

**Arsenic in Drinking Water
and Bladder Cancer Mortality in the U.S.:**
**An analysis based on 133 U.S. counties
and Thirty Years of Observation[†]**

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ABSTRACT:

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 upon groundwater for their public drinking water supply. No arsenic-related increase in bladder cancer mortality was found over the exposure range of 3–60 $\mu\text{g/L}$ using stratified analysis and using 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 SW Taiwan data and required adjusting for differences between the body mass and water consumption rates of U.S. and Taiwanese residents.

INTRODUCTION:

Arsenic has long been known to be a human carcinogen, primarily on the basis of epidemiological 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,¹ and the association between ingestion of arsenic via drinking water and skin cancer.² More recently, studies from Asia [Taiwan, Japan, and Inner Mongolia] and Latin America [e.g., Chile, Argentina, and Mexico]) have indicated that ingestion of arsenic in drinking water may also cause bladder, liver, and lung cancer.³⁻¹⁰

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: SW Taiwan, the regions of West Bengal and Bangladesh, and the United States. Although current Taiwanese regulations allow a maximum of 10 $\mu\text{g/L}$ arsenic in drinking water, between 1920 and the mid-1960s populations in parts of SW Taiwan were exposed to concentrations of hundreds of $\mu\text{g/L}$ arsenic in drinking water from artesian wells. This long exposure period makes SW Taiwan a natural 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 wells,¹¹ and further work attributed it to either the arsenic² or the humic acids in the water.¹² Other studies have investigated the relationship between arsenic exposure in this area and chronic arsenicism and skin cancer,² cancers of the bladder, skin, kidney, lung, liver, and colon,¹³ peripheral and cardiovascular diseases,¹⁴ and non-insulin-dependent diabetes mellitus.¹⁵

In contrast to SW 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 exceed 2,000 $\mu\text{g/L}$.¹⁶ In West Bengal, an estimated one million residents are exposed to groundwater containing up to 3,900 $\mu\text{g/L}$.¹⁷ The large populations of these regions, coupled with concentrations of arsenic in drinking

water in the hundreds or thousands of $\mu\text{g/L}$, already constitute what many consider a public health cataclysm. Furthermore, since some cancers have a latency period of 20–30 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 may be that the full effect of arsenic exposure in West Bengal and Bangladesh is yet to be seen.

SW 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 while 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 water¹⁸ 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 $\mu\text{g/L}$ ^{19–20} were based primarily on the Morales et al. analysis of Wu et al.'s data from SW Taiwan.²¹ Studies from the United States, however, where drinking waters contain arsenic measured up to the tens of micrograms per liter, have not demonstrated arsenic carcinogenicity.

We have conducted an ecological study of male bladder cancer mortality in the United States in order to see whether U.S. populations exposed to U.S. levels of arsenic in drinking water experience the bladder mortality rates predicted from the SW Taiwan data. The present study is designed to be analogous to the Wu et al. 1989 SW Taiwan study,²¹ but has two 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 SW Taiwan study, this study offers potential advantages of statistical power to offset the lower sensitivity inherent in the investigation of low-exposure effects.

METHODS AND MATERIALS:

This study combined county-specific white male (WM) cancer mortality data for the period 1950–1979 from the National Cancer Institute (NCI) and EPA²² with county-specific arsenic groundwater data from the U.S. Geological Survey (USGS).²³ Population data have come from the U.S. Census Bureau, and state departments of health or environment provided the information used to identify those counties that have depended exclusively on groundwater as their source of drinking water. Merging these data produced a database for an ecological study of drinking water arsenic and bladder cancer mortality in the U.S. that includes over 4,500 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

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 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. Each county was weighted equally in the regression analysis. Inspection of the data showed that the scatter in the data is larger than sampling error alone would account for, and that the study counties varied widely with respect to both population and the number of WM bladder cancer deaths observed in each. This variation may be due to the differing populations 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), two further analyses were performed to identify their possible effects on the results: (1) the regression 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^{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 thirty-year SMR for each county was calculated by dividing the number of WM bladder cancer deaths observed over the three decade period by the number of expected WM bladder cancer deaths over the three decades for that county. Least-square linear regression analyses were conducted (as described above) 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, two-tailed 95% confidence limits of each ratio were determined, and a two-sided χ^2 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 populations between 1950–79 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 above) 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.

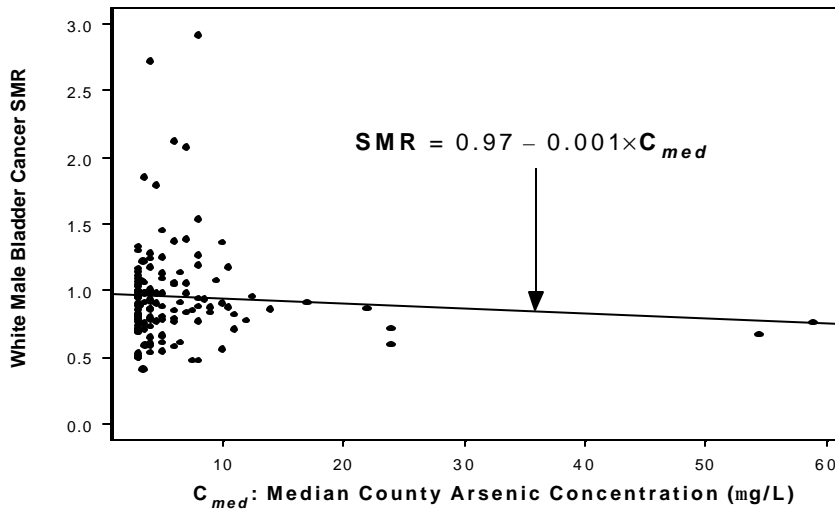
RESULTS:

The study population was comprised of 2.5 million WMs in 133 counties in 26 states. The observation period was thirty 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 4,537 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 3–60 µg/L, with 65% of these counties and 82% of the population in the range of 3–5 µg/L.

Relative Rates (SMRs):

County-specific WM bladder cancer SMRs are shown in Figure 1.

Figure 1: WM Bladder Cancer Mortality Relative Rate [1950–1979]. (U.S. Counties with Median Arsenic Levels of =3 mg/L in Drinking Water)



Linear regression revealed no evidence of an arsenic-dependent rate increase in this 3–60 µg/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 (β) is indistinguishable from zero ($\beta=-0.004$, 95% CI -0.01;+0.01) and the estimated y-intercept (α) 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 3–30 µg/L range shows similar results, with a slope estimate indistinguishable 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 (3.0–19.9 µg/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 may be more heavily influenced by other bladder cancer mortality risk factors such as urbanity, industrialization, and cigarette smoking. At higher levels of arsenic exposure, the SMRs decrease, although none of these results are statistically significant. A χ^2 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 two-sided test; $\chi^2=1.99$).

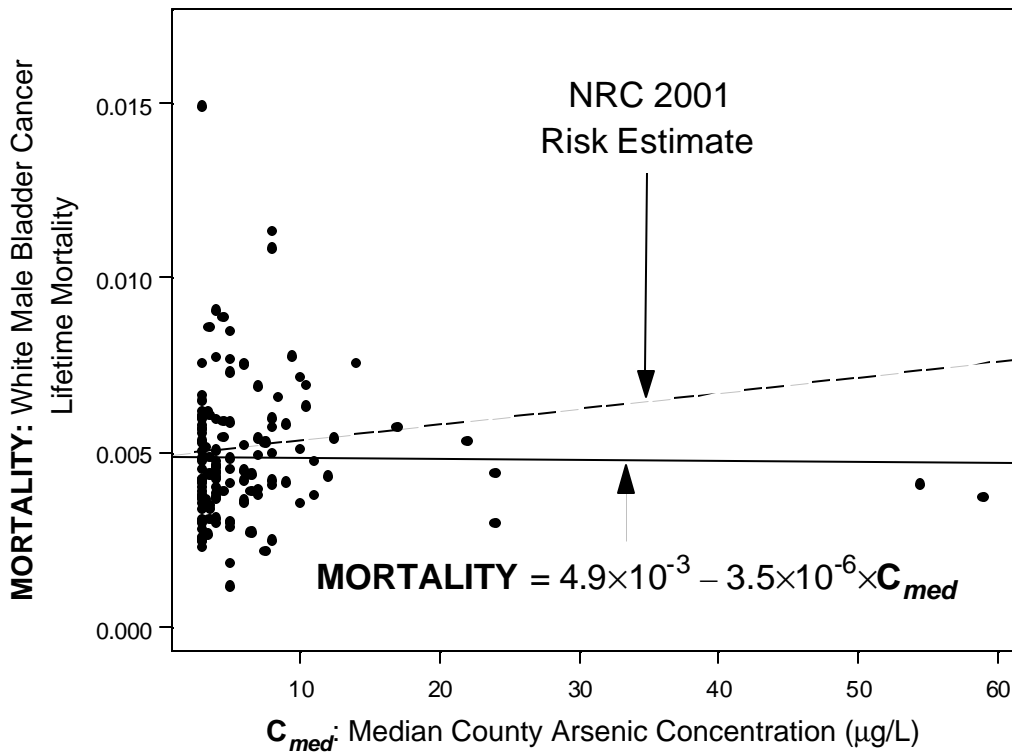
Table 1: WM Bladder Cancer SMRs Stratified by Median Arsenic Concentration in Groundwater

µg/L	Counties	1960 WM Population	Median Arsenic Exposure	Observed	Expected	SMR	95% CI
3.0–3.9	53	1,108,868	3.00	1,962	2,065	0.95	0.89–1.01
4.0–4.9	22	833,587	4.00	1,519	1,604	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		4,537	4,820	0.94	0.90–0.98

Lifetime Bladder Cancer Mortality Rates:

Assuming a lifespan of 75 years for WMs in the U.S., the lifetime rate of bladder cancer mortality for WMs exposed to 3 to 60 $\mu\text{g/L}$ is approximately 0.005 (1/200). Figure 2 plots the county-specific lifetime WM bladder cancer mortality rate against the county-specific median arsenic concentration for (1) all 133 counties and (2) the 98 counties with at least 10 cases. The figure also includes the NRC 2001 predicted U.S. male (white and non-white) risk of 4.5×10^{-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).¹⁸

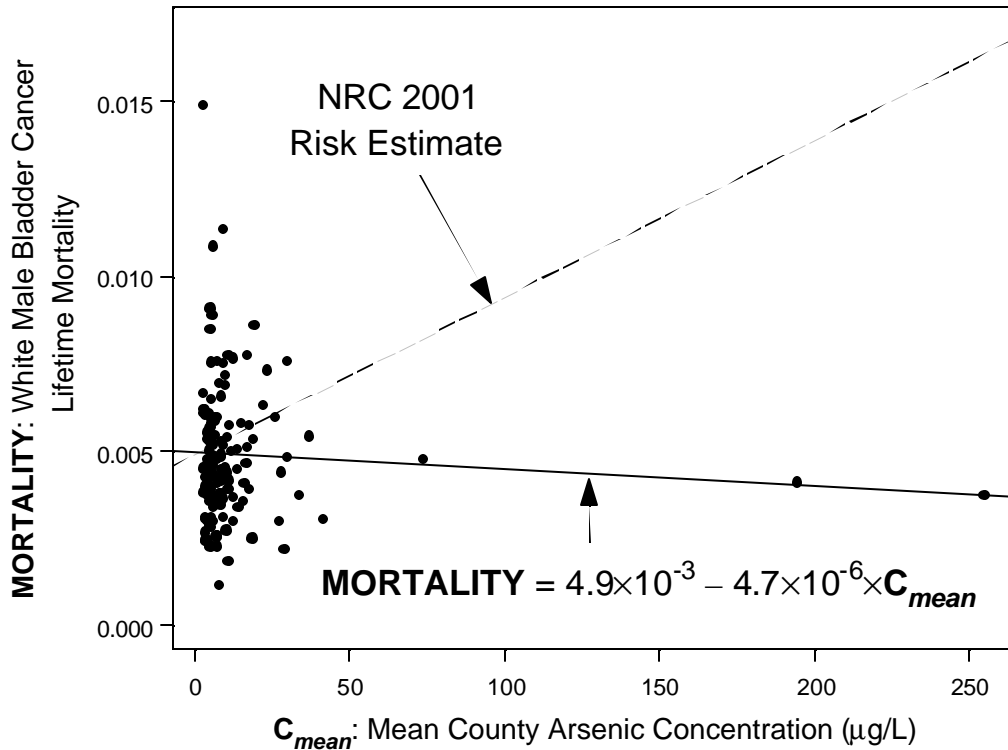
Figure 2: WM Bladder Cancer Lifetime Mortality Rate by Median Arsenic Concentration. (U.S. Counties with Median Arsenic Levels of $\geq 3 \text{ mg/L}$ in Drinking Water)



When all 133 counties are used, the estimated slope (β) of this regression line is -3.5×10^{-6} (95% CI $-5.0 \times 10^{-5}; +4.2 \times 10^{-5}$) and the estimated y-intercept (α) of this line is 4.9×10^{-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 regression ($w_i = (0.06 + n^{-1})^{-1}$), 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).

Figure 3: WM Bladder Cancer Lifetime Mortality Rate by Mean Arsenic Concentration. (U.S. Counties with Median Arsenic Levels of ≤ 3 mg/L in Drinking Water)



When all 133 counties are used, the estimate of β is -4.7×10^{-6} (95% CI -1.7×10^{-5} ; 7.3×10^{-6}) and the estimate of α is 4.9×10^{-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 -1.9×10^{-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 -1.9×10^{-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 µg/L, mean 3–255 µg/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 (4.2×10^{-5} for regression on median arsenic concentration; 8.5×10^{-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 more 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 epidemiological 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.²⁴ 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 ecological 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 "ecological fallacy," it is possible that the relationship between arsenic exposure and mortality at that level do not represent the relationship at the individual level. Even recognizing the inherent limitations of ecological 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 exposures 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 60 $\mu\text{g/L}$.

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 $\mu\text{g/L}$,³ Guo and Tseng found no increase until 640 $\mu\text{g/L}$,²⁵ 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 $\mu\text{g/L}$.⁴ In Latin America, Hopenhayn-Rich et al. reported an increased rate in an Argentinean population with exposures up to 533 $\mu\text{g/L}$,⁸ 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.⁷ In Asia, Tsuda et al. reported no urinary cancers below 1,000 $\mu\text{g/L}$.⁵ 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 1,400 $\mu\text{g/L}$.²⁶ The only apparent

exception was the report of Kurttio et al. of increased bladder cancer rate at exposures above 0.5 µg/L; however, this increase was limited to cigarette smokers.²⁷

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 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 1978.²⁸ While 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 rate of bladder cancer.”

In 1999, Lewis et al. published a population cohort mortality study.²⁹ The Lewis study population consisted of 4,058 residents of towns in Millard County, UT with median drinking water arsenic concentrations ranging from 14 to 166 µg/L. The median and weighted mean arsenic levels for the county are each approximately 100 µg/L. While that study also could not exclude the NRC rate estimate, its authors took their observation of only five bladder cancer deaths (when nine 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 counties in Nevada and California by Steinmaus et al. has recently reported similar results.³⁰ Their analysis of bladder cancer incidence in exposed populations (including Fallon, NV and Hanford, CA, which have historically been exposed to drinking water arsenic concentrations of about 100 µg/L) found no increased risks of bladder cancer at exposure greater than 80 µg/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 is below that which would be predicted using the Taiwan data. Further, they note the possible synergistic effects of smoking and arsenic exposure evident in other studies^{27,28} and conclude that “the results of this study suggest that smokers who drink water containing arsenic at concentrations near 200 µg/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, Crump, and Peto have proposed that for any pollutant whose outcome is indistinguishable from one that occurs naturally, 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.³¹ Taylor’s theorem would then imply that the curve could be approximated by a straight line for “low” doses. While 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 doesn’t 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.^{24,32} Since arsenic is a non-genotoxic carcinogen, it is not necessary to assume that arsenic induced bladder cancers are induced in the same manner that non-arsenic 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 ecological 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 five wells,²³ while in the Wu et al. SW Taiwan study the exposure data for nearly half (47%) of the study villages are represented by one measurement or measurement of only one well.³³ Ecological studies with population-assigned dosages (including this one and the Wu et al. study from SW Taiwan) generally are unable to assess the consequences of in- and out-migration 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 about 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 in the period between 1950 and 1979. Analyses using the mean, while mathematically correct, might unduly weight the groundwater 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 otherwise untreated. This period of exposure precedes the 1980s when 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 as the period of observation had ceased nearly twenty-five 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 1950–1979 since 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 may act synergistically to cause cancer. Since large urban populations are not likely to depend exclusively on groundwater sources for their drinking water, urbanization may 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 may affect the accuracy of the estimates of the arsenic-related change in lifetime mortality (i.e., the slope of the regression line). In order 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. Further, each estimate is lower than the NRC 2001 predicted risk factor for U.S. males of 4.5×10^{-5} and the 95% confidence intervals around the slope estimates from four of the six analyses exclude the NRC's predicted risk.

Table 2: Results of Regression Analyses. Results presented by choice of independent variable (median or mean arsenic concentration), weighting assignments used in the regression, and number of counties used.

Independent Variable	Analysis	Slope Estimate	95% CI (lower; upper)
Median Arsenic Concentration	Equal weights, 133 counties:	-3.5×10^{-6}	$-5.0 \times 10^{-5}; +4.2 \times 10^{-5}$
	Equal weights, counties with $n=10$:	$+6.7 \times 10^{-6}$	$-5.3 \times 10^{-5}; +6.6 \times 10^{-5}$
	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:	-4.7×10^{-6}	$-1.7 \times 10^{-5}; +7.3 \times 10^{-6}$
	Equal weights, counties with $n=10$:	-4.0×10^{-6}	$-1.9 \times 10^{-5}; +1.1 \times 10^{-5}$
	Counties weighted as $(0.06+n^{-1})^{-1}$:	-5.1×10^{-6}	$-1.9 \times 10^{-5}; +8.5 \times 10^{-6}$

NRC 2001 Predicted Slope $+4.5 \times 10^{-5}$

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.) In this case, the risk estimation process was complicated because the NRC mortality estimate was derived from incidence estimates for U.S. males that were in turn based on mortality data from the SW Taiwan population.¹⁸

To convert incidence estimates to mortality estimates, the NRC subcommittee assumed that the U.S. mortality rate of bladder cancer was 20% of the incidence rate. However, for the period of 1969-70, the WM bladder cancer mortality rate was approximately 28% of the WM bladder cancer incidence rate.³⁴ If this higher value were used, the NRC estimate would be higher. The NRC's estimate of U.S. mortality risk also 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 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 3–60 $\mu\text{g/L}$ range and that the estimates of U.S. arsenic-related cancer risk made from SW Taiwan data are higher than what is found in the U.S. data. This inconsistency may be the result of a misinterpretation of the SW Taiwan data³² or it may indicate that one or more of the assumptions necessary to estimate U.S. risk from SW Taiwan data are incorrect. The observed lack of an association between bladder cancer mortality and arsenic concentrations below 60 $\mu\text{g/L}$ 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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