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March 29, 2010

Dear Dr. Elaine Faustman
Chairman, Arsenic Work Group
Science Advisory Board/US EPA
Washington, DC 20001

Re: Arsenic-related cancer risk for low-dose villages
in the Southwest Taiwan study (Wu et al., 1989)

I wish to draw the work group's attention to section F.4. CALCULATION OF ARSENIC-RELATED CANCER RISKS FOR LOW-EXPOSURE VILLAGES in Appendix F of the Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS) released by the EPA on February 19, 2010. This is the closing section of the Tox Review but should be the opening section for the assessment of the Tox Review.

As I understand it, the purpose of this Tox Review is to estimate the arsenic-related cancer risk to the US population from low-dose arsenic in the drinking water using the data from the southwest Taiwan cancer study (Wu et al., 1898) with a focus on low-dose exposures. EPA states that the "way to test the significance of exposure-response relationships at low doses is to simply restrict the [SW Taiwan] analysis to the villages with low arsenic water concentrations (using) the appropriate Poisson regression methodology." We agree.

EPA has presented an analysis [Table F-2] and reports that "when appropriate models are used the (southwest) Taiwanese data show robust and significant positive associations between arsenic exposures and cancer risks for all the endpoints analyzed, even in low-exposure groups." We disagree with this statement with regard to the low-exposure groups and have demonstrated this in our June 8, 2009 and November 12, 2009 letters to EPA [See attached].

We have three primary criticisms of the EPA analysis:

1. The Poisson regression model for the low-dose villages is overwhelmed by the reference population.

Data set is comprised of 18 villages with an average population of 938 residents per village (the range of and a reference population that is treated as an additional village with a population of two million residents – an unbalanced analysis.

EPA should present the cancer risk analysis for the "low-dose" villages in Table F-2 both with and without the reference population as they have done for the 42-village study in Table F-1.

2. Exposure misclassification contributes markedly to the risk assessment for the "low-dose" villages as they include villages with high-dose exposures.

The “low-dose” villages have in common that their median village well arsenic level is less than 150 ug/L. However, these are not all “low-exposure” villages as some have well arsenic levels that are greater than 500 ug/L.

EPA should present the cancer risk analysis for the “low-exposure” villages defined as either that the mean village well arsenic level is less than 150 ug/L or that the maximum village well arsenic level is less than 150 ug/L.

3. The reference population is assigned an exposure of zero ug/L arsenic, which is contrary to available data and to technology.

The Southwest Taiwan region, like the study area, lies atop the Chianan plain [Lewis et al., 2007] and likely have the same drinking water sources. Chen et al. (1962) reported that the median arsenic level in non-endemic area shallow wells was 25 ug/L and non-endemic artesian wells was 380 ug/L. Chiang et al. (1988) reported that 45-54 % of wells in non-endemic area had arsenic content greater than 50 ug/L and 0-6% greater than 350 ug/L. A variety of analytic methods for arsenic assays was used in the 1960’s and 1970’s with limits of detection of 10-50 ug/L. The basis for choosing zero ug/L is unknown and unvalidated.

Finally, the main effect of dose and the meaning of the derived coefficient are unclear, other than that age is a significant mortality factor.

Our primary recommendation is that the assessment of the “exposure-response relationships at low doses” from the southwest Taiwan study (Wu et al., 1989) be based on the data for the residents of the villages that only have low-dose wells (i.e., all well arsenic levels at < 150 ug/L, or at least their mean well arsenic level at < 150 ug/L). This assessment should be compared with that of other low-dose studies, such as the 133 county US study (Lamm et al., 2004) and the bladder cancer case/control studies.

Cordially, and respectfully,

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Impact of Reference Population

The Poisson regression model for the low-dose villages is overwhelmed by the reference population.

EPA, in Table F-2 of Appendix F of the Toxicological Review of Inorganic Arsenic (February 2010), has presented arsenic dose coefficients for study populations with median well water arsenic concentrations less than 150 ug/L. The analysis performed is a Poisson regression model using data on the age-gender specific person-year distribution and cancer mortality distribution for the 18 study villages (median village well arsenic < 150 ug/L) and including the similar data for the Southwest Taiwan region as a 19th "village." The major explanatory variable is the daily arsenic dosage (mg/kg-day) using the median village well arsenic level in ug/L for each of the 18 study villages and zero ug/L for the regional data plus a set of exposure assumptions. These assumptions are that the water consumption rate is 3.5 L/day for males and 2 L/day for females, that the non-water arsenic exposure is 10 ug/day, and that the average body weight is 50 kilograms for both males and females. Thus, the exposure variable has the units of mg/kg-day.

Using these data and assumptions, we have been able to replicate EPA's findings, generating essentially the same arsenic "b" coefficients.

Table 1

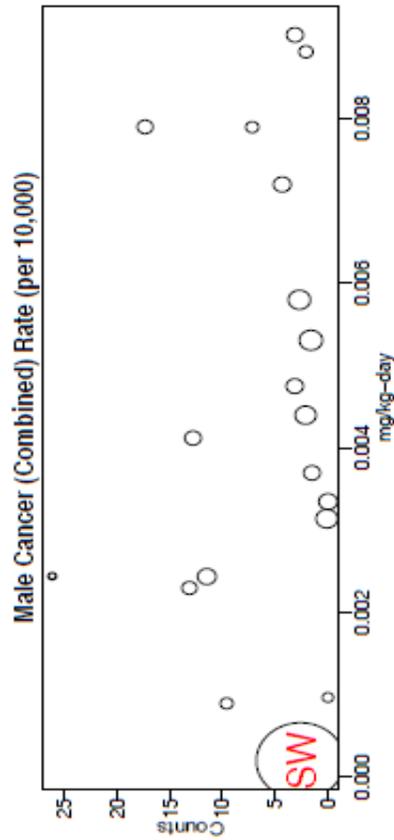
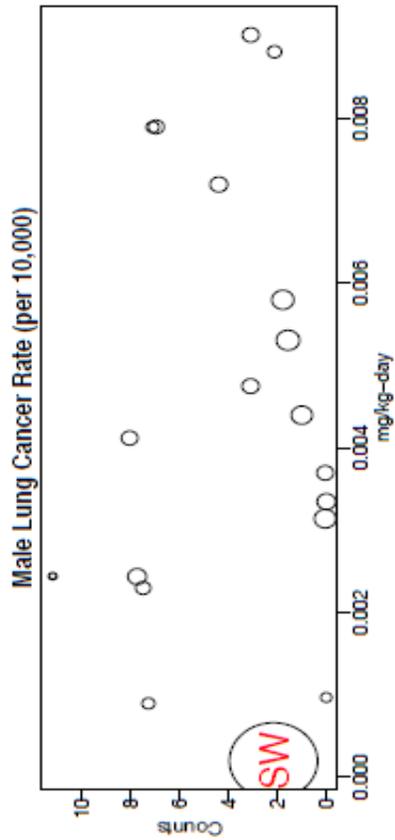
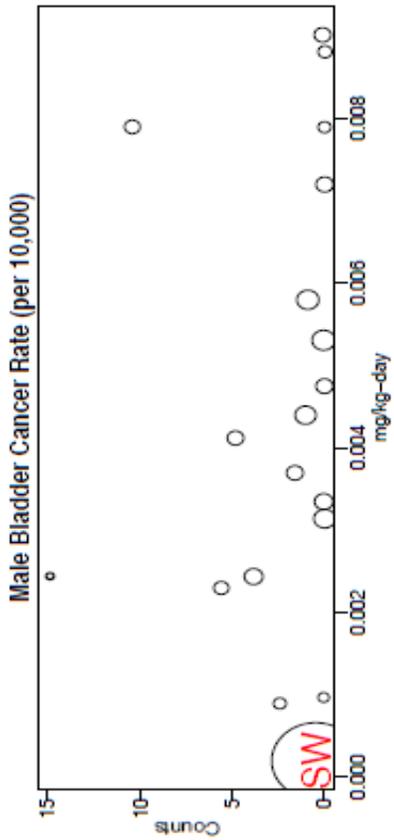
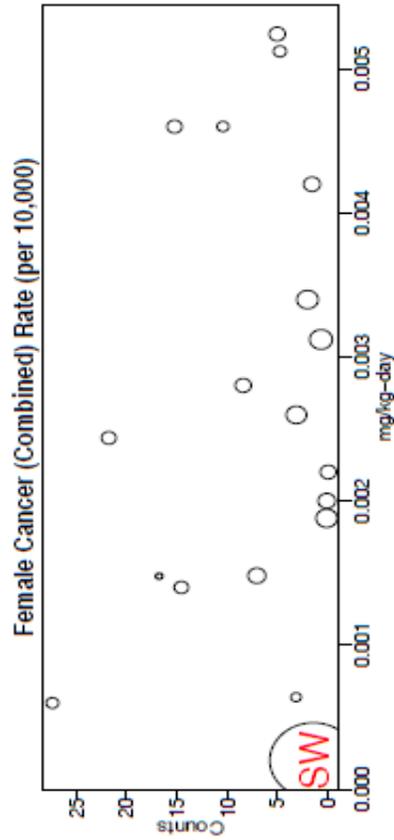
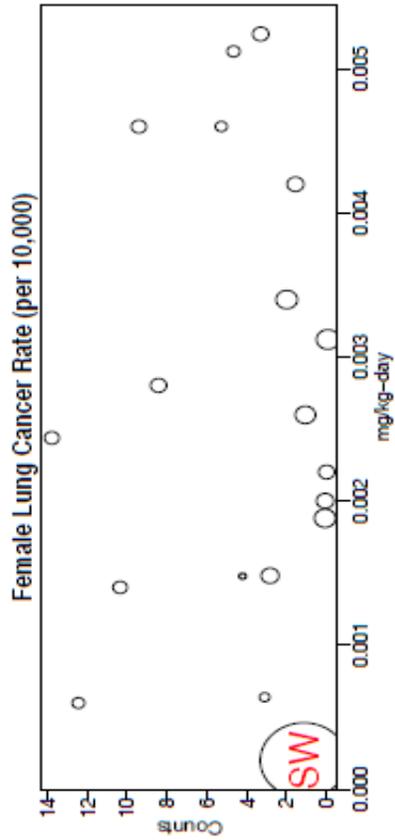
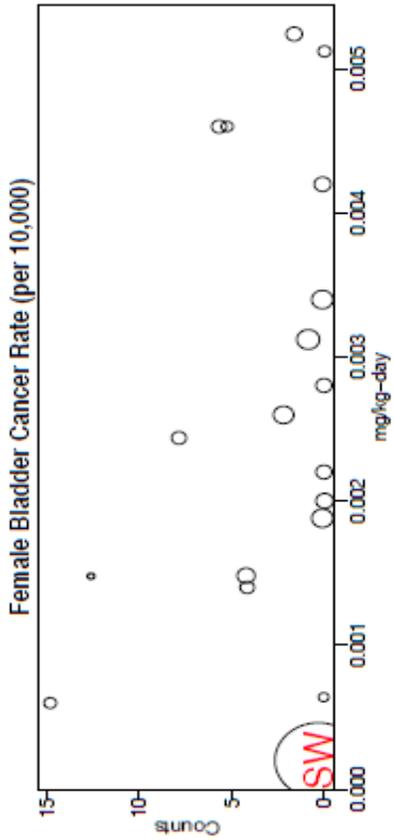
<u>Arsenic "b" coefficients for Study Villages with Median Well Arsenic < 150 ug/L and SW Taiwan</u>		
<u>Cancer</u>	<u>EPA Table F-2 (95% LCL, UCL)</u>	<u>Current Replication</u>
Male Lung	85.7 (13.1, 172.1)	86
Male Bladder	586 (335, 877)	576
Male Combined	160 (83.4, 247)	160
Female Lung	615 (412, 836)	615
Female Bladder	2639 (2021, 3307)	2639
Female Combined	924 (721, 1139)	924

EPA reports that these are "**robust and significant positive associations between arsenic exposures and cancer risks...in low-exposure groups.**" (Page 575)

While we have been able to replicate their results, we disagree with their interpretation. We find that these results are the consequence of the Southwest Taiwan population being used as an enormous village. They do not reflect the differences that exist in drinking water arsenic levels among the low-dose study villages.

We begin our demonstration with Figure 1 (below). Here we present scatter diagrams of the village data with the size of the circle representing the weight that each village contributes to the analysis, weighted to the log (Person-Years). The data for the southwest Taiwan region is handled as if it were an additional village (SW). Visually, we would like you to observe that the distributions appear to show positive slopes and that the major weight is contributed by the SW data. Further, we would like you to block out the SW data and observe that the remaining data no longer appear to show positive slopes.

Impact of Reference Population



Impact of Reference Population

Table 2 (below) demonstrates analytically that the significant positive exposure-responses reported by EPA in Table F-2 are directly dependent upon the data from the Southwest Taiwan population. The same analysis, restricted to the data from the low-dose study villages, produces arsenic “b” coefficients that are negative, not positive.

Table 2

<u>Arsenic "b" coefficients for Study Villages with Median Well Arsenic < 150 ug/L with and without SW Taiwan</u>		
<u>Cancer</u>	<u>With SW Taiwan</u>	<u>Without SW Taiwan</u>
Male Lung	86	-11
Male Bladder	576	-61
Male Combined	160	-32
Female Lung	615	-46
Female Bladder	2639	-139
Female Combined	924	-94

The above demonstrates that the “significant positive associations between arsenic exposures and cancer risks...in low-exposure groups” is not robust but is markedly dependent on the use of, and assumptions applied to, the reference population.

EPA, in their Table F-1 for the 42 study villages, has shown their analytic results with the reference population (Southwest Taiwan) both included and excluded. EPA, in their Table F-2 for the 18 low-dose villages, has only shown their analytic results with the reference population included. We have now extended that analysis in similar fashion to show the analytic results with the reference population excluded.

It is not surprising that the reference population is the only influential data point in the analysis. The reference population is 2 million persons strong [27,552,085 person-years/14 years = 1,968,006 persons] and is set at an exposure of zero ug/L. The study population is comprised of 18 villages with an average population of less than 1,000 persons [490,929 person-years/(14 years x 18 villages) = 938 persons per village] and exposures in the range of 10-126 ug/L.

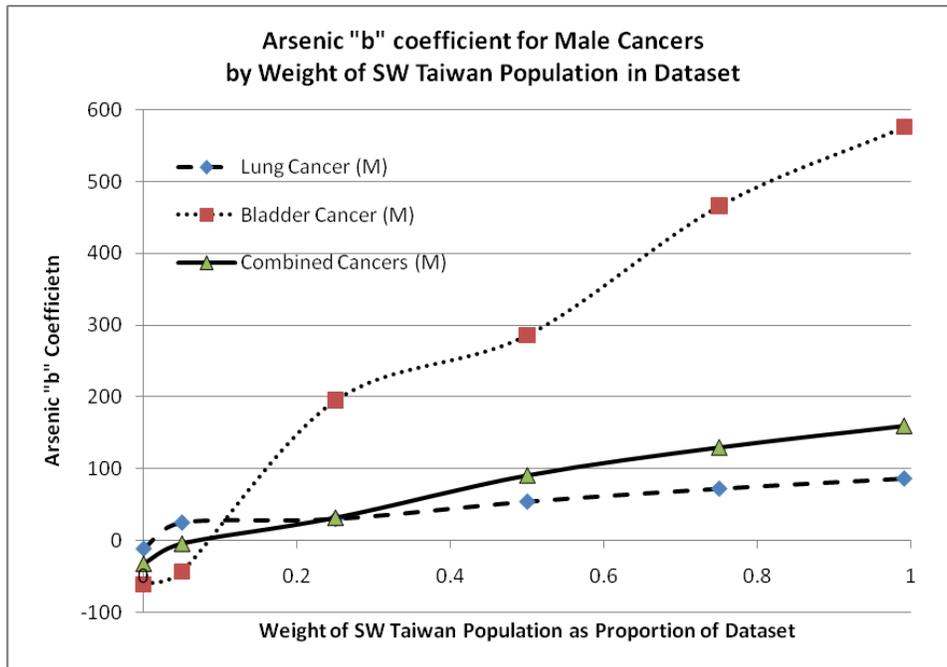
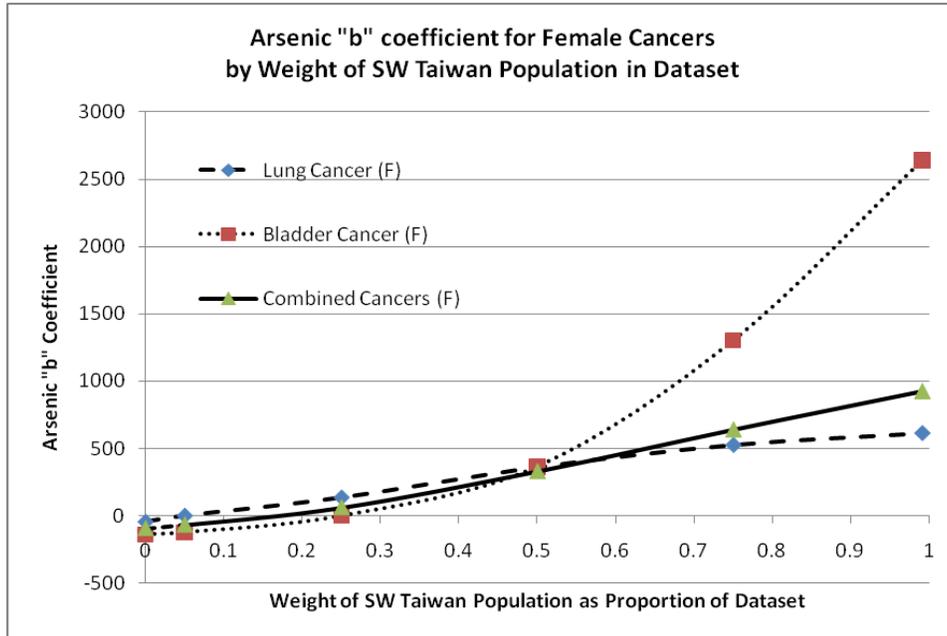
The analysis, in essence, tests whether the cancer rate is higher among the study villages with reported arsenic exposure from the drinking water than it is in the reference population which is defined as having no arsenic exposure from the drinking water. This becomes a test for a difference between these two populations rather than a test of an exposure-related difference within the set of low-dose study villages.

We have presented similar analyses at the Society for Toxicology meeting recently [March 8, 2010] using the median well arsenic level [ug/L] as the exposure metric rather than incorporating a set of assumptions to convert to a mg/kg-day metric. A copy of that poster with its results is attached. No exposure-outcome association was found to be positive. All exposure-outcome associations were found to be negative, and some significantly so.

Significant higher cancer rates were found in the study area, independent of the arsenic exposure, a finding that has been consistently made in the literature and remains unexplained.

Impact of Reference Population

Having now demonstrated the dependence of the direction and significance of the arsenic “b” coefficient on the inclusion or exclusion of the reference population, we demonstrate graphically in Figures 2 and 3 (below) the different arsenic “b” coefficients calculated as the weight of reference population to the total population is ranged from 0.0 to 1.0.



Returning to the issue of the effect of the hyperinfluence of the reference population on the determination of the arsenic “b” coefficient, we have developed a demonstrative model:

Impact of Reference Population

Demonstrative Model

For any age-dose group, the cancer count follows a Poisson distribution. The Poisson parameter is the products of PYR (person-years of observation) and the Risk. Since the Risk is age-dose-specific, EPA used the notation $h(x, t)$, where x denotes the dose and t denotes the age. To simplify the discussion, we will call it Risk(age, dose).

Equation E-1 defines the form of $h(x, t)$. Equivalently, it can be written in linear form:

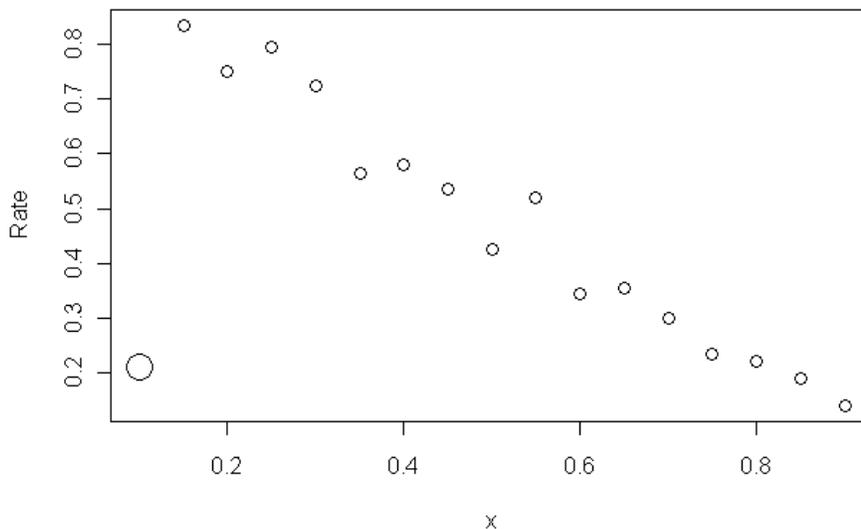
$$\log_e(\text{Risk}(\text{age}, \text{dose})) = a_1 + a_2 \times \text{age} + a_3 \times \text{age}^2 + \log_e(1 + b \times \text{dose}).$$

This linear form is commonly seen in Poisson Regression or Generalized Linear Models. Presumably, EPA used the term $\log_e(1 + b \times \text{dose})$ to account for the case where dose = zero.

The model is set, and MLEs (Maximum Likelihood Estimates) are used to find a way to estimate the 4 parameters of interest: a_1 , a_2 , a_3 , and b . As there is no "closed form" for the MLE, "numerical" approaches are used. Such numerical approaches are available in most statistical software and may differ slightly. "R" is the statistical software used below.

To further illustrate the influence of a single observation with large sample size, we present the following simplified example, where we only consider the dose-response relation. We generate Poisson counts from 17 hypothetical villages. Sixteen villages have 200 PYR each and their cancer rates follow the relationship $\log(\text{Risk}) = b_0 + b_1 * \log(\text{dose})$. The other village has a much larger population (5000) and its risk is arbitrarily to a low value.

This demonstrates the great effect a single large data point can have on the analytic result.



Impact of Reference Population

Without outlier

```
> summary(glm(y2~log(x)+offset(log(n2))), family=poisson(link="log"),
+ data=d1, subset=x>0.1))
```

Call:

```
glm(formula = y2 ~ log(x) + offset(log(n2)), family = poisson(link = "log"),
    data = d1, subset = x > 0.1)
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-5.5245	-1.4098	0.3633	1.5409	3.1257

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.42309	0.05114	-27.82	<2e-16 ***
log(x)	-0.82008	0.04399	-18.64	<2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 423.038 on 15 degrees of freedom
Residual deviance: 87.728 on 14 degrees of freedom
AIC: 192.13

Number of Fisher Scoring iterations: 4

With outlier with large PYR

```
> summary(glm(y2~log(x)+offset(log(n2))), family=poisson(link="log"),
data=d1))
```

Call:

```
glm(formula = y2 ~ log(x) + offset(log(n2)), family = poisson(link = "log"),
    data = d1)
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-9.640	-4.210	2.654	6.339	12.965

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.72414	0.03914	-18.50	<2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for poisson family taken to be 1)

Null deviance: 954.39 on 16 degrees of freedom
Residual deviance: 819.18 on 15 degrees of freedom
AIC: 932.33

Number of Fisher Scoring iterations: 5

Impact of Reference Population

In the model above, the Poisson regression analysis shows a strong negative association when performed without the large outlier [$\log(x) = -0.82$; $p < 2e-16$] and a strong positive association when performed with the large outlier [$\log(x) = +0.27$; $p < 2e-16$].

We hold this model to be analogous to the situation presented in the EPA low-dose analysis. The results in EPA's Table F-2 reflect the effect of the assumptions and use of the reference population rather than the exposure differences among the study villages.

Exposure Misclassification of Low-Dose Villages

Introduction:

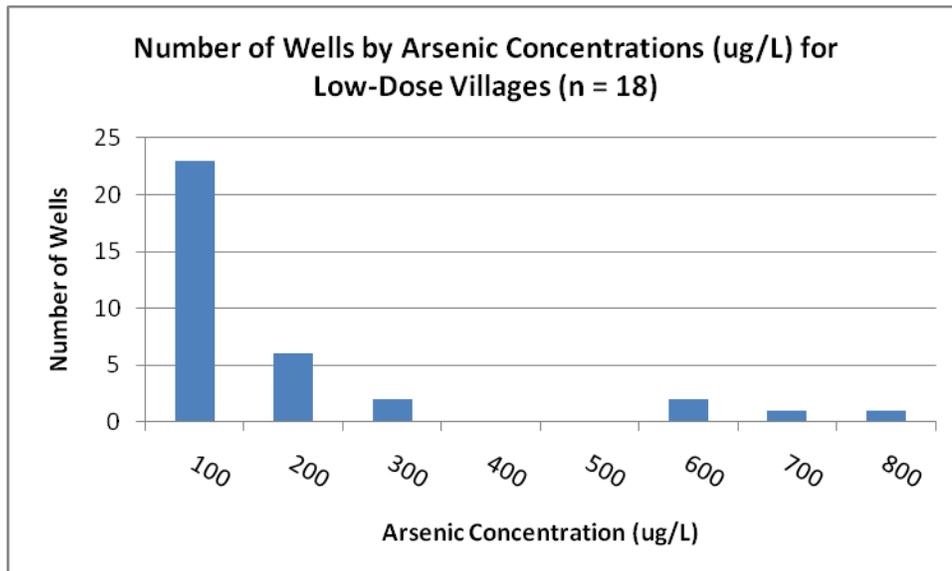
The slope factor for arsenic and cancer mortality from the SW Taiwan study as presented in Appendix F is based on the data for the SW Taiwan region and for the 42-study villages [Table F-1]. This slope factor is dominated both by the high dose village data (Median 256-934 ug/L) and the SW Taiwan regional data (assumed to be zero ug/L). The pattern of exposure and cancer distribution in the “low dose” villages has little effect on the slope factor.

There is no disagreement that high-exposure arsenic (in the 100s of ug/L; > 500 ug/L) is carcinogenic to humans with regard to skin cancer, bladder cancer and lung cancer. In order to examine the carcinogenicity of arsenic at lower exposure levels (< 150 ug/L), EPA presents Table F-2 as an analysis of the carcinogenic risk from low-dose exposures (< 150 ug/L) that do not have the influence of high arsenic exposures. This is an analysis of the cancer risks for the 18 low-dose villages from the Wu et al. (1989) study. We contend that the EPA “low-dose” village analysis is not free of the influence of high arsenic exposures and demonstrate that below.

Exposure Information:

The “low-dose” village group is comprised of the 18 villages with median well arsenic level < 150 ug/L. The data are presented in Table A10-1 in the NAS (1999) monograph on Arsenic in Drinking Water and are seen in the figures and table below. This measure of central tendency does not capture the information on the dispersion of the values. Figure 1 shows the distribution of the arsenic levels for the 35 measured wells in the 18 villages.

Figure 1

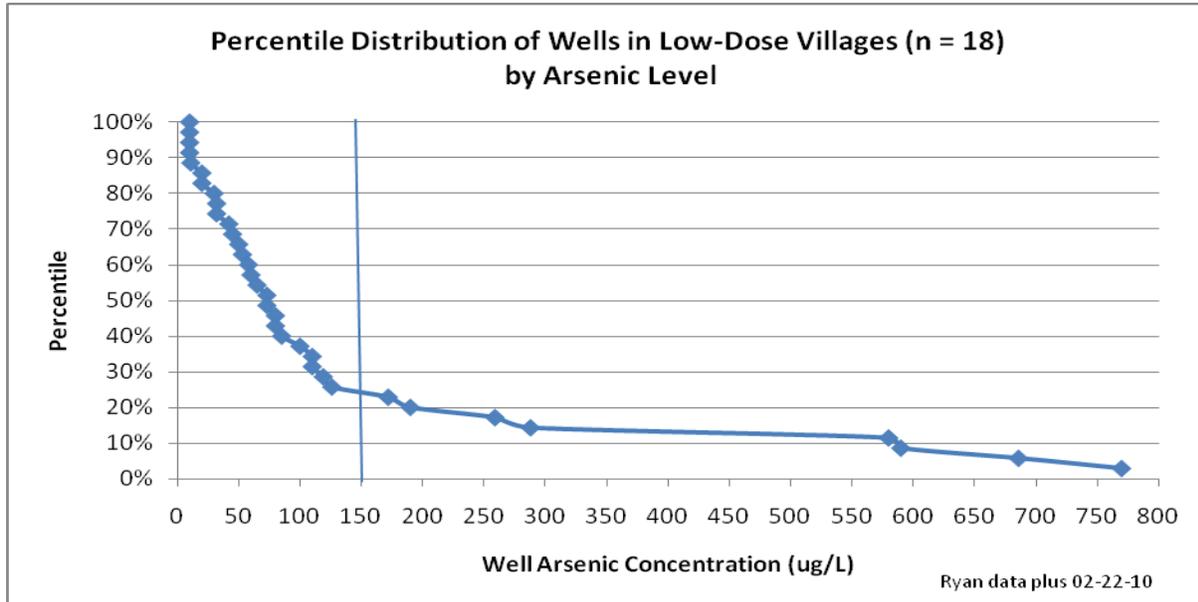


Clearly some of the wells have arsenic measurements that are quite different from those of the other wells.

Exposure Misclassification of Low-Dose Villages

Figure 2 presents a cumulative distribution of the well measurements. It is seen about one-quarter of the wells (8/35 = 23%) have levels greater than 150 ug/L and would not be considered to be low-exposure wells.

Figure 2



While the distribution of the well measurements appear to be distributed log normally, their locations do not appear to be random. Table 1 below presents the well arsenic data for the 18 villages as reported in Table A10-1 of the NAS (1999) report.

The villages are identified by an initial numeral that identifies its township and then a letter which identifies which village within that township. Twelve of the villages have measurements for only one well, three have measurements for two wells, and three have measurements for 5-7 wells. Two of the villages have paired values that are in the low-exposure range.

The villages are ordered by their highest (maximum) well arsenic level, which ranges from 10 to 770 ug/L. The last three have levels exceeding 500 ug/L. These would not meet any definition of low exposures. One could argue the classification of village 4-N which has one well at 172 ug/L.

The published papers contain no information on which wells were used for drinking water with in any village. There are no individual use data. When this area was originally investigated for the epidemiological understanding of Blackfoot Disease (BFD), all the cases were found to either be from villages that only had high arsenic (artesian) wells or to have been a user of the high arsenic (artesian) wells in the villages that had mixed exposures or sources (Ref).

Table 1 below shows the distribution of well arsenic levels by individual villages. The villages at the top of the table tend to come from Township #3 and the villages at the bottom of the table tend to come from Townships #0 or #4. The well arsenic levels greater than 150 ug/L have been italicized. The well arsenic levels greater than 500 ug/L have been bolded.

Exposure Misclassification of Low-Dose Villages

Table 1

<u>Well Arsenic Levels [ug/L] for "Low-Dose" Villages [Median < 150 ug/L]</u>								
<u>Village ID</u>	<u>Well 1</u>	<u>Well 2</u>	<u>Well 3</u>	<u>Well 4</u>	<u>Well 5</u>	<u>Well 6</u>	<u>Well 7</u>	<u>Max</u>
3-H	10							10
2-I	11							11
3-5	32							32
3-N	32							32
4-7	42							42
6-A	45							45
3-L	53	58						58
4-D	60							60
3-P	65							65
6-C	73							73
4-8	80							80
0-J	20	80						80
0-O	100							100
4-J	126							126
4-N	73	172						172
0-I	20	50	110	110	190	580	590	590
0-E	10	85	119	288	686			686
0-G	10	10	30	259	770			770

Thus, 3 of the 18 "low-dose" villages (17%) [0-I, 0-E, and 0-G] have well arsenic levels above 500 ug/L. These should not be considered to be low-exposure villages.

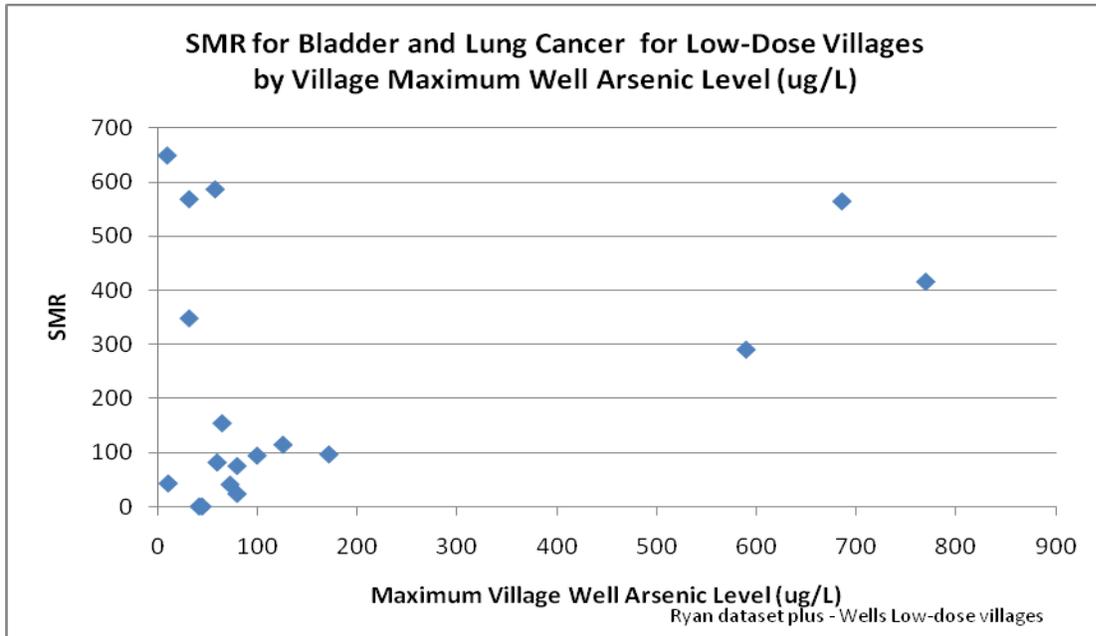
Cancer Risk Information:

The dataset contains age-sex and site specific cancer information for each village as well as the age-sex person-year distributions. The same information is found for the SW Taiwan region. Based on these data, the standardized mortality ratios (SMRs) for each village compared to the SW Taiwan region can be calculated. Figure 3 shows the village-specific Bladder and Lung Cancer SMRs (male and female combined) for the "low-dose" villages distributed by the maximum well arsenic level for each village.

Three clusters of data are seen – (1) high exposure-high risk; (2) low exposure-high risk, and (3) low exposure-low risk. It appears that some factor other than arsenic level alone is necessary to explain the distribution of cancer risk.

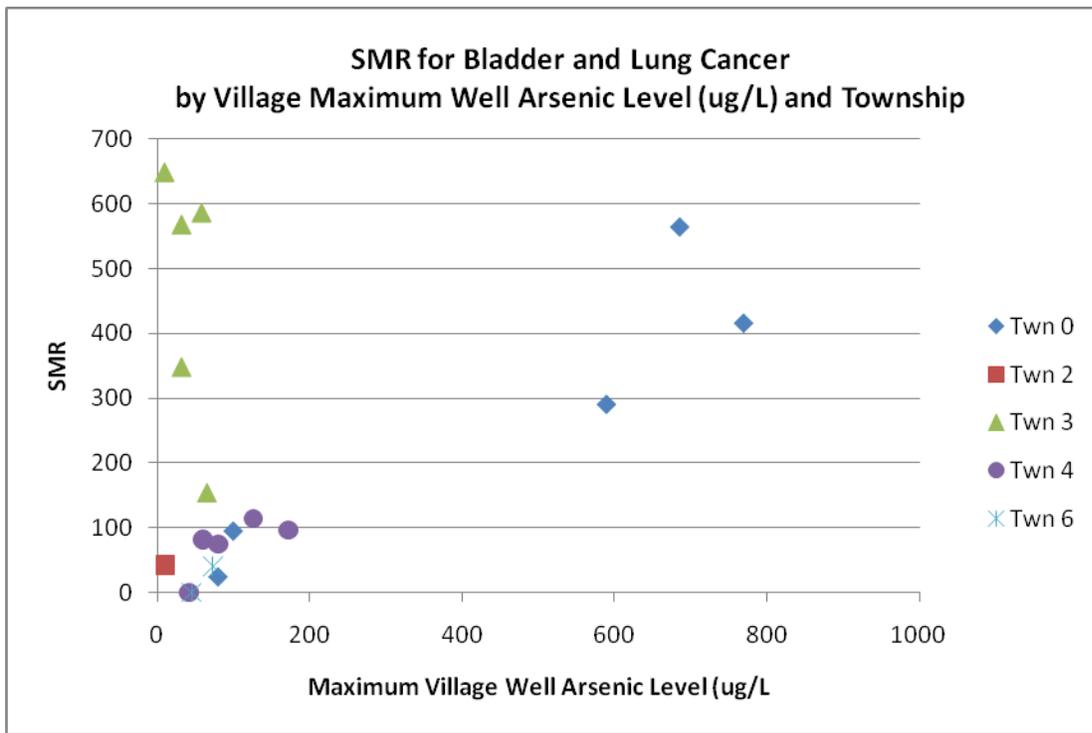
Figure 3

Exposure Misclassification of Low-Dose Villages



We previously have proposed in our analyses of the cancer risks among the 42 villages that “township” reflected some unknown geographical variable. We examine now the township issue among the “low dose” villages.

Figure 4



Exposure Misclassification of Low-Dose Villages

Figure 4 shows the same results as Figure 3, but identifies each village by its township. It appears that the high exposure-high risk villages are in Township 0, while the low exposure-high risk villages are in Township 3. Many of the low exposure-low risk villages are in Township 4. We do not know why.

Effect of Exposure Misclassification:

The “low-dose” villages (n = 18) includes both those villages that only have low-exposure wells (i.e., low = < 150 ug/L) and the villages with both low and very high exposure wells (i.e., > 500 ug/L). We will call this later group “Mixed”. We have calculated the site and sex specific crude mortality rates for these exposure groups and the SW Taiwan population for comparison.

The crude mortality rates (CMR) are a reasonable measure of risk as the age distributions of the study villages and the SW Taiwan population are similar (Figures 5 and 6). The CMRs are presented as they are easily replicated from the NAS (1999) Table A10-1 dataset.

Figure 5

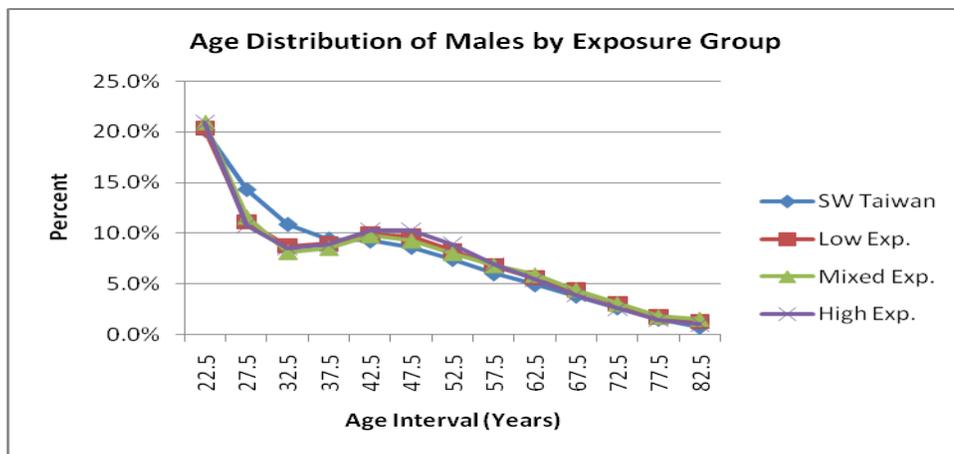
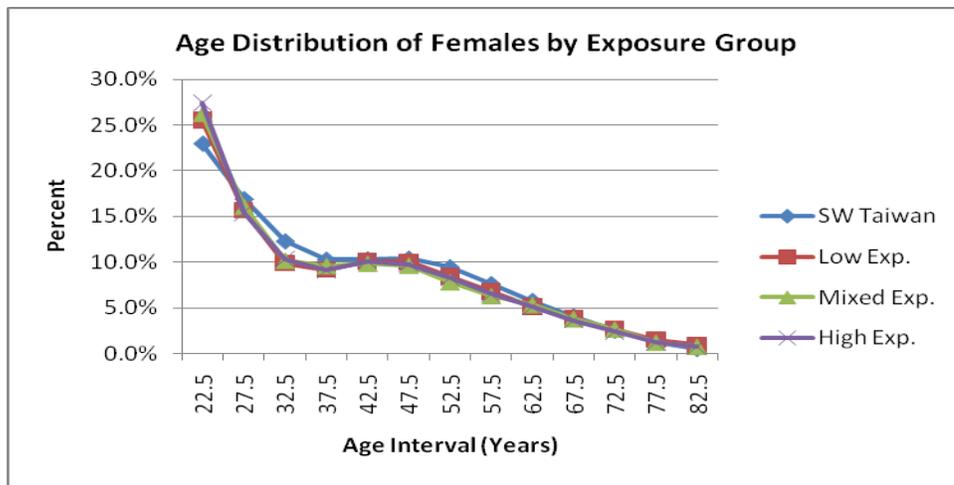


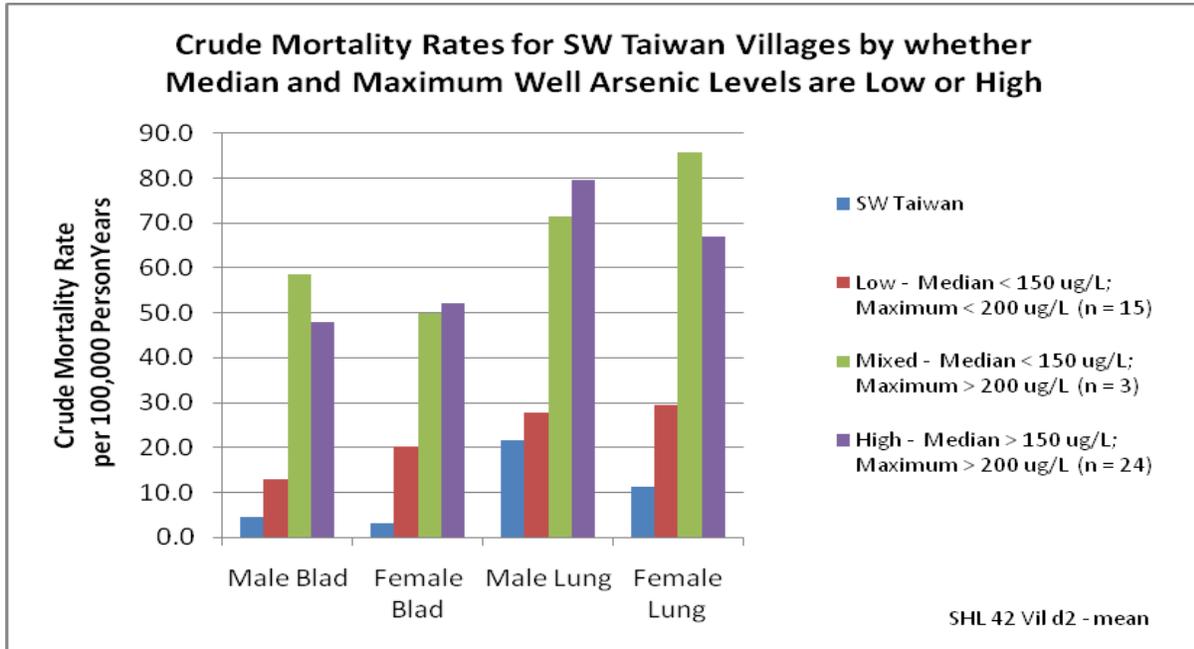
Figure 6



Exposure Misclassification of Low-Dose Villages

In Figure 7 below, we compare the site and sex specific crude mortality rates for the SW Taiwan region, the “Low Exposure” villages, the “Mixed Exposure” villages, and the “High Exposure” villages.

Figure 7



The 15 villages in the Low group all have median < 150 ug/L, mean < 150 ug/L, and (with the exception of village 4-N) maximum arsenic level < 150 ug/L. Although the three villages of the Mixed group have a median < 150 ug/L, their mean arsenic levels are > 150 ug/L and their maximum arsenic levels are > 500 ug/L. The 24 villages in the High group have median > 150 ug/L, mean > 250 ug/L and maxima of 256 ug/L to 1,752 ug/L. Over 60 % of the High exposure villages (15/24 = 63%) have well arsenic levels greater than 500 ug/L, and 80% (19/24 = 79%) have well arsenic levels greater than 400 ug/L. The exposures in the Mixed exposure villages are similar to those in the High exposure villages.

Additionally, it is seen Figure 7 above and Figure 8 below that the cancer risk in the “Mixed Exposure” villages approximates the risk in the “High Exposure” villages rather than that in the “Low Exposure” villages. The risks in the “Low Exposure” villages should be separately assessed to avoid the exposure misclassification from including the “Mixed Exposure” villages.

An analysis similar to that of the crude mortality rates can be performed using the standardized mortality rates (SMR) for the exposure groups. The age-sex specific data from the Ryan or Schulman data sets are incorporated. The Southwest Taiwan population data have been used as the reference population.

Exposure Misclassification of Low-Dose Villages

Figure 8

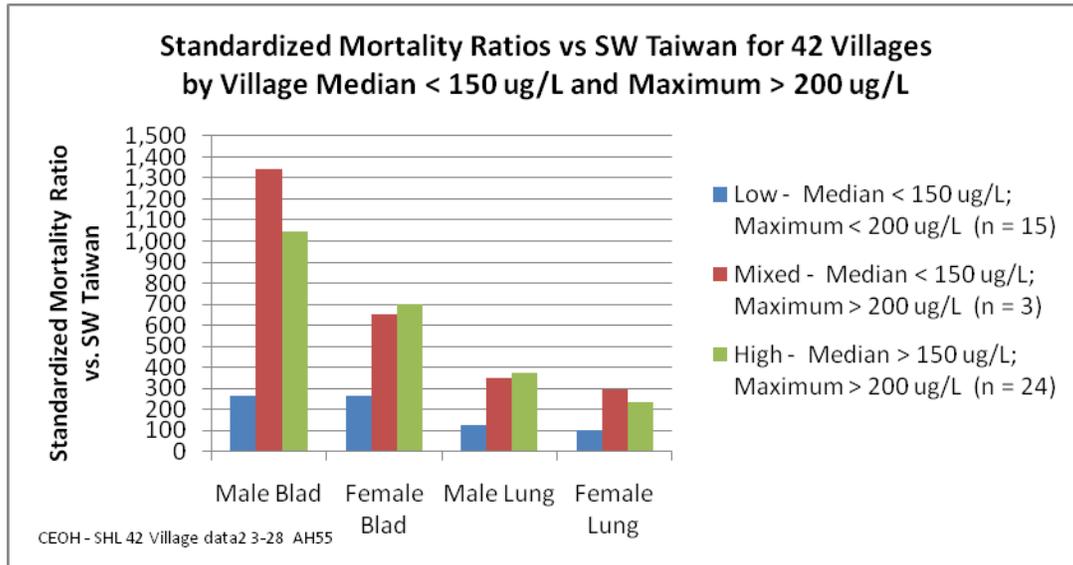


Figure 8 has important findings:

1. The sex-site specific cancer mortality pattern for the Mixed exposure villages [i.e., “Low-dose” villages well arsenic levels greater than 500 ug/L] is quite similar to that of the High exposure villages, and quite different from that of the Low exposure villages.
2. The lung cancer mortality risk for both males and females in the “Low Exposure” villages is not greater than the risks in the Southwest Taiwan comparison area.
3. The bladder cancer mortality risks for both males and females in the “Low Exposure” villages are greater than the the risks in the Southwest Taiwan comparison area.

Figures 9 (below) examines the relationship between the bladder cancer mortality risk in the “Low Exposure” villages and its relationship to the well arsenic levels.

Maximum well arsenic level does not appear to be the primary predictor of bladder cancer mortality among the “Low-Exposure” villages in Southwest Taiwan. Similar analyses for the low-exposure villages with village medians or village means show similar results. The village well arsenic levels do not appear to be the primary predictor of bladder cancer mortality among the Low-exposure villages in the Southwest Taiwan study.

Exposure Misclassification of Low-Dose Villages

Figure 9

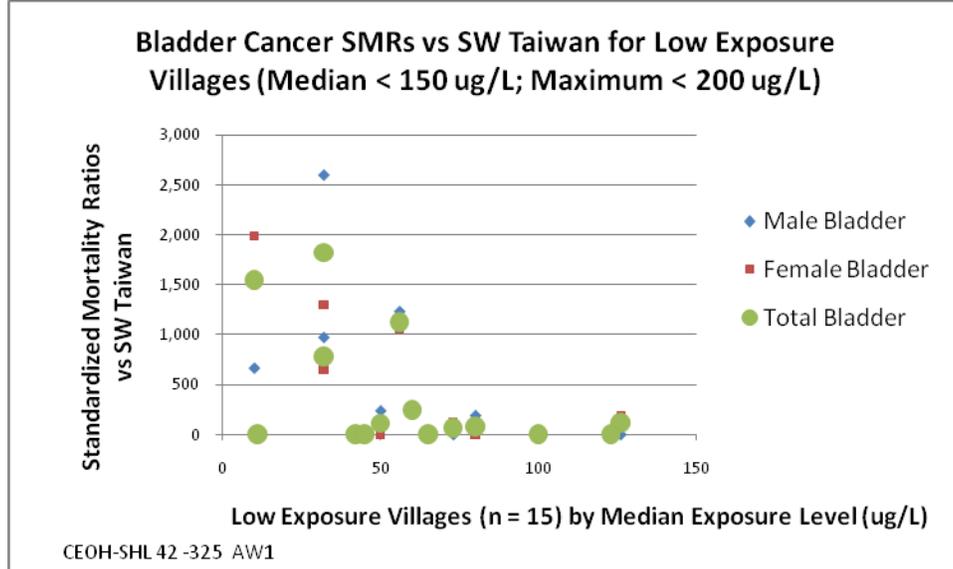
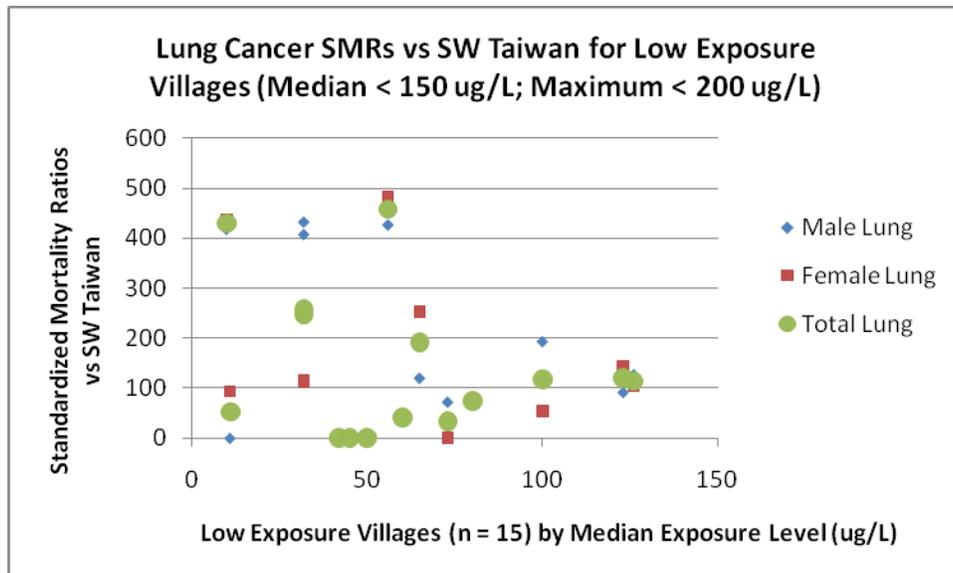


Figure 10 presents similar analysis for lung cancer, finding no association between lung cancer mortality and village well arsenic level for the Low exposure villages in the Southwest Taiwan study.

Figure 10



The above analyses show that well arsenic level is not a primary predictor of either bladder cancer or lung cancer among the residents of the low exposure villages in the Southwest Taiwan internal cancer study (Wu et al., 1989). This is a study population of nearly 15,000 residents of rural Taiwan with 14 years of observation, for a total of about 200,000 person-years of observation with a population-weighted median arsenic exposure of 63 ug/L. The slopes appear to be negative. Linear regression analysis shows $R^2 = 0.23$ for the bladder cancers and 0.06 for the lung cancers, both negatively.

Exposure Misclassification of Low-Dose Villages

Summary:

The above analyses show that the arsenic-associated cancer risks presented for the “Low Dose” villages in Southwest Taiwan in the Toxicological Review on Inorganic Arsenic (February 2010) in Table F-2 reflect the consequences of including villages with high exposures (> 500 ug/L) in addition to the overinfluential use of the Southwest Taiwan population. The cancer mortality risks in the “Low-Dose” villages reflect the risks of the villages that have very high (> 500 ug/L) levels of arsenic in their drinking water rather than the risks of the “Low-Exposure” villages. Previous cancer mortality risk analyses for the “Low-Dose” villages have been severely biased by exposure misclassification.

Analysis of the “Low Exposure” village data find no positive association with arsenic exposure and bladder or lung cancer mortality. These analyses do not stand alone in the literature. The attached Brown (2007) and Lamm et al. (2010) show similar findings with different approaches.

Negative or Neutral Arsenic Slope for Bladder Cancer and Lung Cancer Mortality among Low-Dose Villages (Median well water arsenic level < 150 µg/L) in the Blackfoot Disease Area of Southwest Taiwan

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Introduction

Previous analysis of internal cancer mortality in the Blackfoot Disease (BFD) endemic area of SW Taiwan (Wu et al., 1989) has demonstrated significant associations at high (> 350-400 µg/L) well water arsenic levels, with a wide range of predictions at low arsenic levels (Morales et al., 2000). We present Poisson regression analyses for the low-dose villages (median < 150 µg/L) with and without a reference population.

Materials & Methods

- Analysis of 42 study villages with bladder and lung cancer deaths and person-year distributions by age and sex and well water arsenic levels, generally for one to four wells.
- Exposures are summarized as median, mean, or maximum well water arsenic level with low-dose < 150 µg/L.
 - 3 villages with a maximum well arsenic of 590-770 µg/L
 - 15 villages with mean well arsenic < 150 µg/L and range of 10-172 µg/L
 - 14 villages with max well arsenic < 150 µg/L and range of 10-126 µg/L
- Age-adjusted Poisson regression to examine dose-response relationships for bladder and lung cancer deaths in the 18 low-dose (median < 150 µg/L) villages.
- Analyses of 18 low-dose villages with and without SW Taiwan data as a reference point and with and without an area term.

Results & Conclusions

- Cancer rates in the BFD area are significantly greater than those of the southwest Taiwan region.
- B-coefficients are negative in the analysis of the low-dose village data (Tables 1 -Female and Table 2 - Male).
- Using the SW Taiwan data as a reference data point does not change the results, unless the area term is omitted from the model.
- The b-coefficients were significantly negative for bladder cancers and combined cancers in females when low dose was defined as village median < 150 µg/L and also for males when low-dose was defined as village mean < 150 µg/L.
- When the SW Taiwan data was used as a reference point without an area term in the model, the b-coefficients were significantly positive. Age was always a significant predictor

Figure 1: Arsenic Summary Statistics for 42 study villages in SW Taiwan

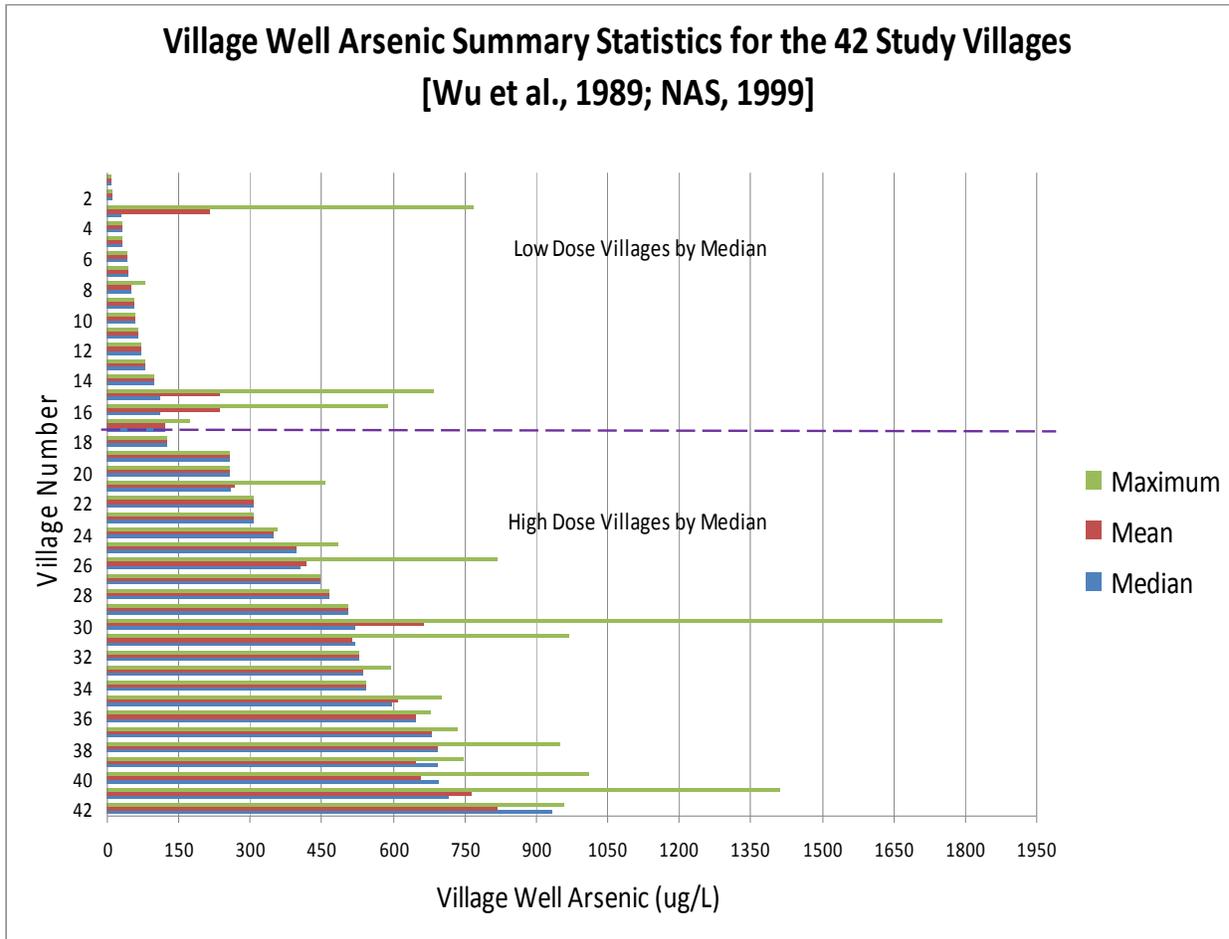


Figure 2: Crude Mortality Rates, for Bladder and Lung Cancers, stratified by gender for SW Taiwan and Low-dose Villages

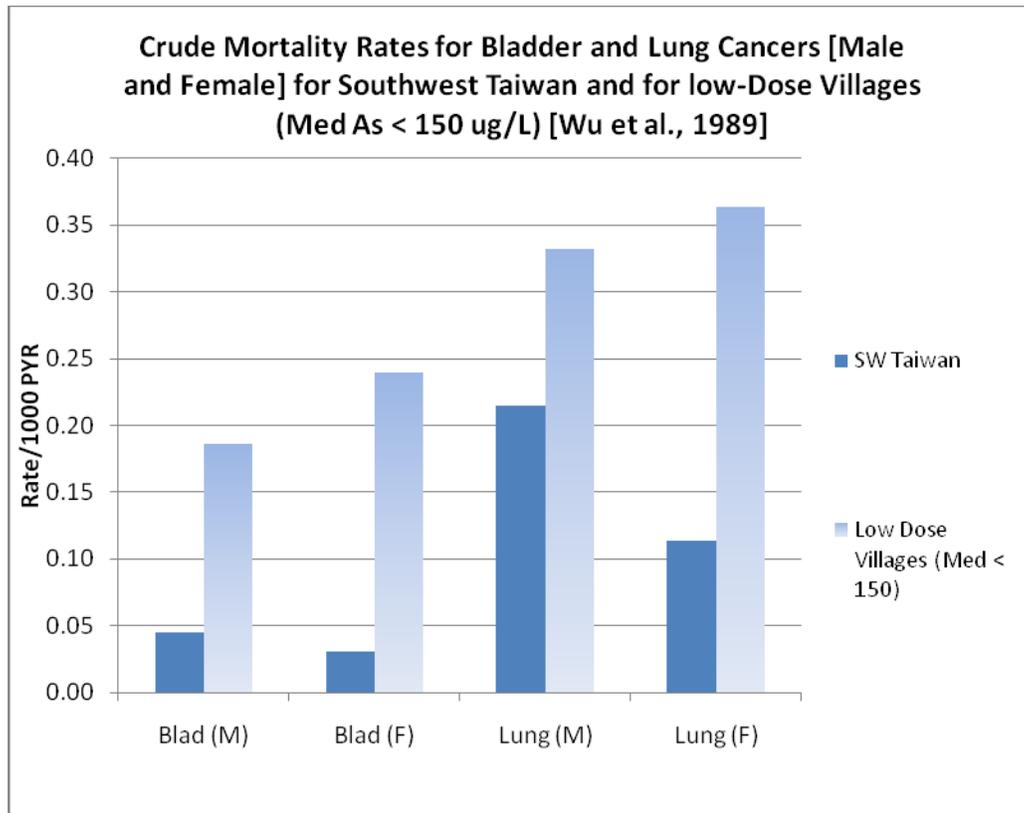


Table 1: Poisson Regression Analyses MLE (Age and Age2 adjusted) (Sex =Female; Exposure = Median < 150 µg/L)

Poisson Regression Analyses MLE (Age and Age2 adjusted)					
(Sex = Female; Exposure = Median < µg/L)					
Low dose (n = 18) Villages					
<u>Female</u>	<u>"b"</u>	<u>95% CL</u>	<u>p</u>		
Bladder	-0.016	(-0.029--0.003)	0.02		
Lung	-0.003	(-0.0123-0.007)	0.55		
Combined	-0.008	(-0.015--0.000)	0.05		
Low dose (n = 18) Villages, SW Taiwan, and Area Term					
<u>Female</u>	<u>"b"</u>	<u>95% CL</u>	<u>p</u>	<u>Area</u>	<u>p</u>
Bladder	-0.016	(-0.029- -0.003)	0.02	2.840	<.0001
Lung	-0.003	(-0.013- 0.007)	0.53	1.230	0.0004
Combined	-0.008	(-0.016--0.0001)	0.05	1.790	<.0001
Low dose (n = 18) Villages with SW Taiwan					
<u>Female</u>	<u>"b"</u>	<u>95% CL</u>	<u>p</u>		
Bladder	0.018	(0.012-0.023)	< .0001		
Lung	0.011	(0.007-0.015)	< .0001		
Combined	0.013	(0.010-0.016)	< .0001		

Table 2: Poisson Regression Analyses MLE (Age and Age2 adjusted) (Sex = Male; Exposure = Median < 150 µg/L)

Poisson Regression Analyses MLE (Age and Age2 adjusted)					
(Sex = Male; Exposure = Median < µg/L)					
Low dose (n = 18) Villages					
<u>Male</u>	<u>"b"</u>	<u>95% CL</u>	<u>p</u>		
Bladder	-0.008	(-0.022-0.006)	0.24		
Lung	-0.001	(-0.011-0.009)	0.86		
Combined	-0.004	(-0.012-0.005)	0.39		
Low dose (n = 18) Villages, SW Taiwan, and Area Term					
<u>Male</u>	<u>"b"</u>	<u>95% CL</u>	<u>p</u>	<u>Area</u>	<u>p</u>
Bladder	-0.008	(-0.022- 0.006)	0.24	1.870	<.0001
Lung	-0.001	(-0.011-0.009)	0.81	0.490	0.170
Combined	-0.004	(-0.012- 0.004)	0.38	0.890	0.002
Low dose (n = 18) Villages with SW Taiwan					
<u>Male</u>	<u>"b"</u>	<u>95% CL</u>	<u>p</u>		
Bladder	0.015	(0.008-0.020)	< .0001		
Lung	0.005	(0.002-0.009)	0.02		
Combined	0.007	(0.004-0.011)	< .0001		

Dose Response Relationship for Bladder and Lung Cancer Mortality in Low-Dose Villages (< 150 ug/L) in the Blackfoot Disease Endemic Area of Southwest Taiwan – Implications in Risk Analysis

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1 INTRODUCTION

Numerous analyses of internal cancer deaths in the Southwest Taiwan Blackfoot Disease endemic area have demonstrated the carcinogenic effect of arsenic in drinking water in high concentrations (>~ 300-500 ug/L) [e.g., Morales et al., 2000; Lamm et al., 2003, 2005], some with a threshold-like effect at about 150 ug/L [Lamm et al., 2006, 2007]. The variation in exposure data has hindered the analysis at low levels. We have attempted that.

2 MATERIALS AND METHODS

Publically available data on the 42 villages from the Wu et al. (1989) study contain cancer death counts and person-years by age, gender, and well arsenic levels (ug/L). Age-adjusted Poisson regression analysis was conducted for the 15 villages with mean well arsenic level < 150 ug/L for lung cancer, bladder cancer and bladder and lung cancer combined. Analyses were conducted for males, females, and males and females combined.

3 RESULTS

Age was a significant variable in all models. “b” coefficient was negative in all models and statistically significant in all models containing bladder cancer deaths.

Expanding the definition of low-dose village to median well arsenic level < 150 ug/L expands the study group by three villages, each having one or more wells with arsenic levels greater than 500 ug/L. It is not evident that these additional three villages should be considered as low-dose villages. Age-adjusted Poisson regressions on arsenic for all villages with median arsenic < 150 ug/L yields negative “b” coefficients in all models with statistical significance in all models containing female bladder cancer deaths. Geographical demonstration is also informative.

4 CONCLUSION:

The dose-response slopes for the low-dose villages in the SW Taiwan study are negative for lung and bladder cancer deaths and significantly so for bladder cancer deaths.

Gender	Cancer	"b"	95% Conf Int.	p-value
Male	Lung	-0.0055	(-0.0174, 0.0064)	0.3644
Female	Lung	-0.0058	(-0.0174, 0.0057)	0.3230
Combined	Lung	-0.0057	(-0.0141, 0.0028)	0.1875
Male	Bladder	-0.0327	(-0.0552, -0.0102)	0.0044
Female	Bladder	-0.0330	(-0.0512, -0.0147)	0.0004
Combined	Bladder	-0.0346	(-0.0491, -0.0200)	<.0001
Male	Combined	-0.0126	(-0.0233, -0.0020)	0.0202
Female	Combined	-0.0151	(-0.0251, -0.0052)	0.0027
Combined	Combined	-0.0141	(-0.0214, -0.0069)	0.0001

Figure 1. Age-Adjusted Poisson Regression "b" for Arsenic for the 15 Villages with Mean Arsenic < 150 ug/L

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