations of ecologic studies, however, the size of this study (with a population of 2.5 million observed for a 30-year period) makes it an important new source of information about the carcinogenic effects of low-level ( $< 100 \mu\text{g/L}$ ) exposure to arsenic in drinking water. The finding that there is no arsenic-related increase in WM bladder cancer mortality for expo-

tures between 3 and 60  $\mu\text{g/L}$  suggests that, at least with respect to bladder cancer mortality, there are diminishing returns on drinking water arsenic levels reductions below the prior arsenic standard of 50  $\mu\text{g/L}$ .

The conclusion of this study is consistent with most of the rest of the world's literature on bladder cancer mortality and drinking water arsenic levels. In Taiwan, Morales et al. found no increase in bladder cancer mortality with arsenic exposure levels below 400  $\mu\text{g/L}$ ,<sup>3</sup> Guo and Tseng found no increase until 640  $\mu\text{g/L}$ ,<sup>25</sup> and Chiou et al. found a statistically significant increase only above 100  $\mu\text{g/L}$ , with half of those residents having exposures over 300  $\mu\text{g/L}$ .<sup>4</sup> In Latin America, Hopenhayn-Rich et al. reported an increased rate in an Argentinean population with exposures up to 533  $\mu\text{g/L}$ ,<sup>8</sup> and Smith et al. reported an increased rate in a population in Northern Chile with exposures of 570  $\mu\text{g/L}$  for 15 years.<sup>7</sup> In Asia, Tsuda et al. reported no urinary cancers with exposure levels below 1000  $\mu\text{g/L}$ .<sup>5</sup> In Britain, Cuzick et al. followed a group of patients treated with Fowler's solution and found excess bladder cancers only for those with estimated exposures of greater than 1400  $\mu\text{g/L}$ .<sup>26</sup> The only apparent exception was the report of Kurtzio et al. of an increased bladder cancer rate at exposures above 0.5  $\mu\text{g/L}$ ; however, this increase was limited to cigarette smokers.<sup>27</sup>

The results of this study are also consistent with results from the only other prior studies of bladder cancer and arsenic in drinking water conducted in the United States. Two of these studies were conducted with populations in Utah, and neither found an association between arsenic and bladder cancer in its study population. In 1995, Bates et al. published a case-control study based on 117 cases and 226 controls from the Utah study area of the National Bladder Cancer Study for 1978.<sup>28</sup> Although the results of that study could not by themselves exclude the NRC

rate estimate, the authors concluded that "there was no overall association of inorganic arsenic with risk of bladder cancer."

In 1999, Lewis et al. published a population cohort mortality study.<sup>29</sup> The Lewis study population consisted of 4058 residents of towns in Millard County, Utah, with median drinking water arsenic concentrations ranging from 14 to 166  $\mu\text{g/L}$ . The median and weighted mean arsenic levels for the county are each approximately 100  $\mu\text{g/L}$ . Although that study also could not exclude the NRC rate estimate, its authors took their observation of only 5 bladder cancer deaths (when 9 were expected) as "perhaps indicating that bladder cancer occurs in response to higher arsenic concentrations"—higher, that is, than those experienced by the Utah population.

A third U.S. study of specific counties in Nevada and California by the Bates group has recently reported similar results.<sup>30</sup> Their analysis of bladder cancer incidence in exposed populations (including Fallon, Nevada, and Hanford, California, which have historically been exposed to drinking water arsenic concentrations of approximately 100  $\mu\text{g/L}$ ) found no increased risks of bladder cancer at exposure greater than 80  $\mu\text{g}$  per day and that "overall, no clear association was identified between bladder cancer risk and the exposures found in [their] study area." Just as we found with respect to bladder cancer mortality, they found that the bladder cancer incidence in the study population was below that which would have been predicted using the Taiwan data. They also noted the possible synergistic effects of smoking and arsenic exposure evident in other studies<sup>27,28</sup> and concluded that "the results of this study suggest that smokers who drink water containing arsenic at concentrations near 200  $\mu\text{g/day}$  may be at increased risk of bladder cancer compared with smokers at lower arsenic exposures."

A positive low-dose linear relationship is generally posited for genotoxic carcinogens. Guess et al. have proposed for any pollutant whose outcome is indistinguishable from one that occurs naturally that there is some exposure level at which the pollutant acts the same way as the natural process and for such a pollutant and at such levels the dose-response curve is continuous.<sup>31</sup> Taylor's theorem would then imply that the curve could be approximated by a straight line for "low" doses. Although Taylor's Theorem implies that a continuous function can be approximated by a straight line around zero, it does not specify how far from zero this approximation holds or that it holds for outcomes that are not comparable to those occurring naturally.

The mechanism by which arsenic causes human cancers (and does not appear to cause cancers in other animals) is unknown. Multiple mechanisms have been proposed that would be consistent with the absence of a positive low-dose linear relationship.<sup>24,32</sup> Because arsenic is a nongenotoxic carcinogen, it is not necessary to assume that arsenic-induced bladder cancers are induced in the same manner that nonarsenic-induced bladder cancers occur.

The strength of the conclusions drawn from this study depends on the validity of the assumptions used to draw them. The present study, like previous ecologic studies of the health effects of arsenic in drinking water, assumes that the study population consumed the local drinking water and that the available arsenic measurement for the local drinking waters are representative of their actual contents. In this study, exposure for each county is based on measures from at least 5 wells,<sup>23</sup> whereas in the Wu et al. Southwest Taiwan study, the exposure data for nearly half (47%) of the study villages are represented by one measurement or measurement of only one well.<sup>33</sup> Ecologic studies with population-assigned dosages (including this one

and the Wu et al. study from South-west Taiwan) generally are unable to assess the consequences of in- and outmigration of individuals.

The USGS database describes the arsenic content of U.S. groundwater rather than water sources used for drinking water. In a comparison between groundwater resources used for public drinking water and other groundwater sources, however, the USGS found that the medians of the groundwater arsenic measurements were “equivalent” to the medians of the public water supply sources and “differ[ed] by no more than 1  $\mu\text{g/L}$ ” for approximately 75% of the data.

This report has limited itself to the analysis of data for counties that have historically received 100% of their drinking water from groundwater sources. The analyses in this report have assumed that the median groundwater arsenic level for a county represents the arsenic concentration of water consumed by that county’s residents between 1950 and 1979. Use of the mean (rather than the median) concentration would yield mathematically exact slope estimates. However, analyses using the mean might unduly weight the sources with high concentrations that may be avoided by residents. Either assumption, therefore, brings in some unmeasured uncertainty to the analysis.

As reported by the USGS, measurements were generally made of water that was filtered to remove large particulates, but was otherwise

untreated. This period of exposure precedes the 1980s when the EPA began major funding of water treatment programs to bring drinking water contaminant levels into compliance with levels in the Safe Drinking Water Act of 1974. Furthermore, since the drinking water arsenic standard was lowered from 50  $\mu\text{g/L}$  to 10  $\mu\text{g/L}$  in 2004, that change could have had no effect on this study population because the period of observation had ceased nearly 25 years earlier. It is also unlikely that bottled water was a major alternative source of drinking water supplies in these counties during the period from 1950 to 1979 because the great rise in that industry did not begin before the 1980s.

A further source of uncertainty is the amount of scatter in the data. The reason for the scatter of the points around the regression lines is unknown, although it does not appear to be correlated with the arsenic concentrations. As has been noted, factors such as smoking, urbanization, and industrialization are associated with bladder cancer and smoking, and arsenic exposure could act synergistically to cause cancer. Because large urban populations are not likely to depend exclusively on groundwater sources for their drinking water, urbanization might not be a major factor in accounting for this variation. However, additional information about smoking, industrialization, and other possible sources of this variation could affect these conclusions or allow

for adjustments that could increase the sensitivity of the analysis.

This excess scatter could affect the accuracy of the estimates of the arsenic-related change in lifetime mortality (ie, the slope of the regression line). To assess the possible effect of this, different analyses (with results summarized in Table 2) have been performed. In each case, the estimated slope is statistically indistinguishable from zero. Furthermore, each estimate is lower than the NRC 2001 predicted risk factor for U.S. males of  $4.5 \times 10^{-5}$ , and the 95% confidence intervals around the slope estimates from 4 of the 6 analyses exclude the NRC’s predicted risk.

The discrepancy between the NRC prediction and the observed mortality rates among U.S. white males highlights the sources of uncertainty that must be considered when predicting risk for one population with data from a different population. (See Table 6–2 of the NRC 2001 report for details on the assumptions used to make its and EPA’s risk estimates.) For instance, the NRC’s estimate of U.S. mortality risk reflects the use of U.S. background bladder cancer rates. Using estimates of Taiwan background rates would yield a substantially lower risk estimate (Table 6–1, p. 218).

Conversion from Taiwan data to U.S. estimates also required making assumptions about the average weights of U.S. and Taiwan residents (70 kg and 55 kg, respectively) and daily water consumption (1 L for

**TABLE 2**  
Results of Regression Analyses\*

Independent variable	Analysis	Slope estimate	95% CI (lower; upper)
Median arsenic concentration	Equal weights, 133 counties:	$-3.5 \times 10^{-6}$	$-5.0 \times 10^{-5}; +4.2 \times 10^{-5}$
	Equal weights, counties with $n \geq 10$ :	$+6.7 \times 10^{-6}$	$-5.3 \times 10^{-5}; +6.6 \times 10^{-5}$
	Counties weighted as $(0.06 + n^{-1})^{-1}$ :	$+1.8 \times 10^{-6}$	$-4.9 \times 10^{-5}; +5.3 \times 10^{-5}$
Mean arsenic concentration	Equal weights, 133 counties:	$-4.7 \times 10^{-6}$	$-1.7 \times 10^{-5}; +7.3 \times 10^{-6}$
	Equal weights, counties with $n \geq 10$ :	$-4.0 \times 10^{-6}$	$-1.9 \times 10^{-5}; +1.1 \times 10^{-5}$
	Counties weighted as $(0.06 + n^{-1})^{-1}$ :	$-5.1 \times 10^{-6}$	$-1.9 \times 10^{-5}; +8.5 \times 10^{-6}$
	NRC 2001 Predicted Slope	$+4.5 \times 10^{-5}$	

CI, confidence interval.

\* Results presented by choice of independent variable (median or mean arsenic concentration), weighting assignments used in the regression, and number of counties used.

U.S. residents, 2 L for Taiwanese). The 2001 NRC report indicated how other plausible values for these quantities could affect the resulting risk estimate (Table 5–8, p. 203).

This, the first nationwide U.S. study of bladder cancer mortality and drinking water arsenic levels, provides an appropriate standard for assessing the accuracy of any quantitative risk analysis for bladder cancer mortality and drinking water arsenic levels representative of the United States. It suggests that there is no arsenic-related increase in bladder cancer mortality in the 3- to 60- $\mu\text{g}/\text{L}$  range and that the estimates of U.S. arsenic-related cancer risk made from Southwest Taiwan data are higher than what is found in the U.S. data. This inconsistency could be the result of a misinterpretation of the Southwest Taiwan data,<sup>32</sup> or it could indicate that one or more of the assumptions necessary to estimate U.S. risk from Southwest Taiwan data are incorrect. The observed lack of an association between bladder cancer mortality and arsenic concentrations below 60  $\mu\text{g}/\text{L}$  are consistent with the findings of previously published U.S. studies and results from non-U.S. studies that considered considerably higher exposure levels.

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