# Arsenic Ingestion and Bladder Cancer Mortality—What Do the Dose-Response Relationships Suggest About Mechanism?

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## ABSTRACT

The Black-Foot Disease (BFD) endemic area of SW Taiwan has historically been the principal data source for assessing cancer risks from arsenic in drinking water in the United States, most recently in a 42-village ecological study. The data showed a discontinuity for bladder cancer risk at about 400 $\mu$g/L. A proposed explanation was that the arsenic-dependent bladder cancer risk was found only for those villages that were dependent on water from the artesian well aquifer (As $>$ 350 $\mu$g/L and co-contamination with humic acids) and not for those villages receiving water from the shallow aquifer (As $<$ 350 $\mu$g/L without humic acids). The humic acids were present from the algae that grew in the uncovered tanks holding the artesian water. The risk factors (slopes) developed from these subpopulations of the SW Taiwan study were applied to the data from an ecological study of median groundwater arsenic concentration and bladder cancer mortality in 133 U.S. counties dependent on groundwater to determine the slope most predictive of U.S. experience for bladder cancer mortality and arsenic ingestion (Lamm *et al.* 2004). The U.S. data excluded the SW Taiwan slope estimate derived from the artesian well–dependent subpopulation but were consistent with the slope estimate derived from the subpopulation using shallow aquifer water. Both the SW Taiwan data in the absence of high arsenic levels ($<$ 350 $\mu$g/L) and humic acids and the U.S. 133-county data with As $<$ 60 $\mu$g/L are consistent with no increased bladder cancer mortality risk from drinking water arsenic concentrations in the exposure range of observation. These analytic results are consistent with both co-carcinogenesis and high-exposure (hundreds of $\mu$g/L As) dependence models of toxicological mode-of-action. These dose-response relationships should influence prioritization in the remediation of arsenic-contaminated drinking water supplies.

**Key Words:** arsenic, SW Taiwan, bladder cancer, humic substances, co-carcinogenesis.

## INTRODUCTION

Inorganic arsenic has long been known to cause skin cancer through environmental and occupational exposure and to cause lung cancer through inhalation. The relationship between ingested arsenic and other internal cancers, however, is less clear. Prior to the 1980s, only rare case reports suggested an association between bladder cancer and arsenic ingestion (Atkinson 1969; Nagy *et al.* 1980), whereas an analysis of a large cohort found no relationship with medical arsenic ingestion and internal cancers (Reymann *et al.* 1978). Beginning with the publication of the Chen *et al.* (1985) study in SW Taiwan, however, the relationship between arsenic ingestion and internal cancers began to attract more attention. Of the cancers considered in that study, bladder cancer stood out as showing the clearest contrast to the rate found in the general Taiwan population.

Since 1985, researchers have conducted several epidemiological studies of the association between arsenic exposure and bladder cancer in other parts of the world, including Latin America, Europe, and the United States. However, a region of SW Taiwan known uniquely for the vascular disorder Blackfoot Disease [BFD] has been regarded as the most significant single source of data regarding the relationship between ingested arsenic and bladder cancer.

In the course of investigating BFD during the 1960s, researchers found that the artesian wells used since the 1920s to provide drinking water to many of the villages in the BFD endemic region had very high arsenic concentrations. Subsequent studies linked arsenic exposure from drinking water drawn from those wells not only to BFD but also to dermatological conditions (chronic arsenicism and skin cancer) and internal cancers (particularly bladder and lung cancer) (Tseng *et al.* 1968; Chen *et al.* 1985, 1986).

More recently, studies by Wu *et al.* (1989) and Chen *et al.* (1992) used a study population of adult ($\geq$20 years old) residents of 42 villages in the BFD-endemic region of SW Taiwan to assess the relationship between arsenic ingestion and cancers. Morales *et al.* (2000) published a detailed analysis of these same data, and their results formed the basis of the new recommendations regarding arsenic in drinking water issued by the U.S. Environmental Protection Agency (USEPA 2001) and the new assessment by the National Research Council (NRC) of the U.S. National Academy of Science (NRC 1999, 2001). This same study has also been an important source for assessments by the United Nations and the World Health Organization.

Those recent risk analyses based on the Wu *et al.* (1989) study share two key features. The first is that they presume that the relationship between arsenic ingestion and the development of human cancers is one that can be meaningfully expressed in terms of arsenic exposure alone. Indeed, to speak of "the" cancer slope factor presumes that there is a single relationship between arsenic exposure and the risk of a particular cancer that is constant across the wide range of possible exposure milieus without any interaction coefficients.

The second common feature is that they assume arsenic's carcinogenic effects are exhibited similarly at all exposure levels and that there is no level below which arsenic exposure does not demonstrate a cancer risk as there would be with a threshold-type model. As a general principle, this premise draws support from the observation that cancers induced by arsenic cannot be distinguished by a pathologist from those that

occur naturally and that a small increase in environmental insult implies a small increase in the associated cancer risk. As a result, this means in analysis that the exposure-response curve is "forced" through the origin, even when the data support a non-zero X intercept.

Each of these premises should be assessed when considering what the SW Taiwan studies indicate about risks of arsenic exposure elsewhere. That is, if each of these premises are true, then the relationship between arsenic exposure and the cancer deaths found in SW Taiwan has a direct application to other regions (such as the U.S. and Bangladesh), and we should expect predictions made from the SW Taiwan data to be validated elsewhere. If, however, either or both of these premises are not true, it becomes much more difficult to see the relevance of inferences drawn from those data to questions about arsenic-related risks elsewhere. The question is whether all of the SW Taiwan data are relevant for predicting risks across all exposure scenarios, or whether parts of the SW Taiwan data set are relevant to different exposure scenarios.

## COMPLICATIONS IN DERIVING A EXPOSURE-RESPONSE CURVE

One way to justify the first of these premises in the context of the SW Taiwan studies is to show that the study population was not exposed to anything *other* than arsenic that might be associated with the outcome of concern (bladder cancer) either directly or in conjunction with arsenic. In this regard, interpretation of the SW Taiwan studies is complicated by the fact that the study population resided in a region that, by virtue of being the only BFD-endemic area in the world, was clearly distinguished from other high-arsenic regions in the rest of the world. This has suggested to some that an unknown environmental component common to the BFD-endemic region might be related to the observed bladder cancer mortality (Chiang *et al.* 1988, 1993). It is noteworthy that with nearly 30,000 arsenicosis patients having been identified in mainland China, not a single one has been found having the symptoms of blackfoot disease (Sun 2004). The absence of blackfoot disease in the Chinese population strongly suggests a major environmental difference as it would be difficult to argue that the difference in response for the two populations is on a genetic or ethnic basis.

Chen *et al.* (1985) provided an interesting perspective on the factors beyond just arsenic exposure that might need to be considered in the context of the BFD-endemic region. The standardized mortality ratios (SMRs) reported in that study for a variety of internal cancers are represented in Figure 1.[1] Interestingly enough, the unit of exposure used in that study was not the arsenic concentration in drinking water, but the type of aquifer (or the well) used as a drinking water source, that is, either the aquifer that feeds the shallow wells in the region or the aquifer tapped by the artesian wells used there, or both.

With the exception of colon cancer, the SMRs of each of these internal cancers appears to be particularly associated with exposure to water from a particular source—artesian wells. As such, this association suggests that differences other than the arsenic concentration of the water drawn from these two well types might be

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[1]SMR = observed mortality rate/expected mortality rate.

**Figure 1.** Internal cancer SMRs by water source type (derived from Chen *et al.* 1985).
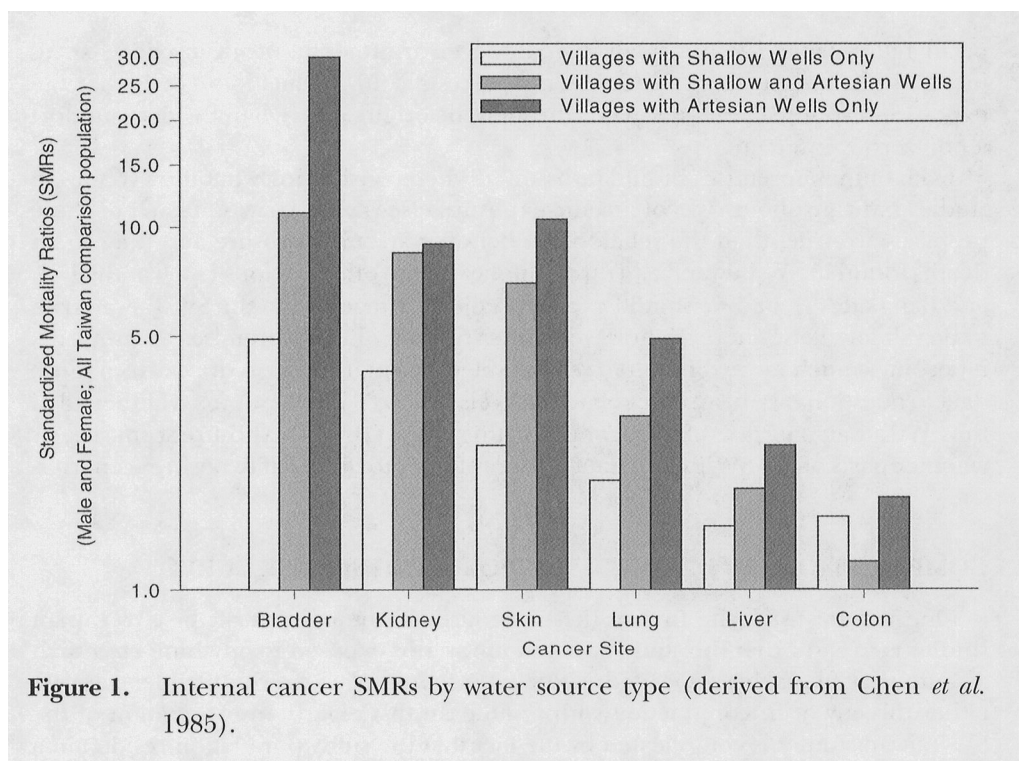
relevant to explain the high observed cancer mortality. This does not, of course, show that arsenic exposure has no role in accounting for these high levels of cancer mortality because artesian wells in the region typically have higher concentrations of arsenic.

Results such as these alert us to the possible effects of exposures other than arsenic and suggest that the relationship between arsenic exposure and cancer outcomes may depend on other factors. In the same way, other studies highlight the potential bias that the assumption of starting the risk curve at zero might have on the exposure-response curves derived in these studies (Byrd *et al.* 1996).

Figure 2 (using SW Taiwan skin cancer prevalence data reported in Byrd *et al.* 1996) illustrates the effect of this assumption on the derivation of an exposure-response curve.

The broken line in Figure 2 indicates the linear relationship found when the line is forced through the origin. When, on the other hand, the line with the best fit to the data is selected—and no other *a priori* assumptions about where the line should go are made—this best-fitting line crosses the X-axis at approximately 90 $\mu$g arsenic per liter drinking water.[2] The issue, then, is: what do these data tell us about skin cancer prevalence at exposures between 0 and about 100 $\mu$g/L? If the start point at zero assumption is correct, then we should expect an increased exposure-related

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[2]To make this estimate of the start point, we found the X-intercept of the straight line that had the best fit with the data. Byrd *et al.* (1996) gave a more sophisticated analysis that used a genuine threshold model and found a start point of 103 $\mu$g/L.
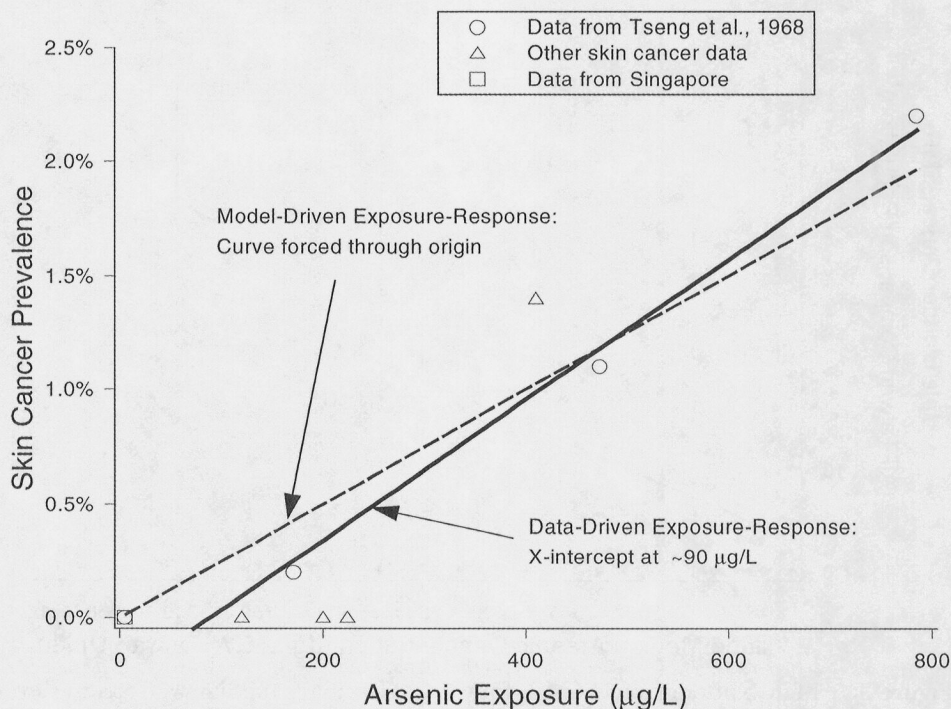
**Figure 2.** Exposure-response curves for skin cancer prevalence (from Byrd *et al.* 1996).

prevalence for the population exposed to those concentrations below 100 $\mu$g/L; if it is not, we should expect no increased exposure-related prevalence in a population exposed to such exposure levels.

Although the initial data on bladder cancer mortality seemed to show a linear exposure response (Byrd *et al.* 1996), a more careful review of the literature on bladder cancer mortality and arsenic exposure showed a displaced start point pattern to the exposure-response (Lamm *et al.* 2003).

## ANOTHER LOOK AT THE SW TAIWAN DATA

The results discussed in the previous section led us to re-examine the Wu *et al.* (1989) data, this time paying special attention to the potential effects of well type and threshold phenomena on the exposure-response curve estimates.

Figure 3 shows the distribution of the male bladder cancer SMRs of the 42 villages by their median well arsenic level, using the entire population of Taiwan as a comparison population to calculate the expected mortality rate.[3] Since the entire

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[3]The underlying data had been provided to us both by Dr. Louise Ryan of Harvard University and Dr. Andrew Schulman of the U.S. Environmental Protection Agency. We thank them both.
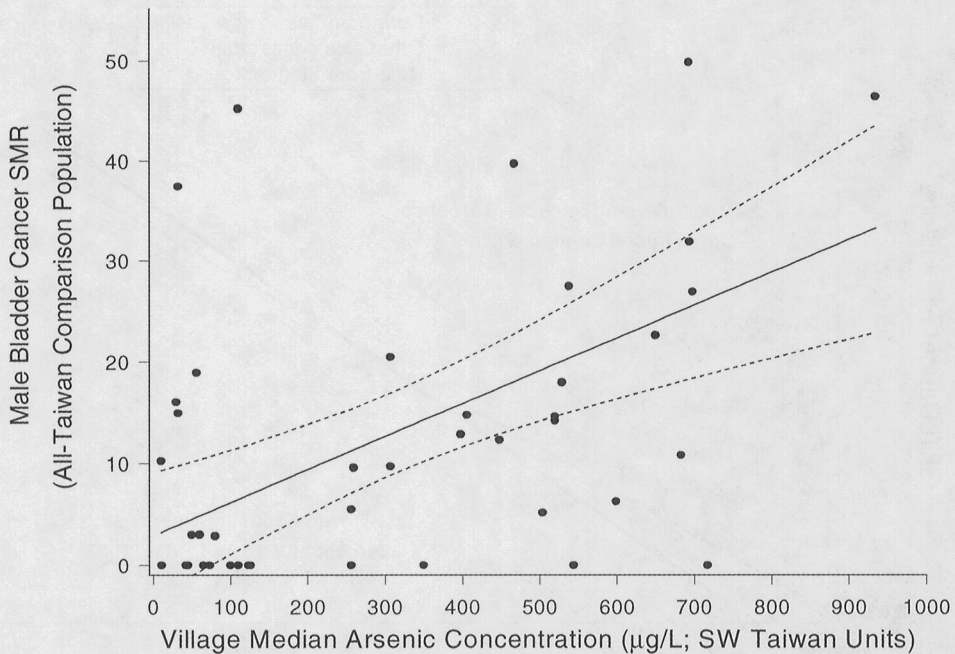
**Figure 3.** Male bladder cancer SMRs for villages by village median well arsenic level ($\mu$g/L) with 95% CI (all-Taiwan comparison population). Regression weighted by village person-years. Slope estimates required to be non-negative.

population of Taiwan includes SW Taiwan where the SMRs are apparently 10-fold, SMR calculation using the non-SW Taiwan population would likely result in even higher SMR values. Generalized least-squares regression analysis was performed with the data weighted by person-years in each village and the estimates of the slope ($\beta$) (constrained to be non-negative). This analysis yielded a Y-intercept of 2.97 (95% CI, $-3.17$; $+9.11$) and a slope of 0.032 per $\mu$g/L (95% CI, $+0.017$; $+0.048$) (F statistic = 18.80, significance of F-statistic < 0.0001).

Figure 3 shows the SW Taiwan male bladder cancer mortality results using the assumption that the arsenic level is the only exposure metric relevant to bladder cancer mortality risk. In particular, this analysis does not treat the differences in water sources in these villages (*i.e.*, shallow *vs.* artesian wells) as a relevant feature of exposure.

Morales *et al.* (2000) also analyzed these same data by stratifying them according to median village arsenic concentration (0–50, 50–100, 100–200, 200–300, 300–400, 400–500, 500–600, and 600+ $\mu$g/L). Figure 4 presents the results of her stratified analysis. It is simply a graphic representation of Table 5 in Morales *et al.* (2000).

Two things stand out in the graphic analysis in Figure 4. The first is that the rate of bladder cancer mortality for residents of the BFD-endemic region of SW Taiwan is very high relative to the rest of Taiwan: even for those exposed to relatively low arsenic concentrations (0–50 $\mu$g/L), the SMR is approximately 10. (This difference

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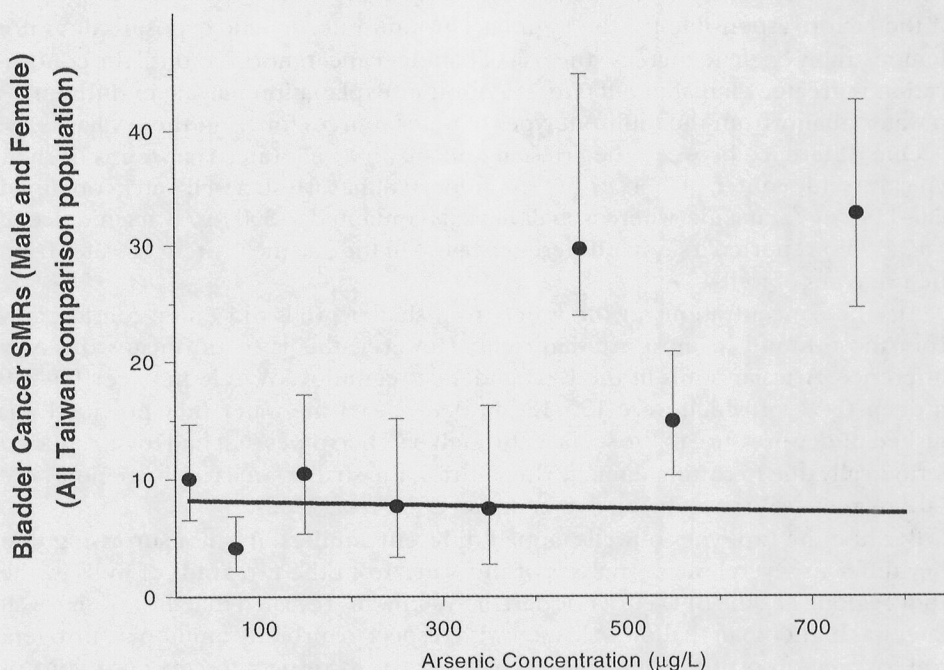
**Figure 4.** Bladder cancer SMRs and 95% CI (using all-Taiwan comparison population) by drinking water arsenic level (from Morales *et al.* 2000, Table 5).

is also reflected in Figure 3, in which the SMR corresponding to a zero exposure [*i.e.*, the Y-intercept of the regression line] is approximately 3.) These high bladder cancer SMRs were observed in Morales *et al.* (2000), but to our knowledge no explanation for this has been given. At the very least, it underscores the point made earlier about the distinctive nature of this region and suggests that inferences made about the risks associated with arsenic exposure using data from this region may not be applicable in other regions. In other words, the relative risk from even the highest arsenic exposures is only 3-fold that of the lowest arsenic exposures, whereas the relative risk from living in the SW Taiwan study area, adjusted for arsenic exposure, is 10-fold that of Taiwan *per se*. This would suggest than another major environmental factor may be driving the bladder cancer risk in this area.

The second point that can be seen from Figure 4 is the apparent discontinuity in the relationship between arsenic exposure and the risk of bladder cancer (as indicated by the SMR). More than 60% of the study population is in the villages with median well arsenic levels below 400 μg/L, and about 40% are at 400 μg/L and above. The three data points (and confidence limits) for the three exposure strata in the 400–934 μg/L range were all above the regression line for the data of the five exposure strata below 400 μg/L (Figure 4). Thus, the data from the higher exposure strata did not fit the model developed from the data from the lower exposure strata; nor would a line through the three high exposure strata fit the data at the lower levels. One possible explanation for this discontinuity could be that in the presence

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of the factor responsible for the high background rate, arsenic exposure does not demonstrably begin to increase the risk of bladder cancer mortality until the concentration is greater than about 400 $\mu$g/L. Another explanation may lie in differences in water quality from the different types of water sources found in these villages.

One difference between the artesian and shallow well water is in terms of their typical arsenic content: Chen *et al.* (1986) reported that artesian well water contained 350–1140 $\mu$g/L arsenic, whereas shallow wells contained 0–300 $\mu$g/L arsenic. Tseng *et al.* (1968) reported a similar difference between the arsenic content of water from the two types of wells.

Arsenic concentrations in the water from shallow wells did differ considerably from those found in most artesian wells; However, this is by no means the only difference. Artesian wells in the BFD endemic region of SW Taiwan were 100–280 m deep (80% of which were 120–180 m deep), and the water they provided was pushed under pressure to the surface through bamboo pipes that had to be replaced periodically due to rotting damage. In contrast, the shallow wells in the region were 4–12 m deep, with most being 5–6 m deep (Chen *et al.* 1962).

Because the two types of wells tapped different aquifers, it is not surprising that they differ in several ways. Analyses of the water from the two kinds of wells in the study region (*i.e.*, the BFD-endemic part of SW Taiwan) revealed that the artesian well water was higher than shallow well water with respect to turbidity, ammonia, nitrogen, iron, oxygen absorption, and silicate, but lower with respect to concentrations of chloride, calcium, hardness, magnesium, and manganese (Chen *et al.* 1962). In addition, differences in the design of these two types of wells may have had an effect on the composition of their waters. For instance, artesian wells in the region collected the water forced to the surface in cement-coated tanks typically measuring 2.5 × 1.5 × 2.0 m. The large opening of these tanks and their lack of covers plus subsequent exposure of the water to sunlight were responsible for the distinctive algae growth associated with water from the artesian wells.

There are, then, dramatic differences between the water from artesian wells and that from shallow wells other than that related to arsenic concentrations. Although these other factors have not been directly implicated in internal cancers, their presence may account for the discontinuity shown in Figure 4. At the very least, such differences should be considered as potential co-factors in any analysis of the relationship between arsenic and cancer.

In order to assess the effect that this factor might have, we separated the wells in the study villages into artesian well villages and shallow well villages. None of the existing studies specified which wells in the study villages tapped the artesian aquifer and which tapped the shallow aquifer. Given that this information was not directly available, we used the reported range of arsenic concentrations for artesian and shallow wells as a marker for well type. C.-J. Chen *et al.* (1985, 1986) and Wu *et al.* (1989) have reported that the median arsenic concentration of individual artesian wells is in the range of 350–1,100 $\mu$g/L, whereas the median arsenic concentration of individual shallow wells is between 0 and 300 $\mu$g/L.

Using these values as guidelines, we classified each well as "artesian" if its arsenic concentration was greater than 325 $\mu$g/L; otherwise, the well was considered "shallow." The arsenic levels for the wells in each of the villages had been published (Addendum to Chapter 10, Table A 10-1) by the National Research Council (NRC

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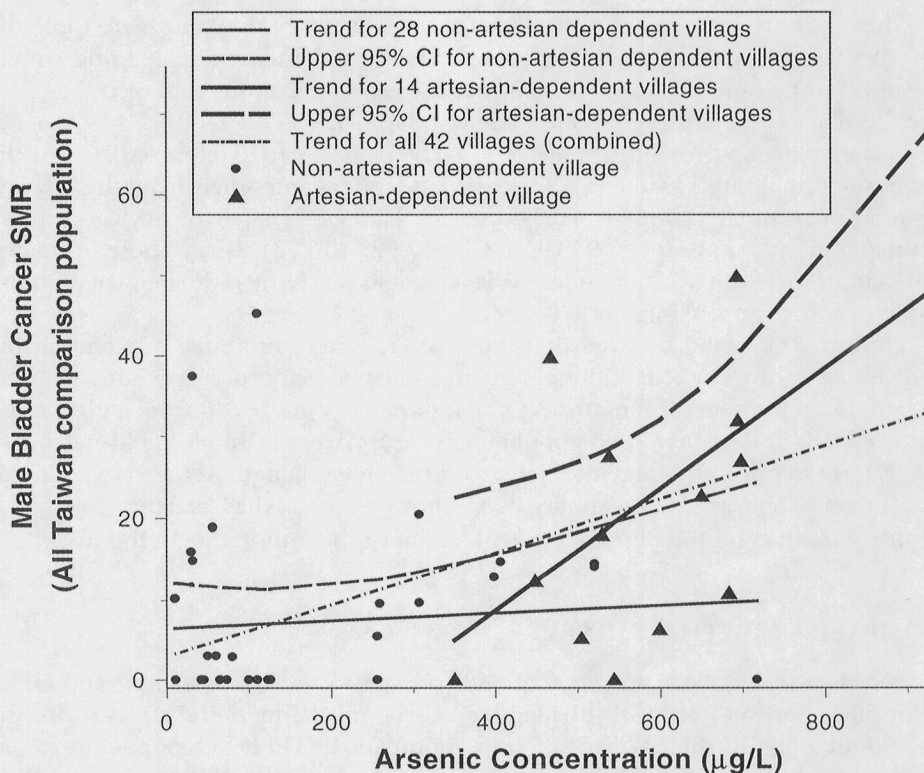
**Figure 5.** Exposure-response curves with upper 95% CI for two different aquifers. (Male bladder cancer SMRs using all-Taiwan comparison population. Regression weighted by village person-years. Slope estimates required to be non-negative.)

1999). Each of the 153 wells in the 42 villages was classified in this way and those villages with only artesian wells were designated as "artesian well dependent." Thus, if a village had any other source of water, even one well that was considered "shallow," the village was designated as "non-artesian well dependent."[4]

Shown in Figure 1 and Figure 3 are bladder cancer mortality risk with two different exposure metrics—water source (Figure 1) and arsenic level (Figure 3). The SW Taiwan bladder cancer mortality risk looking at water source and arsenic level simultaneously are presented in Figure 5.

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[4]Chen *et al.* (1962) originally reported the ranges of arsenic concentrations as 0–150 $\mu$g/L for 14 shallow wells in the BFD-endemic region and 350–1,110 $\mu$g/L for 34 artesian wells in that region. (Note that these wells were not necessarily used by those included in the Wu *et al.* database.) Because this report is cited by Chen *et al.* (1985, 1986) and Wu *et al.* (1989), it is unclear why these more recent studies claim that the range for shallow wells is 0–300 $\mu$g/L instead of 0–150 $\mu$g/L. To account for possible misclassification due to this difference, we repeated our analyses using values of 150 and 250 $\mu$g/L when defining artesian dependent and non-artesian dependent villages. These different values did not appreciably affect the results.

The exposure-response relationships for these two subpopulations are quite different. Regression analysis (weighted by person-years in each village and with $\beta$ required to be non-negative) showed that the estimated Y-intercept of the line for the 28 villages that had at least one shallow well is 6.52 (95% CI +0.76; +12.27) and the estimated slope for those villages is +0.005 (95% CI −0.020; +0.030). In the set of the remaining 14 villages whose drinking water came solely from the artesian aquifer, the estimated slope is +0.074 per $\mu$g/L (95% CI +0.016; +0.133) with an estimated Y-intercept of −20.95 (95% CI −57.62; +15.73). Given these estimates, SMRs in the artesian well dependent villages would reach the estimated background value of 6.52 at approximately 370 $\mu$g/L.[5]
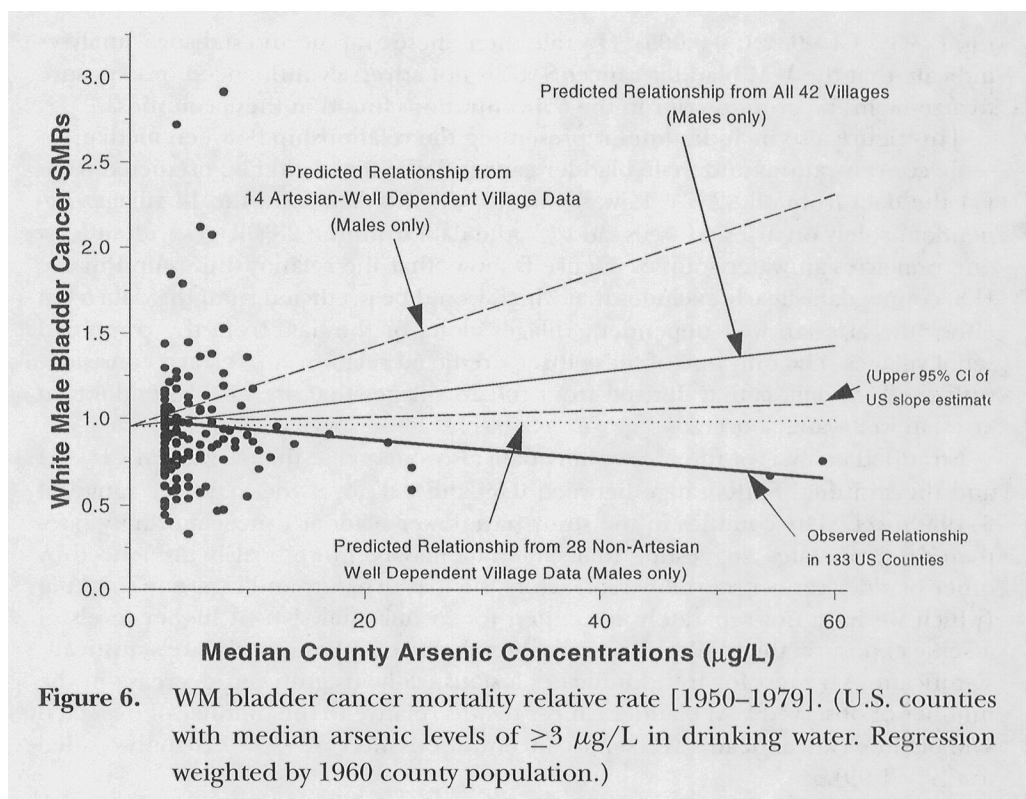
This analysis would indicate that the bladder cancer mortality rate among the individuals in the study area, independent of arsenic exposure, is 6.5 higher than that found in the general Taiwanese population. As we noted earlier, the high bladder cancer SMRs in the unexposed population were apparent in Table 5 of Morales *et al.* (2000), yet to our knowledge they have never been explained. At the very least, this discrepancy suggests the possibility that exposures other than arsenic may have a significant effect on the observed rate of bladder cancer mortality in this area.

## COMPARISON WITH U.S. DATA

The data in Figure 4 suggest that with respect to the relationship between arsenic ingestion and the risk of bladder cancer mortality, there are two distinct sub-populations in the SW Taiwan study population. These sub-populations may be defined in terms of a distinction either between low (<400 $\mu$g/L) and high (>400 $\mu$g/L) arsenic concentrations, or between the types of wells used to supply drinking water (shallow *vs.* deep), which tap different aquifers and whose designs may affect the composition of the water they provide. These re-analyses do not indicate which of these two differences better explains the difference in bladder cancer mortality risk for these sub-populations. However, the mere fact that we are unable to say which of these two explanations is better does not undermine the general point that the data are consistent with there being two different exposure-response relationships within the SW Taiwan population.

Given this, how well do the data from SW Taiwan predict what we find in the United States, and are the U.S. findings better predicted by all of the SW Taiwan data or by some part of it? To address this issue, we investigated the relationship between arsenic exposure and bladder cancer SMRs for white males (WM) in the United States between 1950 and 1979. County-specific median arsenic levels in groundwater were obtained from the U.S. Geological Survey (USGS) database that was compiled

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[5]Similar results are found using the alternative criteria described in footnote 4. Using the concentration of 150 $\mu$g/L to define artesian wells implies that there are 20 artesian well dependent villages, and that the slope estimate is +0.045 per $\mu$g/L (95% CI +0.009; +0.081). For the 22 non-artesian dependent villages, the slope estimate is +0.011 per $\mu$g/L (95% CI −0.026; +0.049). Using the concentration of 250 $\mu$g/L to define artesian wells implies that there are 19 artesian well–dependent villages for which the slope estimate is +0.054 per $\mu$g/L (95% CI +0.020; +0.087); for the 23 non-artesian dependent villages, the slope estimate is +0.001 per $\mu$g/L (95% CI −0.028; +0.029).

**Figure 6.** WM bladder cancer mortality relative rate [1950–1979]. (U.S. counties with median arsenic levels of $\geq 3$ $\mu$g/L in drinking water. Regression weighted by 1960 county population.)

as part of the USGS's study of arsenic in U.S. groundwaters (Focazio *et al.* 1999). County-specific white male bladder cancer mortality rates for the years 1950–1979 were obtained from the National Cancer Institute (NCI/EPA 1983). The analysis was restricted to those counties that depended solely on groundwater for drinking water supplies, as determined by each state's environment department or health department.

Combining these data yielded a study population of 2.5 million white males (WM) in 133 counties in 26 states, with county-specific age-adjusted bladder cancer mortality data over a thirty-year period (1950–1979). County-specific WM bladder cancer SMRs are shown in Figure 6. The least-squares regression line is also plotted along with its upper 95% CI bounds.

When no constraint is placed on the slope estimate, the Y-intercept is 0.995 (95% CI +0.939; +1.005) and the best least-squares estimate of the slope is −0.006 per $\mu$g/L (95% CI −0.014; +0.002). When the estimate of the slope is forced to be non-negative, the estimated Y-intercept ($\alpha$) of this line is 0.967 (95% CI +0.927; +1.007) and the estimated slope ($\beta$) of this line is 0 per $\mu$g/L.[6] Regression analysis limited to the 3–30 $\mu$g/L range (and in which the slope estimate was not forced to be non-negative) yielded similar results ($\alpha = 1.000, 95\%$ CI +0.931; +1.008; $\beta = -0.008$ per

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[6]No confidence interval could be calculated for this slope estimate because the line that fit the data best had a negative slope and so (because of the non-negative constraint on the model) was forced to 0.

$\mu$g/L, 95% CI $-0.021$; $+0.005$). Overall, then, these graphic and statistical analyses 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.

This figure also includes lines representing the relationship between median arsenic concentrations and male bladder cancer SMRs that would be predicted from (1) the data from all 42 SW Taiwan villages, (2) the data from the 14 villages dependent solely on artesian wells, and (3) the data from the 28 villages with at least one non-artesian water source.[7] Figure 6 shows that the relationship found in the U.S. county data clearly excludes that which would be predicted from the data from either the artesian well–dependent villages alone or the data from the combined set of villages. The only one of these three predicted relationships clearly consistent with the U.S. data is that derived from the 28 villages that are not dependent on artesian well water sources.

Stratified analysis of the U.S. county data also shows that the overall SMR is 0.94 and the stratified SMRs range between 0.89 and 0.97 over the exposure range of 3–19.9 $\mu$g/L. 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 and cigarette smoking (which we have not separately accounted for in our analysis). At higher levels of arsenic exposure, the SMRs decrease, although none of these results are statistically significant. A $\chi^2$ 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; $\chi^2 = 1.99$).

## DISCUSSION

These analyses have shown that there are two discernable sub-populations within this group of 42 SW Taiwan villages with respect to the relationship between arsenic exposure and bladder cancer mortality—one associated with the dependency on the artesian well water supply and the other not. The risk associated with the artesian water–dependent villages showed a statistically significant slope of $+0.074$ per $\mu$g/L. The risk associated with the villages that were not artesian water–dependent showed a slope of $+0.005$ per $\mu$g/L that was indistinguishable from zero.

Further, they have shown that the arsenic exposure–bladder cancer risk distribution for the 133 U.S. counties is consistent with the risk distribution for the SW Taiwan villages that are not artesian well water supply dependent and they are inconsistent

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[7]The estimated slope of the arsenic-SMR curve for male bladder cancer in all 42 villages is 0.032 per $\mu$g/L (95% CI, $+0.017$; $+0.048$). The estimated slope in the 14 artesian well–dependent villages is $+0.074$ per $\mu$g/L (95% CI $+0.016$; $+0.133$) and the estimated slope in the other 28 villages is $+0.005$ per $\mu$g/L (95% CI $-0.020$; $+0.030$). The predicted relationships were obtained by plotting the line $= 0.967 + $ (Estimated Slope) $\times$ (1/3) $\times$ (As Median). The factor of 1/3 comes from the conversion factor used by EPA and the National Research Council to convert the daily mg As/kg body weight exposure in Taiwan to a comparable exposure for U.S. residents, and depends on assumptions about differences in average body weight and daily water consumption.

with the risk distribution of the SW Taiwan villages that are artesian well water supply dependent. These analyses, however, do not demonstrate a specific reason for the difference in risk distribution between the two sets of villages.

As noted earlier, the arsenic concentrations in water from the deep artesian wells are typically higher than those in water from shallow wells. For the 14 villages considered to be artesian well water dependent, the arsenic measurements for the individual wells ranged from 350 to 934 $\mu$g/L with village median well arsenic levels ranging from 398 to 934 $\mu$g/L. For the other 28 villages that have access to surface water, the arsenic measurements for the individual wells ranged from 10 to 717 $\mu$g/L with village median well arsenic levels ranging from 10 to 307 $\mu$g/L. It may be that the carcinogenicity of ingested arsenic depends on the concentration in drinking water, such that arsenic-related bladder cancer mortality increases are seen only for exposures above 350–400 $\mu$g/L. Authors from the U.S. Environmental Protection Agency have recently reported that "arsenic... is known to... cause skin and internal cancers in people exposed to levels greater than 300 ppb in their drinking water" (Calderon *et al.* 2004). A recent case/control study of bladder cancer cases diagnosed in the Tainan City area (1996–1999) found no increased risk with arsenic exposure with the exception of those with at least 12 mg/L-year (30 years at average of >400 $\mu$g/L) and low secondary methylation index [DMA(V)/MMA(V) <4.8] (Chen *et al.* 2003).

An alternative explanation may be that some feature (or combination of features) found only in water from the artesian wells is responsible for the increase in bladder cancer mortality. As we observed earlier, Chen *et al.* (1962) noted that "one of the most remarkable differences in physical characteristics between artesian well and shallow well water was the growth of algae in artesian well water," (19) which led to high levels of organic material in the artesian well tanks. The decay of this organic material is responsible for the high levels of fluorescent humic acids found in the artesian well water in this area (Chen *et al.* 1962; Lu *et al.* 1975; Chiang *et al.* 1993).

Studies in rodents have indicated that the humic acids may be a cause of the vascular constriction seen in Black-Foot Disease (Lu 1990), demonstrating that these humic acids may be biologically active. Humic acids form a bridged complex with arsenic and other metals in the presence of a polyvalent cation, such as iron—which, as noted earlier, Chen *et al.* (1962) had also found was higher in artesian wells than in shallow well. Thus, a number of mechanistic processes have been proposed whereby humic substances might act as a co-carcinogenic or co-pathogenic factor with high arsenic levels. The simultaneous exposure to arsenic, fluorescent humic substances, and iron may be a plausible explanation for these unique results from SW Taiwan.

An interesting interpretation of the SW Taiwan data is that the demonstration of arsenic carcinogenesis for the bladder at the whole animal level needed a second factor, such as the humic acids, because in parallel argument at the cellular level, an *in vitro* study seeking the effects of metals on promoter-regulated gene expression found that it was necessary to add humic acid to the bath water in order to demonstrate that arsenic activated gene expression (Tully *et al.* 2000).

As the median arsenic exposure levels in the U.S. county study did not exceed 60 $\mu$g/L and the study had no information on potential humic acid content in the waters, it does not provide additional information to assist in distinguishing between the two alternative interpretations of the risk pattern from the SW Taiwan study.

Additional studies have looked quantitatively at the relationship between arsenic level in the drinking water and bladder cancer with exposures in the 60 to 400 $\mu$g/L range. The arsenic health effects research group at the University of California at Berkeley has published two relevant articles. In Steinmaus *et al.* (2003), they examined the dose-response relationship for arsenic in drinking water in a case/control study of bladder cancer cases in seven California and Nevada counties in 1994–2000. These seven counties contained the largest U.S. populations (Hanford, California and Fallon, Nevada) historically exposed to drinking water arsenic at concentrations near 100 $\mu$g/L. Annual exposure levels were stratified at <10 $\mu$g/day, 10–79 $\mu$g/day, 80–120 $\mu$g/day, and >120 $\mu$g/day. The top two groups were collapsed in the analysis. These authors reported that the bladder cancer incidence in the seven counties was not associated with arsenic exposure including among the group with greater than 80 $\mu$g/L, that the overall risks in these counties was below that predicted using the SW Taiwan data, and that the linear trend was negative, but not significantly so ($p = 0.48$). The only statistically significant association they reported was for cigarette smokers with estimated arsenic intakes >80 $\mu$g/day occurring 40 or more years prior to the diagnosis.

They also, in Bates *et al.* (2004), reported the results of a population-based bladder cancer case/control (1996–2000) study from two counties in Cordova, Argentina, the same area from which they had previously published an ecological study showing a significant association between arsenic exposure and bladder cancer mortality (Hopenhayn-Rich *et al.* 1996). Well water samples (n = 389) had been recently collected, and the arsenic levels were found to range from 0 to 3,033 $\mu$g/L [mean of 164 $\mu$g/L; median of 101 $\mu$g/L]. Springwater samples (n = 11) ranged from 9 to 70 $\mu$g/L [mean of 40 $\mu$g/L; median of 37 $\mu$g/L]. They found no association between bladder cancer cases and arsenic exposure (>200 $\mu$g/L) over the 6–40 years prior to the interview, neither for smokers nor non-smokers, even after adjusting for education and home tap-water consumption. Although cigarette smoking was a significant risk factor (OR = 2.4; $p = 0.003$), the linear trend for arsenic exposure level was negative, but not significantly so ($p \sim 0.10$). The only statistically significant association was found among ever-smokers who reported that well water was the source of their water consumption 51–70 years prior to the interview. The arsenic content of the waters from the wells they might have used is unknown, as is whether they contained humic acid or not. The authors were surprised that their study "found no association between estimated arsenic exposures and bladder cancer risk for cases diagnosed during 1996–2000 . . . and even a suggestion of a risk reduction at high arsenic levels."

The results of the three recently published studies, two on populations from the U.S. [Lamm *et al.* 2003; Steinmaus *et al.* 2004] and one on a population from Argentina [Bates *et al.* 2004], yielded dose-response relationships consistent with the flat slope of the findings from the non-artesian well dependent villages from SW Taiwan. The U.S. studies did not have sufficiently high arsenic levels to bring additional evidence to distinguish between the two potential explanations of the SW Taiwan data. The Argentina study may have had sufficiently high arsenic exposures but had few cases exposed at those levels and did not assess their water samples for other chemical constituents, such as iron, selenium, or humic acids.

Today, arsenic contamination of groundwater in the Bangladesh and West Bengal (Bengal delta plain) is considered to be the biggest arsenic catastrophe in the world,

**Table 1.** Cancer slope estimates in three different exposure contexts.

| Region | Description | Cancer Slope Factor (per $\mu$g/L) |
|---|---|---|
| SW Taiwan, BFD-Region | Artesian well water (350–1,140 $\mu$g/L) | +0.074 (95% CI +0.016; +0.133) |
| SW Taiwan, BFD-Region | Non-artesian well water (0–300 $\mu$g/L) | +0.005 (95% CI–0.020; +0.030) |
| U.S. 133 Groundwater-Dependent Counties | Groundwater (3–60 $\mu$g/L) | Slope forced to be non-negative 0.000 |
| | | Without non-negative constraint −0.006 (95% CI −0.014; +0.002) |

with contamination of 50–3,200 $\mu$g/L arsenic in the ground water of 36 million people over an area of 173,000 KM$^2$ (Bhattacharyya *et al.* 2003). Although dermal arsenicosis has been widely reported from the area, there are no excess rates of either external or internal cancers (including bladder cancer) reported so far (Khan *et al.* 2003). Because the arsenic contamination problem began only in the 1980s and 1990s, it may be too early to see such excesses (although cancers with latencies of 10–25 years should have been making their appearances).

The arsenic content in the waters in Bangladesh and West Bengal are high. Anawar (2002) reported that 51% of their 2,508 water samples from 10 districts of Bangladesh contained 50–2,500 $\mu$g/L arsenic. They reported that 3.6 million people (20% of the 18 million people in the study area) had arsenic exposures greater than 200 $\mu$g/L and that skin changes of arsenicosis were found at exposures down to 103 $\mu$g/L. They also reported that the water showed high intensity of fluorescent humic substances in the drinking water and very low levels of heavy metals.

In addressing the cancer risks for populations such as those of Bangladesh and West Bengal, public health interventions should be designed in consideration of the shape of the dose-response curve based on the world's literature. Remediation of the wells that have high levels of arsenic (in the hundreds of $\mu$g/L and possibly with organic material contamination) should be recognized as the sources with the highest risk of causing cancers and be handled first. Remediation might also focus not only on the reduction of the arsenic level but also on reducing or eliminating the presence of the humic substances in the water. Investigations of health effects and the development of remediation programs should be designed for better understanding of the variety of causative elements so that the design of remediation programs can be modified as the mechanistic elements are better understood. Public health interventions have to be designed to be assessed for their efficacy and safety in the same way as pharmaceutical or surgical interventions are.

**CONCLUSION**

Re-examination of the bladder cancer mortality data from the southwest Taiwan studies reveals that the assumption that the arsenic level in the drinking water is the only determinant of increased bladder cancer risk may not be the best available

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explanation of the underlying data. It may instead be the case that the relationship between arsenic and cancer may vary from situation to situation—that there may be multiple cancer slope factors for arsenic rather than just one, and that the cancer slope factor may be dose range–dependent.

We have explored two ways in which the context of exposure may affect the carcinogenicity of drinking water arsenic levels in SW Taiwan: (1) the distinction between high (>350–400 $\mu$g/L) and low concentrations (<350 $\mu$g/L) arsenic concentrations, and (2) the distinction between water characteristics as reflected by aquifer and well type found in SW Taiwan. The results from our analyses of data from SW Taiwan and the United States are summarized in Table 1.

The U.S. WM bladder mortality data from the 133 U.S. county study (Lamm *et al.* 2004) indicate an exposure-response relationship over the arsenic range of 3–60 $\mu$g/L that, like the data from the non-artesian well water dependent SW Taiwan villages, shows no increased risk with increasing level of arsenic exposure. These results suggest either that the relationship between arsenic ingestion and bladder cancer mortality is a high-exposure phenomenon (>350–400 $\mu$g/L) or that the observed carcinogenicity of arsenic is affected by some other difference between the water supplied by artesian and shallow wells. The Taiwan study would suggest that humic acids in the high-arsenic artesian waters may be a co-carcinogenic factor; the case-controls studies from the United States and Argentina would suggest that cigarette smoking may be a co-carcinogenic factor with high exposure. The three recent studies and the re-analysis of the older Taiwan study consistently find no increased bladder cancer risk with increasing arsenic concentration in drinking water up to the range of about 50 to 200 (+) $\mu$g/L.

## ACKNOWLEDGMENTS

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