Bladder/lung cancer mortality in Blackfoot-disease (BFD)-endemic area villages with low (<150 μg/L) well water arsenic levels – An exploration of the dose–response Poisson analysis

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Objective: To examine the analytic role of arsenic exposure on cancer mortality among the low-dose (well water arsenic level <150 μg/L) villages in the Blackfoot-disease (BFD) endemic area of southwest Taiwan and with respect to the southwest regional data.

Method: Poisson analyses of the bladder and lung cancer deaths with respect to arsenic exposure (μg/kg/day) for the low-dose (<150 μg/L) villages with exposure defined by the village median, mean, or maximum and with or without regional data.

Results: Use of the village median well water arsenic level as the exposure metric introduced misclassification bias by including villages with levels >500 μg/L, but use of the village mean or the maximum did not. Poisson analyses using mean or maximum arsenic levels showed significant negative cancer slope factors for models of bladder cancers and of bladder and lung cancers combined. Inclusion of the southwest Taiwan regional data did not change the findings when the model contained an explanatory variable for non-arsenic differences. A positive slope could only be generated by including the comparison population as a separate data point with the assumption of zero arsenic exposure from drinking water and eliminating the variable for non-arsenic risk factors.

Conclusion: The cancer rates are higher among the low-dose (<150 μg/L) villages in the BFD area than in the southwest Taiwan region. However, among the low-dose villages in the BFD area, cancer risks suggest a negative association with well water arsenic levels. Positive differences from regional data seem attributable to non-arsenic ecological factors.

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used in 1964–1966 and had been analyzed then in a national survey. Two clusters are observed in the 1989 study – one with 18 low arsenic exposure villages with median village arsenic levels ranging between 10 and 126 ug/L and the other with 24 high arsenic exposure villages with median village arsenic levels ranging between 256 and 934 ug/L. Significantly elevated bladder and lung cancer mortality have been clearly demonstrated for the villages with arsenic levels in the hundreds of ug/L (Lamm et al., 2006).

Previous dose-response analyses have been published for the entire set of 42 villages using either the age-adjusted mortality rates (Chen et al., 1988; Wu et al., 1989), or standardized mortality ratios with all Taiwan as the reference population (Morales et al., 2000) or with standardized mortality ratios with southwest Taiwan as the reference population (Lamm et al., 2006). The Morales et al. (2000) risk analysis, using the entire 42 village set, produced a variety of risk analyses based on a generalized linear model or multistage Weibull model using either no reference population or either of the two reference populations.

Dose-response analyses for the low-dose villages are fewer. Lamm et al. analyzed the village-specific standardized mortality ratios (SMRs) and found either downward or level regressions (Lamm et al., 2006, 2007). EPA analyzed the village-specific mortality data using Poisson regression analysis and found statistically significant positive (upward) regressions for each cancer outcome (EPA, 2010). Both groups analyzed data on bladder and lung cancers using the data from the southwest region of Taiwan as a reference population. Lamm in an SMR analysis and EPA in a Poisson analysis. EPA has also presented analyses using all-Taiwan as the reference population. EPA has recommend that the “better way to test the significance of exposure–response relationships at low doses is to simply restrict the analysis to the villages with low arsenic water concentrations but use the appropriate Poisson regression methodology” (EPA, 2010) (7, page F-6).

We now follow the EPA methodology and present here a Poisson regression analysis of bladder and lung cancer mortality for the low-dose (<150 ug/L) villages with respect to the median, mean, and maximum village well water arsenic levels. This paper demonstrates the dependence of the EPA analyses on the comparative differences in cancer risk of an external reference population (southwest Taiwan) rather than on the distribution of well water arsenic levels and cancer rates among the low-dose villages in the Blackfoot disease endemic area.

2. Materials and methods

The total dataset is comprised of demographic information (the age-gender-specific person years of observation distributions for 1973–1986), outcome information (bladder and lung cancer deaths distributions), and exposure information (well water arsenic measurements or assumptions) for each of the 42 study villages in the Wu et al. (1989) study as well as for two reference populations – southwest region of Taiwan and all Taiwan- with the EPA assumption that the water arsenic levels were zero for the reference populations. The data, other than the age-distributions, were publicly released as village-specific summary data in the NRC (1999) report [Table A10-1]. The age-gender-stratified data for the reference populations were published in Morales et al. (2000) and for the villages were publicly released by EPA in 2004.

Mortality information was obtained from death certificates for the years 1973–1986 were collected for each village from the local household registration offices of the studied townships and coded for their underlying cause of death according to the Eighth Revision of the International Classification of Diseases (ICD-8). Mid-year populations by age and sex for the studied villages were abstracted from demographic reports of the local household registration offices. Registration of in- and out-migration is mandatory in Taiwan, as are registrations of births, deaths, marriages, and divorces.

Well water arsenic data had been abstracted from the 1964–1966 survey (Kuo, 1968). The measurements had been made with either the silver diethyldithiocarbamate method or the mercuric bromide stain method (AWWA, 1955). These methods had standard deviations of 10 and 60 ug/L, respectively, for a synthetic sample of 50 ug/L (AWWA, 1955). Wu et al. (1989) entered the analyses based on the village medians and stratified with cut points at 300 and 600 ug/L. The NRC (1999) table listed the well water arsenic measurements for each village with the village medians. Village means and maxima could be developed from that list.

Arsenic exposure entered the analyses as daily dosage (ug/kg/day) for the male and female adult (20+ years) population of each village and area using the same exposure assumptions used by EPA-non-water arsenic intake of 10 ug/day, drinking water consumptions of 3.5 L/day for Taiwanese males and 2.0 L/day for Taiwanese females, and body weights of 50 kilogram for both Taiwanese males and Taiwanese females. That is, arsenic dosage for Taiwanese males was (10 ug/day + [3.5 L/day * As (ug/L)]/50 kg/person) and for Taiwanese females was (10 ug/day + [2.0 L/day * As (ug/L)]/50 kg/person).

Poisson regressions were conducted using the GEN MOD procedure of SAS with village cancer mortality counts as the dependent variable in a model with arsenic dosage as a linear parameter, age as a quadratic parameter, and person-years of observation as an offset variable. While there was some variation in age-distribution between the study villages and the reference populations, there was little variation in age-distribution among the study villages. The models were fit for males, females, and all, respectively. An exact method was used when the model converged, and an approximation was used when the second derivative matrix (the Hessian matrix) could not be inverted. The scale parameter was held fixed. The p-values were reported based on the 95% upper and lower confidence bounds.

The primary analysis related to the data for the 18 low-dose villages with median <150 ug/L. Subsequent analyses included the southwest regional data and/or restricted the low-dose villages to those with mean <150 ug/L or with maximum <150 ug/L. In analyses including the regional data, an indicator area variable was added to the analytic model in order to separate the differences in cancer risk factors for the study villages and those of the regional data into those related to arsenic (and age) and those differences not related to arsenic (and age). The indicator value for area is “1” if the village is a study village in the Blackfoot-disease endemic area and “0” if the area is not.

3. Results

The basic data on population, exposure, and outcome for the 18 villages that comprise the low-dose villages, defined as those with median well arsenic levels less than 150 ug/L, are presented in Table 1. The villages are numbered in ascending order by median well water arsenic level as presented in the NRC (1999) report [Table A10-1; pages 308–309]. The individual village’s identification numbers consisted of a numeral that represented the township number (0 I-chu; 2 Pu-tai; 3 Hsieh-chia; 4 Yen-shui; 5 Pemien; and 6 Hsia-ying) (Guo et al., 2007) and a letter that distinguished between the various villages within each township.

The dataset for the 18 villages included 123,569 male person-years of observation and 112,827 female person-years of observation over the 14 year period 1973–1986 for an estimated total population of 16,885 adult residents. The estimated village populations ranged between 363 and 1765 adults with an average of 938 adults. The six-township area had 126 villages, only 42 of
which were in the full Wu et al. (1989) study population and only 14–18 of which were the low-dose villages. Thus, only 10–15% of the BFD-endemic area villages were in these analyses. The remainder contributed to the southwest reference populations. The two comparison or reference areas (southwest Taiwan and all Taiwan) had adult populations of about two million and 10 million, respectively. All populations have been truncated at <85 y/o.

The eighteen “low-dose” villages had measurements for a total of 35 wells. The median concentration for these 35 wells was 73 μg/L and the mean was 144 μg/L. Fifteen of these villages had measurements for only 1 or 2 wells; three had measurements on 5–7 wells. Two-thirds of the villages (12/18 = 67%) had a report on only one well, and thus for these villages, their minimum, maximum, median, and mean arsenic levels were identical.

Of the three villages with measurements from two wells, the paired measurements were quite similar in one village (53 and 58 μg/L) and dissimilar in the other two (20 and 80 μg/L; 73 and 172 μg/L). That third village (N-4) had an elevated arsenic level at 172 μg/L. Its maximum (172 μg/L) exceeded 150 μg/L, but its mean (123 μg/L) and its median did not.

In contrast, each of the three villages that had measurements from more than two wells (0-G, 0-E, 0-I) had at least one well with a very high arsenic level (i.e., greater than 500 μg/L) of 590–770 μg/L. The means (216, 236, and 236 μg/L) and maximums (770, 686, and 590 μg/L) of these villages exceeded the low range of <150 μg/L. Of the 18 “low-dose” villages with median arsenic level <150 μg/L, only fifteen had a mean arsenic level <150 μg/L and only fourteen had their maximum arsenic level at <150 μg/L. The analytic set for the analyses by mean included the 15 villages with mean <150 μg/L, and the analytic set for the analyses by maximum included the 14 villages with maximum <150 μg/L.

US EPA (2010) assumed for each of the two reference populations (southwest Taiwan and all Taiwan) that the median and mean drinking water arsenic levels were 0 μg/L. An early study

Table 1
Population, exposure, and cancer Data for the 42 villages in the BFD-endemic area of southwestern Taiwan (Wu et al., 1989).

<table>
<thead>
<tr>
<th>Village No.</th>
<th>ID</th>
<th>Population (Age 20–84)</th>
<th>Arsenic Exposure</th>
<th>Observed Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Person-Years</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>1</td>
<td>3-H</td>
<td>4,159</td>
<td>586</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2-I</td>
<td>3,529</td>
<td>480</td>
<td></td>
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<tr>
<td>3</td>
<td>0-G</td>
<td>5,388</td>
<td>732</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3-S</td>
<td>7,851</td>
<td>1,063</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3-N</td>
<td>2,689</td>
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<td>6</td>
<td>4-7</td>
<td>10,629</td>
<td>1,490</td>
<td></td>
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<tr>
<td>7</td>
<td>6-A</td>
<td>7,716</td>
<td>1,038</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0-J</td>
<td>6,501</td>
<td>885</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3-L</td>
<td>6,238</td>
<td>809</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
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<td>1,546</td>
<td></td>
</tr>
<tr>
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<td>0-O</td>
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<td>949</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0-E</td>
<td>5,753</td>
<td>790</td>
<td></td>
</tr>
<tr>
<td>16</td>
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<td>4,249</td>
<td>577</td>
<td></td>
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<tr>
<td>17</td>
<td>4-N</td>
<td>4,709</td>
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<tr>
<td>18</td>
<td>4-J</td>
<td>6,508</td>
<td>895</td>
<td></td>
</tr>
</tbody>
</table>

Low-dose: 123,569 | 112,827 | 16,885 | 35 | 482 | 73 | 144 | 10–770 | 23 | 41 | 27 | 41 | 132

SW Taiwan: 14,689,807 | 12,862,006 | 1,967,987
All Taiwan: 71,885,910 | 9,736,767 | 5,830,191

Fig. 1. Distribution of village arsenic exposure metrics (median, mean, and maximum) for the 18 villages with median <150 μg/L (Wu et al., 1989; NRC, 1999).
of wells above the Chianan plain that underlies the study area (Lewis et al., 2007) reported median arsenic levels of 30 and 380 µg/L, respectively, for shallow and artesian wells in the non-endemic areas (Chen et al., 1962) and a later report (Chiang et al., 1988) reported that 45–54% of wells in the non-endemic area had arsenic content greater than 50 µg/L and 0–6% had levels greater than 350 µg/L. The nation-wide survey in 1974–1976 reported that 5.7% of the wells outside of the BFD-endemic area had arsenic levels of 50 µg/L or greater and that 0.3% had arsenic levels greater than 350 µg/L (Lo et al., 1997).

Fig. 1 demonstrates that the analytic set of 18 villages with median arsenic level <150 µg/L that EPA has described as "the villages with low arsenic water concentrations" includes three villages that have wells with arsenic levels >500 µg/L with an additional village having a well with an arsenic level of 172 µg/L. Table 1 shows the range of measurements for these villages with their median and mean levels as summary metrics. Wu et al. (1989) had used the median village well water arsenic level as the metric of central tendency and as the sole village-specific summary arsenic level. The arsenic levels used by Wu et al. (1989) had come from the Kuo (1968) survey which had used the mean as the metric of central tendency. The median has the advantage (or disadvantage) that it is influenced by each of the well water measurements rather than being dependent on only the central measure(s). The mean and the maximum allow for the examination of the hypothesis that the high exposure levels are critical. The median does not.

In total, the 18 villages with median <150 µg/L had 132 bladder or lung cancer mortalities during 1973–1986, 64 in males and 68 in females (Table 1). The per-village cancer death counts ranged between zero (villages 4–7 and 6-A) and 19 (village3-L). There were 23 male bladder cancer deaths in the 18 study villages and 27 female bladder cancer deaths. There were 41 male lung cancer deaths and 41 female lung cancer deaths. While the numbers of male and female cancer deaths were similar among the study villages, the numbers of male cancer deaths in the reference populations were about twice the number of female cancer deaths. Further, while bladder cancers accounted for 38% of the bladder and lung cancers combined counts for the villages, they accounted for only 19% of those for the regional southwest Taiwan reference population and 11% of those for the all Taiwan reference population.

Table 1 presents the summarized data across all age 20–84 age groups. The population (person years of observation) and outcome (bladder and lung cancer deaths) data were made available by EPA (2004) stratified by gender and age in five-year intervals (20–84 years of age). Table 1 presents the data on the three summary exposure metrics for the village arsenic levels in the EPA data set – the median, the mean, and the maximum. The exposure (village well water arsenic levels) data were made available by NRC (1999) and summarized as three summary exposure metrics for the individual villages by EPA (2004) – the median, the mean, and the maximum. The individual village well water arsenic data have been published in NRC, 1999 report (Table A-10), and the three summary exposure metrics are in Table 1. Fig. 1 graphically demonstrates the medians, means, and maxima for the 18 low-dose villages. It is clear that the median values are insensitive to the very high well water arsenic levels that were found in some of these villages. The analyses by means separates out the three villages with the most markedly high levels (i.e., greater than 500 µg/L), and the analyses by the maxima separates out the four villages that have any well water level known to be greater than 150 µg/L.

The dose–response relationship between arsenic level and cancer risk can be examined using a variety of metrics of risk. The most straightforward metric is the crude mortality rate which is the ratio of the number of cancer deaths divided by the number of person-years of observation for each village. Fig. 2 shows the distribution for the crude mortality rate for bladder and lung cancer combined for the eighteen low-dose villages. Simple linear regression shows a downward slope that is not statistically significant ($p = 0.40$) and has little explanatory power ($R^2 = 0.045$, or 4.5%).

Wu et al. (1989) presented cancer risks as age-adjusted mortality rates, standardized to the 1976 world population. A further refinement in the development of the risk metric, the standardized mortality ratio, includes not only the age structure (distribution of the person-years of observation) of the reference population but
also includes the age-specific mortality rates in the reference population. Fig. 3 presents the results of the standardized mortality ratio analysis for bladder and lung cancer mortality for the eighteen villages using either southwest Taiwan or all Taiwan as the reference population. The mortality rates for individual cancers in the southwest region are different from those of the all Taiwan data (from 15% lower for male lung cancers to 90% higher for female bladder cancers), although both groups were assigned an arsenic drinking water exposure of 0 ug/L. Nonetheless, there is little difference in the distributions of the SMRs for the cancers combined between the two reference populations.

Linear regression analysis of the SMR data can be weighted by the size of the population of each village. The analytic advantages of the SMRs include that they account for the age distributions within the villages, each village is separately compared with the reference population, and they are weighted by the village population. The disadvantage is that it assumes that the uncertainty of the point estimate of the SMR is distributed normally, which may not be certain when the numbers of cases are small. The Poisson analysis is a further analytic refinement that accounts for the small number of cases by assuming that their uncertainty follows a Poisson distribution.

Poisson regression models have been analyzed for the low-dose villages for each cancer-gender group (male lung, male bladder, female lung, and female bladder) and their combinations (males, females, lung, bladder, and all) using the median, mean, or maximum village well water arsenic level as the summary exposure metric.

Table 2 shows the results of the Poisson analyses for each of the gender cancer groups and for each of the combined groups for the 18 low-dose (median < 150 ug/L) villages. All nine cancer endpoint models show a negative dose–response. The slope is significantly negative for the female bladder cancer model (p = 0.0178) as well as for the model of both female and male bladder cancers (p = 0.0201) and the model for female bladder and female lung combined (p = 0.0471). No statistically significant association is found for the male cancer deaths or for the female lung cancer deaths. This finding indicates that for population groups with median well water arsenic concentrations <150 µg/L, the dose–response relationships are negative and occasionally (3/9) statistically significantly negative.

The set of low dose villages based on the mean village well water arsenic level being <150 µg/L is comprised of 15 of the previous 18 villages. Excluded from it are the three villages which have well arsenic levels >500 µg/L (villages 0-G, 0-E, and 0-I in Chi township) and have mean village well water arsenic level that exceeds 200 µg/L. Table 3 presents the results of the Poisson analyses the cancer data for the 15 low dose villages with mean village well arsenic level <150 µg/L. The slope of each model is negative. The slopes are statistically significantly negative for the bladder and combined cancer models but not for the lung cancer models.

The villages with mean village well water arsenic level <150 µg/L does include one village (4-N) with a well water measurement greater than 150 µg/L. Redefining low dose villages or “villages with (only) low arsenic water concentrations” as those with all known exposures being <150 µg/L is accomplished by using as the village exposure metric that the maximum well water arsenic level is <150 µg/L. Table 4 presents the results of the Poisson analyses for those 14 villages. The slope of each model is negative. As with the analyses by the village mean, none of the lung cancer slopes are statistically significantly negative, while all the bladder cancer and combined cancer slopes are.

EPA (2010) conducted the Poisson analyses using only the median as their village-specific summary metric of the arsenic exposure, though they explored the use of the minimum and of the maximum in their sensitivity analysis (pages 139–140). They demonstrated that their use of the mean or of the maximum had a substantial (>20%) effect on the risk estimates. We have conducted the Poisson analyses using three summary exposure metrics – the median, the mean, and the maximum. Poisson analyses are presented for the villages with low arsenic concentrations (median <150 µg/L) in Table 2, for the villages with low arsenic concentrations (mean <150 µg/L) in Table 3, and for the villages with low arsenic concentrations (maximum <150 µg/L) in Table 4.

The Poisson analyses of the “low-dose” village cancer mortality reach similar and consistent findings, whether based on the median, the mean, or the maximum for the villages. In all cases, the cancer slopes with a range up to 150 µg/L are negative with respect to the arsenic level. Tables 2–4 demonstrate in the Poisson analyses that as the definition of low dose arsenic is tightened, the number of models with a statistically significantly negative slope increases. Previous analysis based on standardized mortality ratios (SMRs) have also demonstrated negative slopes at low exposures.
Morales et al. (2000) showed lower risks at 50–100 μg/L than at 10–50 μg/L for bladder cancer mortality in both CMR and SMR analyses. Lamm et al., 2006 showed for low-dose villages a nonsignificant negative dose response for bladder and lung cancer SMR. Thus, the dose–response results based on the low-dose village data and presented as SMR or Poisson analyses are similar with negative slopes, some of which reach statistical significance, particularly those that include female bladder cancers.

The Poisson analyses in Tables 2–4 have been limited to the data for the 14–18 low-dose villages in the study area. The Poisson analyses in Tables 5 and 6 include also the data for the southwest region of Taiwan as an additional “village” and the EPA-assumed drinking water exposure metric of 0 μg/L. Table 5 includes “19 villages” in the analysis, which are the 18 villages with median <150 μg/L plus the southwest region, using the southwest region data as if it were a 19th low-dose village. This Poisson analysis is analogous to that of Table F-2 in EPA (2010; page F-6). These results similarly indicate that “the arsenic dose coefficients are positive with lower confidence limits that are also positive” and that “the dose–response relationships are positive and statistically significant.”

Table 6 presents alternatively an extension of the Poisson analysis in Table 5 with the contribution from the southwest regional data contributing both as an arsenic-related component and as a non-arsenic-related (area) component. The arsenic-related slope factors are all negative, with some statistically significantly negative. None of the slopes for the models limited to lung cancers have statistically significant slopes, nor do most of those containing male bladder cancers. However, most of the models containing female bladder cancers have slopes that are statistically significantly negative.

In contrast, the area slope factor, or non-arsenic-related slope factor, in Table 6 is strongly statistically significantly positive in all models except for that of the male lung cancers. The strongly statistically significantly positive contribution to the slope factor by the southwest regional data is seen to come from the non-arsenic related (area) component and not to be related to the arsenic related cancer slope factor. The arsenic-related cancer slope factors in Table 6 are essentially identical to the arsenic-related cancer slope factors in Table 2. The non-arsenic-related (or area) slope factors seem to mimic the findings in our Table 5 and EPA’s Table F-6. This analytic refinement has separated the arsenic-related influence from the non-arsenic-related (area) influence that the inclusion of the southwest regional data as an additional data point has brought into the analysis.

In Table 7, we have separated the 42 villages in the six-township BFD-endemic area that have known well water arsenic levels into three groups — the 24 high exposure villages (median and mean exceed 150 μg/L), the 3 low exposure villages with very high level arsenic water (mean but not median exceeds 150 μg/L), and the 15 low exposure villages without very high arsenic levels (neither median nor mean exceed 150 μg/L). All three villages in the middle group include well arsenic levels that exceed 500 μg/L, with maximum recorded levels of 590, 686, and 770 μg/L.

Table 7 shows the crude mortality rates for bladder and lung cancers (and combined) for the three groups of villages and the two reference populations (southwest Taiwan and all Taiwan). The rates for the two reference populations are similar. The rates for the low-dose villages (median and mean <150 μg/L) are about twice that. The rates for high exposure villages, whether high-dose villages or low-dose villages with high well arsenic levels, are also similar. They are about three times as high as the low-dose, low-exposure villages and six times as high as the reference populations.
Table 7 indicates that the low-dose villages with very high arsenic levels have cancer risks that are consistent with those of the high-dose villages rather than those of the low-dose villages. Table 7 thus also demonstrates an exposure misclassification bias in the low-dose analyses that are based solely on the median village well arsenic level, a bias that is corrected by use of the mean or the maximum.

All analyses have assumed that the well measurements are complete and representative. While there is no specific evidence to the contrary, Table 1 has shown for the low-dose villages that two-thirds of the villages have measurements for only one well and that the number of villagers per well ranges from about 80 to 1800 – a range to suggest that not all water sources have been identified. The risk pattern based on the villages with measurements from only one well is accentuated compared to those with multiple wells. Further, there is no information on the distribution of well usage in multi-well villages or whether villagers used wells from other villages, which may explain some of the variability in risk.

Fig. 4 graphically presents the full set of cancer slope factor calculations for lung, bladder, and lung and bladder cancers combined and for males, females, and both using the five data sets analyzed above – the 18 villages with median <150 µg/L, the 15 villages with mean <150 µg/L, the 14 villages with maximum <150 µg/L, the 19 “villages” which includes the southwest Taiwan population as the 19th village, and the 19 “village” including the area variable. The graph demonstrates that, with the exception of the 19 “village” analyses, all the cancer slope factors are negative. It is only the 19 “village” analysis that EPA (2010) used that uniquely yields positive cancer slope factors.

4. Discussion

Poisson analysis of the bladder and lung cancer mortality data of the low arsenic exposure (<150 µg/L) villages in the Wu et al. (1989) study in the BFD-endemic area of southwest Taiwan consistently yields negative slopes (arsenic “b” coefficient; cancer slope factor [CSF]) whether exposure is defined on the basis of the median, mean, or maximum village well water arsenic level being <150 µg/L. When based on the village medians, the slopes are statistically significantly negative for most of the models containing female bladder cancers. Further, when based on the mean or the maximum village well water arsenic level, the slopes are statistically significantly negative for the bladder cancer or lung and bladder cancer models but not for the models that only contain lung cancers.

There are a number of ways in which our analyses differ from those of EPA (2010), in addition to the inclusion of analyses based on the village means and the village maxima. Some of the differences yield a shift in frame where the units are different but neither the pattern nor the statistical significance is different. The EPA model was developed for the purpose of using the Taiwan data to estimate the risks from arsenic in drinking water for US populations – as stated, “this risk assessment assumes that the observed carcinogenic potency in the Taiwanese population, with suitable corrections for differences in drinking water intake and background cancer incidence, is an appropriate predictor of the potential for human cancer risk in the US population.” (EPA, 2010) (7; page 152) They furthered their analysis for US populations by converting from mortality risks to incidence risks using BEIR IV modeling and assuming that the male and female US populations had a mean body weight of 70 kilograms and an average daily water consumption of 2 L/day (EPA, 2010 (Page 139; Table 5–10). Their analysis presented arsenic levels as ppm rather than as µg/L, but that too would only affect the decimal point and not the statistical findings.

Other differences affect the nature of the association as a consequence of unstated assumptions. The primary difference between our analyses and that of EPA (2010) is that their analysis included the data from the southwest region of Taiwan as if it were an additional or “19th” low-dose village and has assigned the regional data a drinking water arsenic concentration of 0 µg/L. Their analysis was limited to the use of the median as the measure of central tendency. Table 5 is our replicate of their analysis for the low-dose villages as it relates to the Taiwanese population (EPA, 2010) (7, Table F-2). This finding is limited to the analysis based on the median. The same analysis based on either the mean or the maximum show positive slopes that are not statistically significant for the male cancers (lung, bladder, or both).

The results of Table 5 are consistent with EPA interpretation of its own results, that is, “For all of the endpoints, the arsenic dose coefficients are positive with lower confidence limits that are also positive. This finding indicates that for population groups with water arsenic concentrations less than or equal to 126 ppb [µg/ L], the dose-response relationships are positive and statistically significant.” (page F6) The 18 villages that EPA groups as those with median <126 µg/L are the same 18 villages that we group as those with median <150 µg/L.

An underlying, and unstated, assumption in the “19 village” model is that the only explanatory factor accounting for bladder and lung cancer distribution between the study villages and the southwest region is the drinking water arsenic concentration. This

![Fig. 4. Cancer slope factor by cancer and by exposure metric for low-dose (<150 µg/L) villages in BFD-Area (Wu et al., 1989; Morales et al., 2000).](image-url)
assumption can be tested. As the NRC (2001) states, “A potential disadvantage, however, of using an external comparison group is that the analysis can be biased if the study population differs from the comparison population in important ways” (Page 190).

Fig. 3 demonstrated that the SMRs differed little, whether based on the southwest regional data or the all Taiwan data, thus suggesting that the background risks in the two reference populations differed little. Both reference populations in the analyses included both urban populations in the cities and rural populations in the counties. In contrast, the BFD-endemic area was strictly a rural population that by Taiwanese standards was nutritionally and socioeconomic depressed (Yang and Blackwell, 1960). Both have been reported to be risk factors for arsenic-related diseases (Ch¹l and Blackwell, 1968; Chen, 2001). The carbohydrate source in the diet was sweet potatoes rather than rice, and samples of dried sweet potatoes from the BFD-endemic area showed a mean arsenic level of 0.180 mg/kg (Blackwell et al., 1961). The association between poor nutritional status and arsenicosis had been shown in Bangladesh (Milton et al., 2004). Table 6 presents an analysis that tests the assumption that there are no other factors differentiating the study villages and the regional data that influences the cancer risks other than age and median arsenic concentration. The same analyses have been done based on the village means and on the village maxima and yield analogous results. The negative arsenic slopes are statistically significant for all 12 models containing bladder cancers but only for one of the six models restricted to lung cancers [see Supplemental tables].

This comparison demonstrates that the differences in risks between the study villages and the comparison areas are significant and are not explained by their differences in arsenic exposure. The positive slopes in Table 5 thus appear to be a consequence of non-arsenic related aspects of the comparison area. Table 6 demonstrates the effect of non-arsenic related factors that distinguish the bladder and lung cancer risks in the Blackfoot disease (BFD) endemic parts of the southwest region from risks in the non-BFD endemic parts of the southwest region. The basis for this residual difference in risk is neither known nor demonstrated. Whether the area differences in cancer risk can be explained by the use of the artesian wells, by the organic substances in the well water, or from other aspects of the differences in the areas cannot be ascertained from these data.

The first clearly known difference is the presence of Blackfoot disease in the study area and its absence in the comparison area. The second clearly known difference is the markedly lower education and socio-economic status of the villagers in the BFD area compared with the general and urban populations of Taiwan, and the third is that their diets had insufficient amounts of fresh vegetables and animal protein (Tsai et al., 1999). Unlike the local reference population in the Tsai et al. (1999) study which was limited to Tainan and Chia-Yi counties, the southwest Taiwan reference population used in the Morales et al. (2000) analysis of the Wu et al. (1989) study included the populations of Tainan and Chia-Yi cities in addition to the populations of the counties. The urban (city) populations made up 37% of the southwest Taiwan population. The effects of the social and economic differences between the cities and the counties are reflected in the life expectancies with the life expectancies in these two cities being more than a year greater than the life expectancies in these two counties (Taiwan Ministry of Interior, 2012).

Blackfoot disease has been uniquely found in the BFD-endemic area of southwest Taiwan and not elsewhere in the world. The wells in I-Lan county in northeast Taiwan have the same levels of arsenic as found in the BFD-endemic area of southwest Taiwan and the duration of drinking from the wells is similar, yet BFD is not a disease of I-Lan county Chen et al. (1995). Further, endemic BFD has not been reported from the high arsenic areas in India, China, Mexico, Argentina, or Chile, particularly from Antofagasto, Chile where the drinking water arsenic levels were as high as 860 µg/L for thirteen years. Secondly, Blackfoot disease has been specifically associated only with the high arsenic artesian well waters in the endemic area (Chen et al., 1962). Thirdly, bladder cancer incidence in the Blackfoot disease endemic area has been specifically associated with elevated levels of humic acids found in the artesian well waters of the area Lu et al., 1986).

The early epidemiological studies of Chen et al. (1962) demonstrated that the BFD-endemic area had both a shallow aquifer obtained by a hand pump and a deep aquifer obtained by artesian wells and that BFD occurred only in the villages that had artesian wells. Chen et al. (1962) demonstrated that the waters of the artesian wells differed from those of the shallow wells primarily by high arsenic levels and secondarily by both algae and high iron content. Lu et al. (1986) demonstrated that the artesian waters green fluorescent substances, later summarized as humic acid, was associated with bladder cancer incidence. Chen et al. (1985) showed the bladder and lung cancer mortality in the BFD-endemic area to be associated with BFD-endemicity at the village and township level and to the use of artesian wells. Chen et al. (1986) related cancer risk to the duration of artesian well use, and Lu et al. (1986) related cancer risk to the specific presence of humic or fluorescent substances. Further, additional studies or analyses showed that BFD (which is uniquely found here) is a known risk factor for the skin cancers (Tseng et al., 1968) and for the bladder cancers (Chiang et al., 1988), or that the dose–response patterns for bladder and lung cancers here are consistent with a threshold model at about 150 µg/L (Lamm et al., 2006, 2007). These are all factors which differentiate the BFD-endemic area from the non-BFD endemic areas of southwest Taiwan.

The inclusion of the southwest regional data could affect the analysis both because of its size and because of its values. The southwest region has a population of 1.97 million persons and contributes 27.6 million person years of observation. It is more than 2000 times greater than the average village (935 persons and 13,089 person-years of observation). It is an over-influential data point as it has 98% of the bladder and lung cancer deaths and 99% of the adult population and person-years in this analysis. Modeling indicates that the major influence of the southwest data is from its size rather than its values. The regional data is the elephant in the dataset, and the village data are the tail.

The bladder and lung cancer risks in the BFD-endemic area have been shown in Chen et al. (1985) to be elevated above that of Taiwan with SMRs for lung cancers that are elevated by a factor of 4 and for bladder cancers by a factor of 10–20. The population-weighted median drinking water arsenic level for the low-dose villages was found to be 66 µg/L. There was no positive trend among the low-dose villages themselves. The southwest region was assigned a drinking water arsenic level of 0 µg/L. Clearly any analysis would show a positive slope between the two areas, even without considering the exposure distribution among the study villages. The critical question is the dose–response or risk relationship for differences in arsenic exposure among the low-dose villages.

5. International perspective

The first report of arsenic content of drinking water in the Blackfoot-disease endemic area was summarized as a mean of 0.59 mg/L (590 µg/L) for 13 deep well samples in Blackwell et al. (1961) and later as a mean of 0.52 mg/L (520 µg/L) for 126 artesian well samples in Kuo (1968). Other reports from the BFD-area used the median (Chen et al., 1962; Wu et al., 1989), as has EPA in its toxicological reviews (EPA, 2010). Elsewhere, the mean has been widely used to summarize arsenic exposure from drinking water.
The mean has been used as the summary statistic in southwest Taiwan (Kuo, 1968), Argentina (Hopenhayn-Rich et al., 1996), USA (Bates et al., 1995, 2004; Steinmaus et al., 2003; Meliker et al., 2010), Denmark (Baalstrop et al., 2008), Taiwan (Guo, 2004), and in tox studies from USA (Vig et al., 1984; Warner et al., 1994; Moore et al., 1996), Inner Mongolia (Fujino et al., 2005), Bangladesh (Argos et al., 2006), India (De Chaudhuri et al., 2006; Ghosh et al., 2006), Mexico (Gonsebatt et al., 1997).

The results of the Poisson analyses of these data are unique in finding statistically significant negative slopes in the low-dose range (<150 μg/L). However, they are consistent with the rest of the literature in not finding significant positive slopes in the exposure range below 100–200 μg/L. No association between bladder cancer and low arsenic exposures was found either in multiple case-control studies from multiple areas – Utah (Bates et al., 1995), Finland (Kurttio et al., 1999; Michaud et al., 2004) California/Nevada (Steinmaus et al., 2003), Argentina (Bates et al., 2004), New Hampshire (Karagas et al., 2004), and Michigan (Meliker et al., 2010), or in cohort or ecological studies from multiple areas – Utah (Lewis et al., 1999), southwest Taiwan (Guo and Tseng, 2000), USA (Lamm et al., 2004), Denmark Baalstrop et al. (2008), and northeast Taiwan (Chen et al., 2010b). The Mink et al., 2008 meta-analysis of epidemiological studies of low-level arsenic exposure in drinking water and bladder cancer concluded that arsenic exposure did not appear to be a significant independent risk factor of bladder cancer, though smoking was a possible effect modifier (Mink et al., 2008). Similarly, no association between lung cancer and low arsenic exposures was found in cohort or ecological studies – Utah (Lewis et al., 1999), southwest Taiwan (Guo, 2004), Denmark (Baalstrop et al., 2008), Bangladesh (Mostafa et al., 2008), New Hampshire/Vermont (Heck et al., 2009), and northeastern Taiwan, (Chen et al., 2010a). These analyses of the data from the Blackfoot-disease endemic area of southwest Taiwan show negative associations for bladder cancer and for bladder and lung cancers combined and low arsenic exposures in any of the analyses based on the low-dose (<150 μg/L) village data unless the southwest Taiwan population is entered as an additional village.

These analyses have demonstrated that the village exposure can be summarized as a median, a mean, or a maximum value. The use of the mean or the maximum value has eliminated exposure misclassification introduced by the median and with it the inclusion of villages with wells containing >500 μg/L arsenic. Thus, in this case, the use of the mean or the maximum has the advantage of using cleaner data. Further, if the results are to be used in risk analysis or for regulatory purposes, the mean and the maximum have the advantage that they can be used to describe other populations. The median is not a useful metric for describing exposures for regulated populations.

Fig. 4 graphically presents the full set of cancer slope factor calculations for lung, bladder, and lung and bladder cancers combined and for males, females, and both using the five data sets analyzed above – the 18 villages with median <150 μg/L, the 15 villages with mean <150 μg/L, the 14 villages with maximum <150 μg/L, the 19 “villages” which includes the southwest Taiwan population as the 19th village, and the 19 “village” including the area variable. The graph demonstrates that, with the exception of the 19 “village” analyses, all the cancer slope factors are negative. It is only the 19 “village” analysis that EPA (2010) used that uniquely yields positive cancer slope factors.

6. Conclusion

The bladder and lung cancer mortality data from the 18 “low-dose” villages in the Blackfoot-disease endemic area of southwest Taiwan that are from the Wu et al. (1989) study have been analyzed, initially based on median <150 μg/L, then on mean <150 μg/L and then on maximum <150 μg/L. Simple linear regression (or population-weighted) linear regression of the crude mortality rates and of the standardized mortality ratios (with respect to either southwest Taiwan or all Taiwan) yielded negative or non-positive slopes. Poisson regression of the mortality distributions based on village medians showed only negative slopes, some of which, mostly those including female bladder cancers, were statistically significantly negative. Use of the mean or maximum as the exposure metric eliminated confounding from villages with very high (>500 μg/L) well water arsenic levels. Poisson analyses based on the use of the mean or the maximum levels were statistically significantly negative for bladder cancer models and for models with bladder and lung cancers combined. Extension of the analytic population to include southwest regional data similarly demonstrated statistically significantly negative slopes for arsenic levels when the models included a variable for non-arsenic area factors. Significant positive slopes could only be obtained when models assumed that all differences between areas could only be attributed to arsenic exposure levels.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.yrtph.2012.10.012.

References


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