Drinking Water Exposure Information on Southwest Taiwan

EPA has assumed that the drinking water arsenic level for the Southwest Taiwan region, at least up to 1986, was zero. This assumption is extreme.

Arsenic assays of the wells in Southwest Taiwan had been conducted in the early 1960s and early 1970s. The two major methods for measuring arsenic in drinking water were the silver diethyldithiocarbamate method and the mercuric bromide stain method (AWWA 1965). The silver stain method had a standard deviation of 10 ug/L for a synthetic sample of 50 ug/L. The mercuric method had a standard deviation of 60 ug/L for a synthetic sample at 50 ug/L.

The Taiwan drinking water standard for arsenic was 50 ug/L, and water survey results were typically reported as the proportion of wells or water sources greater than 50 ug/L (alternatively, greater than 350 ug/L). The Chen et al. (1988b) paper referenced by EPA for the Southwest Taiwan study cited both the epidemiological study of Chen, Wu and Wu (1962) and data from the national survey of well water arsenic levels from Lo MC et al. (1977).

Chen, Wu and Wu (1962) reported that the median arsenic level was 25 ug/L for the non-endemic shallow wells and 380 ug/L for the non-endemic artesian wells. Lo et al. (1977) reported that well water arsenic levels were greater than 50 ug/L in 29% of the wells in the four BFD-endemic townships (Peimen, Hsuechia, Putai, and Ichu) and that 5.2% of the wells had well water arsenic levels greater than 350 ug/L.

Chen et al. (1985) report that the four Blackfoot disease endemic townships had a 1968 population of 141,733 residents in 1968. As approximately 50% of the residents were 20 years of age or older, the adult resident population of these four townships would have been about 70,000 people. The EPA database, however, has only 21,000 adult residents from these four townships, indicating that most of the residents of these townships (another 50,000 residents) were in the Southwest Taiwan part of the analysis and not in the study villages. The arsenic exposure of these residents also had 29% of their wells with arsenic levels greater than 50 ug/L. It is hard to see how they can be represented as having zero arsenic exposure from their drinking water.

Other studies of well arsenic levels not in the study area include Lo et al. (1977) and Chiang et al. (1988). Lo et al. (1977) found that 5.7% of the wells in Taiwan outside of the endemic area had arsenic levels greater than 50 ug/L. Chiang et al. (1988) found for one of the two control groups outside of the BFD-endemic area that the arsenic content was greater than 50 ug/L in 45% of the wells and greater than 350 ug/L in 6%. The other area had 54% of the wells greater than 50 ug/L with none over 350 ug/L. It is difficult to conclude that, except for the study villages, Southwest Taiwan had no drinking water arsenic exposure.

Stepping back and recognizing how important the exposure assessment is to the risk assessment, it is astounding that the toxicological review does not show any contribution from the geological, hydro-geological, or exposure measurement expertise of the Agency. There is no recognition given to the fact that the Southwest Taiwan area is located on top of the Chianan plain (Lewis et al., 2007) and most likely has similar groundwater characteristics.

EPA needs to justify its exposure assumption for the Southwest Taiwan population as it is one of the most critical data points in the EPA analysis. The sensitivity analysis for the low dose villages might be presented with the Southwest Taiwan exposure over the range up to 40-50 ug/L.
Drinking Water Exposure Information on Southwest Taiwan


The Chianan Plain is shown above. The borders of the plains are in accordance with the groundwater zones of Taiwan.

Source: Chianan Plain Wikipedia.com
EPA and the SAB have raised a number of issues concerning the US 133 county bladder cancer study (Lamm et al., 2004), some of which are generic to ecological studies and some of which are specific to this study.

Lamm et al. (2004) is an analysis of US government data on white male bladder cancer mortality (NCI/EPA 1983) and groundwater arsenic levels. The counties studied are limited to those identified by the individual state departments of the environment or of health as having groundwater sources for their entire drinking water supply in the time period prior to 1980. The mortality period of observation was 1950-1979. We have assumed that bottled water was not a major contributor to drinking water in the 50 year period, 1930-1980.

EPA Cited Weaknesses -

The Toxicological Review of Inorganic Arsenic (February 2010) identifies five weaknesses in the Lamm et al. (2004) ecological US study. We will contrast them with the characteristics of the Wu et al. (1989) ecological Taiwan study.

1. No individual exposure data

Neither the US study nor the Taiwan study have individual exposure data. However, given the available exposure data, they both can be analyzed for the dose-response relationship for those without very high (> 400 ug/L) arsenic drinking water exposure. We demonstrate that analysis below for the US study and have already presented that analysis for the Taiwan study.

2. Study participants are assumed to have consumed local drinking water

That assumption is true for both the US study and the Taiwan study.

3. Available data are assumed to represent actual arsenic content of water.

That assumption is true for both the US study and the Taiwan study.

4. Analysis did not directly adjust for smoking, urbanization, and industrialization.

That issue was raised and considered for the US study but not for the Taiwan study. Whether it applies to the US study hinges on the meaning of the word “directly”. The US study discusses this issue in the results section regarding the relative risk (SMRs) analysis on page 301, column 1, as follows:

Stratified analysis presented in Table 1 shows that the overall SMR is 0.94 (95% CI = 0.90-0.98). The counties in the study have lower bladder cancer mortality rates than do the states, suggesting that state data could be more heavily influenced by other risk factors such as urbanity, industrialization, and cigarette smoking.

The discussions of the Taiwan study comment on the lifestyle similarities of the populations. That is not true for the Southwest Taiwan population that is used as the reference population. The study villages are a few rural villages near the southwest coast. The SW Taiwan regional population
Response to EPA 2010 Comments on US Study

includes the population of two of the four major industrialized cities in Taiwan – Tainan and Kaohsiung. The SW regional data have not been separated out by rural and urban, which provide a measure of the effect of the three factors. In the mid 1950s, when medical school opened in Kaohsiung, the study population was getting their first missionary physicians.

Guo et al. (1997) conducted an ecological study urinary cancer incidence in 243 townships in Taiwan using cancer registry data. They evaluated the effects of well arsenic level, urbanization and smoking on various urinary cancers. High arsenic level (greater than 640 ug/L) were positively associated with two of the three types of bladder cancer in males (transitional cell, adenocarcinoma, but not squamous cell) Neither urbanization nor per capita cigarette sales was found to be associated with male bladder cancers. Similarly, Chiu et al. (1995) reported a cohort study from the study area in which cigarette smoking was a risk factor for lung cancer (RR = 4.31) but not for bladder cancer (RR = 1.00).

That urbanization and cigarette smoking have not been found to be risk factors for bladder cancer in the study area in two independent studies has not been discussed in the EPA report, though the issue has been raised concerning the US study.


5. Arsenic contribution from food was not measured.

Neither the US study nor the Taiwan study make use of any data on dietary arsenic.

The existent data on arsenic content of foods in the study area (Blackwell, Yang, and Ai, 1961) do not enter the risk assessment. Rather, the dietary exposure assumption has been reduced from 50 ug/day to 10 ug/day without any clear data source. Dietary arsenic exposure in the US has recently been modeled using 2003-2004 data. Earlier data is not known to us.


Review of the five stated weaknesses of the US 133 county study (Lamm et al., 2004) have been reviewed above and found to be as applicable to the SW Taiwan study (Wu et al., 1989).

EPA Cited Strengths –

The Toxicological Review cites two strengths for the US 133 county study (Lamm et al., 2004) – that it is nationwide and that it included 75 million person-years of observation.

1. Dispersed - The US study concerns 133 counties in 26 states, generally distributed within the contiguous United States. The SW Taiwan study has 15 low exposure villages in a small sector of the country.
2. Numerous in study population – The US county study has 75 million person-years for 2.5 million persons; The SW Taiwan study has 200 thousand person-years for 15 thousand persons. The number of male person-years (PYM) in the US 133 county white male bladder county study is the same as that for the entire country of Taiwan, five times greater than that of the southwest region, and nearly 700 times that of the low exposure villages.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>PYM</th>
<th>PYF</th>
<th>PYT</th>
<th>Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Taiwan</td>
<td>72,291,321</td>
<td>64,556,415</td>
<td>136,847,736</td>
<td>9,774,838</td>
</tr>
<tr>
<td>SW Taiwan</td>
<td>14,689,807</td>
<td>12,862,278</td>
<td>27,552,085</td>
<td>1,968,006</td>
</tr>
<tr>
<td>42 villages</td>
<td>253,000</td>
<td>233,959</td>
<td>486,959</td>
<td>34,783</td>
</tr>
<tr>
<td>24 High Dose Villages</td>
<td>129,431</td>
<td>121,132</td>
<td>250,563</td>
<td>17,897</td>
</tr>
<tr>
<td>18 Low Dose Villages</td>
<td>123,569</td>
<td>112,827</td>
<td>236,396</td>
<td>16,885</td>
</tr>
<tr>
<td>15 Low Exposure Villages</td>
<td>108,179</td>
<td>98,823</td>
<td>207,002</td>
<td>14,786</td>
</tr>
<tr>
<td>US Counties</td>
<td>74,945,550</td>
<td>-</td>
<td>74,945,550</td>
<td>2,498,185</td>
</tr>
</tbody>
</table>

Additionally,

3. Numerous in cases – The US study has twice as many male bladder cancers as does the All Taiwan group and nearly 350 times as many as do the low-exposure villages.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Blad-M</th>
<th>Blad-F</th>
<th>Lung-M</th>
<th>Lung-F</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Taiwan</td>
<td>2,246</td>
<td>2,619</td>
<td>18,390</td>
<td>7,791</td>
</tr>
<tr>
<td>SW Taiwan</td>
<td>657</td>
<td>393</td>
<td>3159</td>
<td>1462</td>
</tr>
<tr>
<td>42 villages</td>
<td>85</td>
<td>90</td>
<td>144</td>
<td>122</td>
</tr>
<tr>
<td>24 High Dose Villages</td>
<td>62</td>
<td>63</td>
<td>103</td>
<td>81</td>
</tr>
<tr>
<td>18 Low Dose Villages</td>
<td>23</td>
<td>27</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>15 Low Exposure Villages</td>
<td>14</td>
<td>20</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>US Counties</td>
<td>4,537</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Numerous in exposure data – The US study has data on 6,392 water sources with an average of 48 sources per county (median 18) and minimum of five. The 15 low exposure villages in the Taiwan study have 18 wells with an average of 1.2 wells per village.

Not-cited Strengths -

This study was analyzed as a US replicate of the Southwest Taiwan study. It had the comparative advantage that it was a study of US population and did not need to be adjusted for differences in US and Taiwan populations.

It provided for a direct measurement of cancer risk to the US population from arsenic exposure levels that the US population experienced. It required no specific estimate of bodyweight for the exposed population. It required no specific assumption on the water consumption rates in the US.
population or of the non-drinking water arsenic exposure, other than that they were similar across the study population.

Unlike in rural Taiwan, the US has had a nationwide distribution of food and the proportion of the diet that comes from locally grown vegetables is small. Unlike in Taiwan, rice is a small part of the US diet and few in the United States consume locally grown rice [possible exception of wild rice in Minnesota].

The particular published data were on white males and bladder cancer mortality. Similar analyses have also been done on white female bladder cancer, white male lung cancer mortality, and white female lung cancer mortality. They are available but have not yet been published. These advantages, or strengths, of the US 133 county study are not described in the Toxicological Review.

Not-cited Weaknesses –

The Wu et al. (1989) study is noted to have similarity in lifestyle, access to medical care, and socioeconomic status among the study villages, though these characteristics are notably different for the reference population. Information on these factors is not known for the counties in the US study.

Summary:

Among ecological studies, the US 133 county study has multiple strengths that are not found in the Taiwan study. The strengths in the Taiwan study that are not in the US study are limited. The weaknesses of the two studies are similar.

We would point out that the US 133 county study demonstrated that the NRC’s 2001 risk estimate fell above the upper 95% confidence limit for white male bladder cancer lifetime mortality but that the EPA’s 2001 slope did not. Since the EPA’s 2010 slope is considerable greater than its 2001 slope, it should be assessed to see whether it fits within or above the upper 95% confidence limit of the US data.

We are not advocating that the risk assessment be based on the US study instead of the Taiwan study. We are urging that they be similarly assessed for their dose-response relationships. We recommended in 2005 that the arsenic risk assessment be based on the prospective studies, and we still do. The prospective studies have now been published with longer follow-up periods than for the studies available in 2005.
Response to EPA 2010 Comments on US Study
Response to SAB (2007) Comments on US Study (Lamm et al., 2004)

The Science Advisory Board, in its “Advisory on EPA’s Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic: A Report of the US EPA Science Advisory Board” to Stephen L. Johnson, Administrator US EPA, dated June 28, 2007 (Page 44), raised issues regarding the utility of the US 133 county study (Lamm et al., 2004). We wish to address those issues.

The SAB has suggested that the low exposure (median < 100 ug/L) studies such as Lamm et al. (2004) are problematic because of (1) lack of statistical power and (2) unstable risks with high degree of uncertainty and (3) underrepresentation of effect of higher exposures.

Lack of Statistical Power or Sensitivity – The SAB had recommended that “the other relevant epidemiologic databases from studies of arsenic-exposed populations be used to compare to the unit risks at high exposure that emerge from the Taiwan data. Michael Kruse’s 2005 award-winning paper in HERA (Lamm and Kruse, 2005) did that. His figure 6 below demonstrates that the predicted risk based on either the high dose villages or all 42 villages is outside of (above) the 95% confidence interval of the US slope estimate for male bladder cancer mortality.

Figure 6

The US County study (Lamm et al., 2004) analyses included both SMR and SMR strata analyses, and lifetime bladder cancer mortality rate analyses with their slopes based on medians (3-60 ug/L) and means (3-255 ug/L). The 95% upper confidence limits of the slopes would be the upper bound of a unit risk that would still be consistent with the data. They reported that “the NRC’s lifetime mortality estimate falls above the upper 95% confidence limits indicated for WM bladder cancer lifetime mortality (4.2 X 10^{-5} for regression on median arsenic concentration; 8.5 x 10^{-6} for weighted regression on mean concentration).” (Pages 301-302).

The EPA (2010) unit risk for male bladder of 3.2 x 10^{-4} based on median arsenic concentration [page 131] would be significantly greater than the 95% upper bound of the US data (4.2 X 10^{-4}). Thus, the US 133 county study has sufficient power to assess the calculated unit risks.


**Instability and high degree of uncertainty at low doses** –

The low dose range (< 100-150 ug/L) is the exposure range of concern. Therefore those data are most relevant. The SW Taiwan dataset has 15 data points from the low exposure villages (median < 150 ug/L; Maximum < 500 ug/L). While these data show considerable variability, there are probably non-arsenic explanations that should be sought. Figure 2 below shows that the data which appear aberrant are all from Township 3 (Hsieh-chia), one of the original Blackfoot-disease endemic townships. An investigation should be conducted to find what is historically different about Hsieh-chia. They may have had deep (artesian) wells that were closed off before the well water arsenic survey was conducted?

**Figure 2**

![Graph showing SMR for Bladder and Lung Cancer by Village Maximum Well Arsenic Level (ug/L) and Township](image)

Similarly, exploratory investigation could be undertaken on the US 133 county dataset. Figure 1 above demonstrated the range of SMRs for different exposure levels as expressed by the median. The data expressed as the means has also been published, and the data as expressed by the 75th %ile, the 90%ile, or the maximum can also be developed. Risk variability is not great above 10 ug/L.

The uncertainty in the slope estimate has been explored and has shown little variation. All slope estimates are indistinguishable from zero. The slope estimate based on the median arsenic levels (3-59 ug/L) are (beta) = -0.004, 95% CI = -0.01 to +0.01 with an estimated y-intercept (alpha) of 0.97, 95% CI = 0.88-1.05]. The results are similar for median arsenic levels (3-30 ug/L), for mean (2.8-255 ug/L), 98 counties with 10 or more cases, and population-weighted. Results have been expressed as continuous exposure and with exposure strata, as SMRs and as lifetime mortalities. Thus, the uncertainty in the slope estimate is not great.
Underrepresentation of effect of higher exposures -

The issue has been raised as to whether the US 133 county study findings were biased by not accounting for the possibility that a reasonable proportion of the population may have had greater exposures than were accounted for by either the county groundwater median or mean arsenic level. We have had the opportunity to assess this question regarding the lung cancer mortality for these counties. Figure 3 gives the distribution of the female lung cancer SMRs by the county groundwater arsenic median (3-59 ug/L) in which none of the risk has been attributed to the high exposure and Figure 3 gives the distribution of the female lung cancer SMRs by the maximum level, thus attributing all of the risk to the highest arsenic level. Our data set also gives exposure metrics of 10th, 50th, 75th, and 90th percentile as well the maximum, and those distributions are available.

Figure 3

![Female Lung Cancer SMRs by County Arsenic Median](image_url)

Figure 4

![Female Lung Cancer SMRs by County Arsenic Maximum](image_url)
Response to SAB (2007) Comments on US Study (Lamm et al., 2004)

The slope for the medians is slightly negative, and the slope for the maxima is slightly positive. In either case, the slope is indistinguishable from zero. Arsenic measures provide essentially no explanatory power (0.3% and 0.5%). Alpha is 0.89 and std dev is 0.22. While this exercise does not deal specifically with the heterogeneity of exposure that may exist within the county populations, it has examined the extremes of the assumptions – i.e., that none of the residents have had the highest exposure or that all of the residents have had the highest exposure.

A second method for dealing with potential exposures to high arsenic levels is to truncate the exposure range. We have separately examined the SMR distribution for the counties whose maximum is less than 150 ug/L, as seen in Figure 5. The variability does not differ much across the range.

Figure 5

Again the slope is positive, low, and indistinguishable from zero. The explanatory power is 0.5%. Alpha 0.88, std dev 0.17. The US data have been analyzed in a parallel methodology as that of the Southwest Taiwan study, which also has the similar issue of not knowing the specific exposure levels of the residents in the study area. Case/control studies of bladder and lung cancers, particularly bladder cancers, with arsenic exposure as a risk factor have been conducted and published both from Taiwan and the United States. Some of these questions are more appropriately asked of those studies.

We have tried to be responsive to the issues raised in SAB (2007) considering the utility of the low exposure studies, particularly with respect to the Southwest Taiwan study. The ecological, cohort, and case-control studies of cancers with exposures to low levels of arsenic are relevant to the assessment of risk from low exposures to arsenic. They can serve as a basis for estimating the best or most likely fit (slope, unit value) from low level exposure as well as the upper bound estimate of that slope. The high dose data can yield a generic “worst case” or upper bound estimate, but the relevance of that to the risk from low level exposure has to be considered. For arsenic, there is a large literature on the relationship of low levels of arsenic exposure to cancer incidence or mortality. The set of studies are informative for the question of concern to the community – What is our risk from the levels of arsenic that we are being exposed to? There is considerable human data available to characterize the shape of the dose-response curve below a given departure point of < 150 or < 200 ug/L.