To: Angela Nugent, PhD, DFO (by e-mail: nugent.angela@epa.gov)
Chair, Science Advisory Board
US Environmental Protection Agency [US EPA]
Washington, DC 20460

From: Steven H. Lamm, MD, DTPH and associates
Consultants in Epidemiology and Occupational Health, LLC. [CEOH]
Washington, DC 20016

Date: November 15, 2010

Re: Comments in Response to Arsenic Workgroup report of October 25, 2010

Thank you for the opportunity to address problems that we see in the carcinogenic risk assessment for inorganic arsenic as presented by EPA in the Toxicological Review on Inorganic Arsenic (February 2010) and in the Science Advisory Board's Arsenic Workgroup report of October 25, 2010.

We have reviewed the above documents and wish to submit our comments as part of an on-going dialogue on the assessment of cancer risk from the ingestion of inorganic arsenic.

We have been involved in the assessment of the cancer risk from exposure to inorganic arsenic for over thirty years, in examining workers, in conducting primary analyses and in developing rigorous secondary analyses of epidemiological studies. Our primary focus has been to identify the range of exposures under which arsenic exposure is carcinogenic to humans, including identifying confounders of those risks. We have flagged that arsenic appeared to be the carcinogenic agent in areas where others have not recognized it, and we have flagged that arsenic does not appear to be carcinogenic at exposures that others have asserted it. We have published our analyses and assisted governmental agencies in their inquiries regarding inhaled arsenic and lung cancer and on ingested arsenic and skin, bladder, and lung cancer.

In that spirit, we continue as public citizens and scientists to submit our analyses to agencies and journals in hopes that public policy will be based on an open and rational analysis of the relevant and reliable data. That has been the purpose of our submissions over the years, and particularly over the last two years regarding the current assessment.

Unfortunately, although the workgroup report states the SAB report incorporates the "public comments, both written and oral, which were received throughout the advisory process (page 4)," we just don't see it. Nonetheless, we continue to ask that a broader exploration of the data regarding the study of internal cancers in the Blackfoot-disease endemic area of Southwest Taiwan be conducted than has been performed.

Toward that regard, we have expanded upon our previous submissions for the SAB's consideration and ask that it, our previous comments, and the other public comments, be similarly reviewed and addressed. In that spirit of open scientific deliberation, we have attached a copy of a primary data set in an excel file that will permit individual SAB members to review our analyses and to conduct their own. We welcome such a scientific dialogue.

The SAB workgroup has developed responses to the specific charges it received from the EPA and has limited itself to those charges. Unfortunately, it states that it was not charged with assessing the validity of the cancer risk assessment in EPA's Toxicological Review of Inorganic Arsenic (February 2010). While that might be its understanding, the public perception is and will be, that the SAB has given its stamp of approval to the cancer risk assessment, its methodology, its choice of data, and its conclusions. We find problems in each of these and urge that the SAB reviews these and other issues raised in the performance of the cancer risk assessment.

In our view, the EPA analysis has two major flaws – (1) it includes SW Taiwan as an additional (43rd) study village of enormous size (~98% of the weight) to which it assigns a zero arsenic water value and (2) it fails to recognize the inherent geographic heterogeneity in the risk, a heterogeneity that has been variably analyzed as township, aquifer source, and fluorescent intensity.

We recommend that these be addressed by the SAB – (1) that alternative analyses not so dependent upon the reference group be developed and examined and (2) that among the research recommendations be a request that field investigation of the sources of the geographic heterogeneity in the SW Taiwan study area be undertaken.

We begin our comments with a response to the workgroup's request for a reality check on the EPA cancer risk estimates, particularly as it relates to the US experience. Based on the EPA 2010 lifetime risk estimate at 10 ug/L for male bladder cancer incidence and adjusting for an 80% mortality rate, we calculate that the EPA analysis would yield a 6.4E-05 lifetime risk of bladder cancer mortality among US males with an increased exposure to 1 u/L arsenic in their drinking water. This is derived from the EPA Poisson-weighted analysis of the Southwest Taiwan data in Table 5-10. Analysis of the US data (Lamm et al., 2004) showed a slope of -3.5E-06 against the median with a 95% upper confidence limit of the slope to be 4.2E-05 on an unweighted analysis and 8.5E-06 on the population-weighted analysis. Thus, the EPA analysis yields a 7.5 (64/8.5 = 7.5) fold risk about the UCL of the slope and in the opposite direction of that of the slope itself. This is unlikely to be explainable by migration issues.

Regarding the analysis, the first inquiry should be to ask: What is the question? and What are the relevant and reliable data upon which to base an analysis? The determination has already been made for the primary analysis that it is to be based on the bladder and lung cancer mortality data from the Wu et al. (1989) SW Taiwan study using the SW Taiwan regional data as a reference population. The two questions that the Agency should be addressing are: What is the dose-response relationship between bladder and lung cancer mortality and low arsenic exposure levels (i.e., 10-200 ug/L) among the low-exposure villages in the SW Taiwan study, and How does this translate into an assessment of risk (cancer incidence) at such exposure levels for the US population.

The best way, as we see it, is to examine the data for the 15 villages in the study population that have a maximum or mean arsenic exposure of < 200 ug/L. With one exception at 172 ug/L, these 15 villages only have documented well arsenic levels at 126 ug/L or below. We propose the exposure metric to be the village mean well arsenic level, the outcome measure to be the standardized mortality ratio based on the SW Taiwan regional data, and the analytic method to be a population-weighted linear regression for the cancer mortalities by gender and site.

EPA has not chosen to either answer this question or to use these data and this methodology. EPA modeled a dose-response relationship for bladder and lung cancer incidence in the US after transforming the data from the SW Taiwan study, using data for the low-exposure villages, the high-exposure villages, and SW Taiwan region. Their Poisson analysis weighs according to case count and gives 98% of the weight to the SW Taiwan population that is assumed to have 0 ug/L (zero) in its drinking water. Their model uses the SW Taiwan data as if they represent an additional village in the study population rather than as a reference population.

We present below the distribution of the village SMRs for the low exposure villages. These are the data that should form the core of the analysis.

The EPA analysis is insensitive to the critical data, i.e., the mortality at low arsenic levels (as we demonstrate in an attachment below), and ignores well-documented evidence of uncertainty and of confounders.

1. The mean rather than the median is an adequate representative of the village-specific exposure data. The median is not an adequate representative of the mean village arsenic exposures and biases the analysis. The variance in exposure estimates that exists in the median does not, for the low-exposure villages, exist in the mean. Analysis of villages by mean arsenic levels gives a cleaner finding than analysis of villages by median arsenic levels.
2. Township is a predictor of cancer risk, as demonstrated in Lamm et al. (2006, 2007). For the 15 low-exposure villages, increased risk is only found among the villages in township 3 and not among the villages in the other four townships that have villages in the low-exposure group.
3. The EPA analysis attributes all the variability in cancer risks to be due solely to the drinking water arsenic levels and gives no consideration or mention to the presence of humic substances in the drinking water. Lu et al. (1986) [submitted to the EPA and study group in English translation] is the only study that examined for a dose-response relation between bladder cancer and fluorescence intensity (i.e., humic substance).

In summary, we find that the EPA cancer risk analysis for inorganic arsenic is deficient in being overly dependent on its use of the SW Taiwan population as an additional data point, on its insensitivity to the risk distribution among the low-exposure villages, and its ignorance of the geographic heterogeneity as seen with the identified confounders of township, median, water source, and non-arsenic water constituents.

We recommend that the SAB have these issues resolved in an open and responsive fashion before a cancer risk assessment of inorganic arsenic is finalized. The most important issue is the misuse of the SW Taiwan population as an additional data point rather than as a reference population and the overdependence of the risk assessment on this.

Choice of Analytic Model

The use of the Poisson model appears to cause additional problems that do not occur with the use of the SMR model. Each Poisson analysis includes only those villages that have cases relevant to the analysis. For instance, one-half of the low-dose villages (9/18 = 50%) have no male bladder death in the study. Thus, the data from these villages does not contribute to the analytic result. Similarly, 8 of the 18 low-dose villages (8/18 = 44%) have no female bladder cases. Because the Poisson linear regression weights cases and not villages, these villages disappear from the analysis. However, in the SMR linear regression which weights villages rather than cases, these villages do not disappear from the analysis. The SMR linear regression analysis can be performed either by giving equal weight to each village or by giving population-weights to each village. The Poison analysis is overwhelmed by the use of the SW Taiwan data as if they were from an additional village containing 97-99% of the analytic weight rather than as a reference population. The SMR analysis uses the SW Taiwan data as a reference population in which for each village the mortality observed is compared to that which would have occurred if the village had the same age-specific mortality rates as did the SW Taiwan population, i.e., where the SW Taiwan population is truly used as a reference population.

The Poisson regression model is fundamentally in error for this data set, but the SMR regression model is not. The underlying theory of the Poisson model is that a population is understudy, that all the cases within that study are the analytic units, and that each case appears in the analysis only once. This is not true for the SW Taiwan cancer study. The analytic unit in this study is the village and its population. The population of the SW Taiwan region is distributed among a large number of villages, although the number of villages has not been reported in any of the published studies. The initial internal cancer study in SW Taiwan was reported in CJ Chen et al. (1985). Their study area was the 84 villages in the four major Blackfoot-disease endemic townships (Peimen, Hsuechia, Putai, and Ichu) of SW Taiwan. That study found that "a dose-response relation between standardized mortality ratios of various cancers and the prevalence of Blackfoot Disease, a peripheral vascular disorder related to cumulative arsenic exposure, was observed among villages in a limited area along the southwest coast of Taiwan (Page 1184 of Wu et al. 1986). Subsequently, Wu et al. (1986) expanded that study in order to examine the dose-response relations for arsenic and various internal cancers and vascular diseases.

Wu et al. (1986) found that well water arsenic content data from the 1964-1966 survey (TL Kuo, 1968) existed for only 27 of the 84 villages (27/84 = 32%). In order to enlarge their study population, Wu et al. (1986) expanded their study area to include an additional 15 of the 36 villages from two neighboring Blackfoot Disease endemic townships of Yensui and Hsiaying - 12 of the 20 villages in Yensui and 3 of the 16 villages in Hsiaying. Thus the entry criteria for this study was that the village had to be in the Blackfoot Disease endemic area and have well-water arsenic data from the 1964-1966 survey in order for the village to be a study village. These entry criteria did not apply to the SW Taiwan population which was used as an additional village in the analysis. Nonetheless, it is clear that the entry unit for the study was the village and not the individual. The SMR analysis has the advantage that it is based on the village rather than on the cancer death.

The selection factors behind those data are not publicly known, e.g.: (1) which of the village had their wells tested 45 years ago, (2) which of their wells were tested, (3) how many specimens were tested per well, (4) whether the available data points represent a median, a mean, or a single value, and (5) what data were retained.

It is not unlikely that the villages whose wells were tested were primarily those villages that had reported cases of Blackfoot Disease, a biasing selection factor. Further, since the well testing was performed at a time period during which the general perception was that Blackfoot Disease was related to the deep artesian wells and that piped water was being brought to the villages, it may well be that deep artesian wells that had been used by the village and were sources of their exposure had been closed down prior to the performance of the well testing. Failure to include wells that had been historically used in the villages may be a major source of exposure misclassification bias.

While it is conceptually important though possibly not quantitatively significant, it should be noted that the cases in the "SW Taiwan village" includes all the cases in the 42 study villages plus the cases in the high risk villages without well arsenic data.

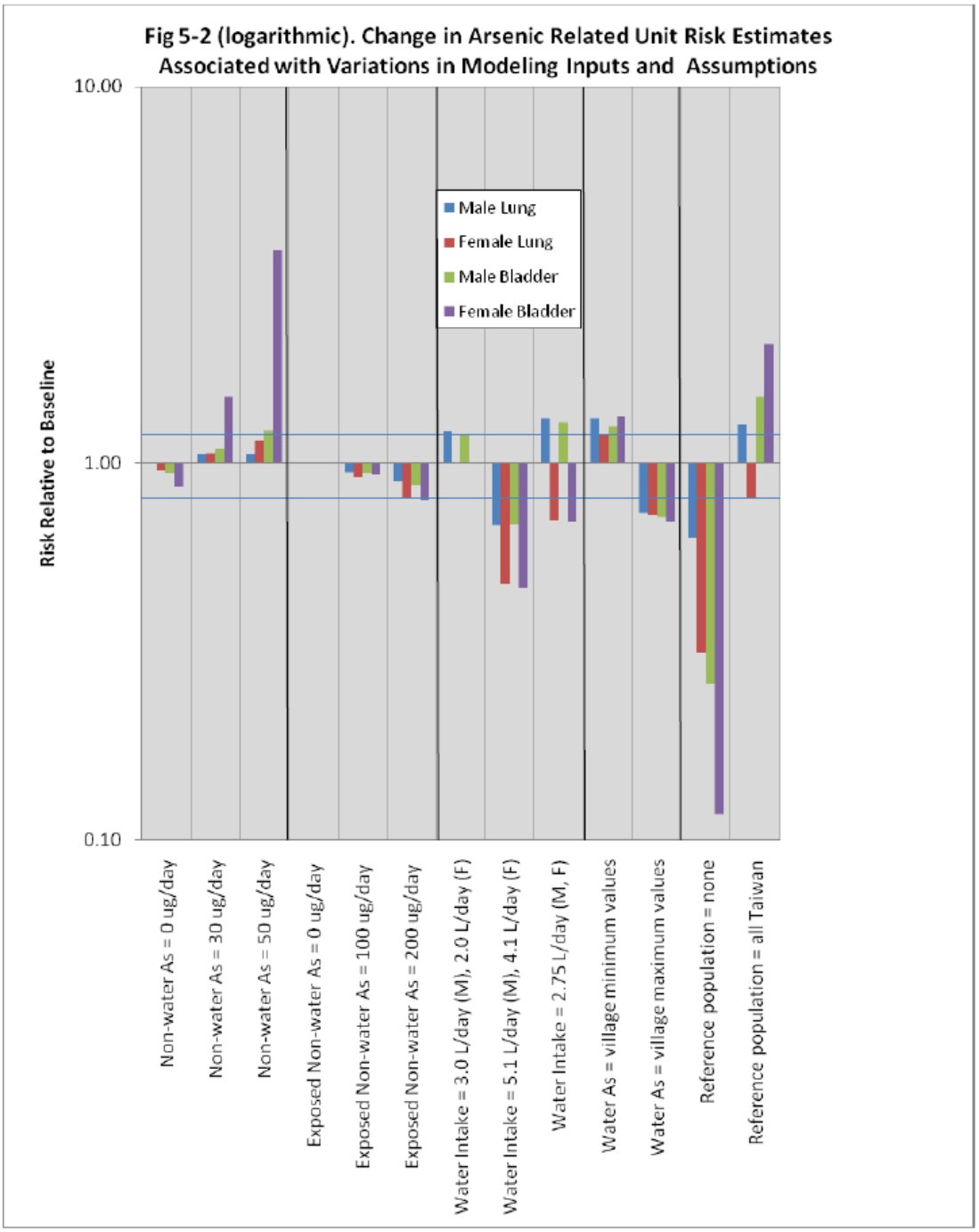
Sensitivity Analysis of Dose-Response Modeling

EPA has presented (Tables 5-10 and 5-11; Figure 5-2) a sensitivity analysis of their modeling which begins with the data for the 42 study villages and the SW Taiwan population compares the baseline values with those following changes in specific assumptions of either quantitative arsenic consumptions or categorical input variables. Table 5-10 presents the absolute risk values, table 5-11 presents the relative risk values, relative to the baseline assumptions, and Figure 5-2 gives a graphic representation of the relative risk values from Table 5-11. Figure 5-2 is a misrepresentation of the results of the sensitivity analysis, as we showed in our August 15, 2010 submission to both the EPA and the workgroup.

The EPA figure 5-2 presented a relative risk of zero as the reference risk rather than 1.0 and failed to plot the relative risk as a logarithmic function. It also did not have horizontal lines to indicate which calculations demonstrated a substantial effect on the cancer risk. These errors have been corrected in our submitted figure which we resubmit below and recommend be substituted into the report as providing greater clarity to the reader. This change should be non-controversial and accepted.

The primary observations from the EPA analysis is that for all four cancer outcomes (male lung, female lung, male bladder, and female bladder) the baseline risk estimate is substantially dependent upon the inclusion of SW Taiwan population as an included data point and on the use of the median as the summary exposure metric. The unit risk is also dependent quantitatively on the consumption volume – double the volume and the unit risk is halved. EPA had set the criteria that a 20% change in the risk estimate was evidence of a substantial effect.

We have replicated these analyses and examined the effect of examining the effect of shifting two input assumptions simultaneously – the median to the mean as the summary exposure metric and the restriction of the analysis to only include the data from the 42 study villages and their sub-groups, i.e., with the exclusion of a reference population as an additional data point. These results are available upon request.



Horizontal lines represent +/- 20%, the indication of substantial effect on the risk estimate.

We have performed the same calculations asking whether the inclusion of the SW Taiwan population has inordinately affected the estimate of the arsenic dose "b" coefficient for the 42 village analysis..

	42 Study Villages without SW		**42 Study Villages with SW**		% Change
Male Lung	44.5	(20.5, 95)	74.4	(56.6, 97.6)	**67%**
Male Bladder	71.3	(29.0, 172.5)	295.9	(220.0, 392.2)	**315%**
Male Combined	54.1	(30.4, 95.7)	111.5	(91.6, 135.4)	**106%**
Female Lung	71	(32.7, 151.5)	243	(184.6, 316.6)	**242%**
Female Bladder	98.1	(42.6, 221.8)	932.6	(669.6, 1259.8)	**851%**
Female Combined	82.1	(46.7, 143.5)	371.6	(303.7, 450.6)	**353%**

This table demonstrates that the addition of the SW Taiwan population to the model that includes the high-end dose-response curve increases the slope by 67 to 851%. It is not a judgment call to say that the inclusion of the SW population data has had an inordinate affect on the estimate of the arsenic dose "b" coefficient. It is noteworthy that the greatest effect is on the coefficient for female bladder, which the EPA sensitivity analysis (page 140) showed to be similarly affected with a change in the arsenic exposure characteristics of the SW Taiwan population.

EPA has conducted its sensitivity analysis only for the 42 study village analysis and not for the 18 low-dose village analysis (Table F-2, page 574). We have, and we submitted those analyses as Table 2 in our March 29, 2010 submission to EPA and the workgroup. We show them again below.

	18 Low-dose Villages without SW		**18 Low-Dose Study Villages with SW**	
Male Lung	**-11**	**(-30.0, 194.9)**	85.7	(13.1, 172.1)
Male Bladder	**-61**	**(-134.5, 20.7)**	586	(335, 877)
Male Combined	**-32**	**(-97.6, 38.8)**	160	(83.4, 4247)
Female Lung	**-46**	**(-181.5, 117.2)**	615	(412, 836)
Female Bladder	**-139**	**(-209.7, -62.5)**	2639	(2021, 3307)
Female Combined	**-94**	**(-167.0, -11.2)**	924	(721, 1139)

This sensitivity analysis shows that the arsenic risk “b” coefficient as calculated by EPA is a direct consequence of the inclusion of the SW Taiwan data as an additional data point set at zero arsenic. We have attempted to measure the magnitude of effect on the coefficient from the inclusion of the SW Taiwan data point in the Poisson analysis and are unable to. It is not possible to calculate a percent change in the coefficient from the inclusion of the SW Taiwan data point, as it shifts the coefficient from a negative in their absence (red is statistically significant; purple is not) to a positive in their presence (all statistically significant). This is a categorical shift in the character of the coefficient, not a quantitative shift in the magnitude of the coefficient.

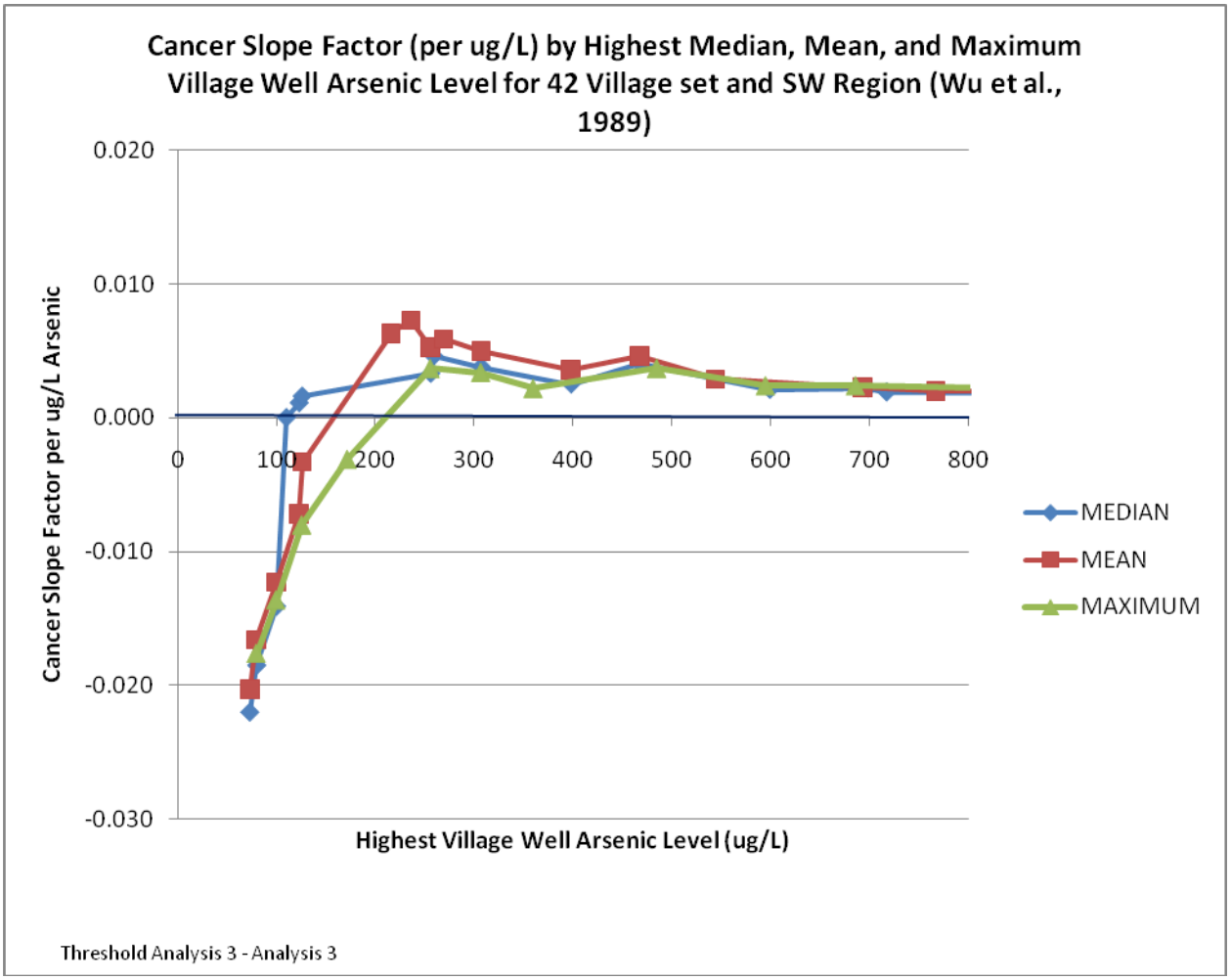
The analysis above clearly demonstrates that the arsenic dose coefficient "b" is inordinately affected by the inclusion of the SW Taiwan population data to the analysis of the data for the 18 low-dose study villages. The coefficients which are negative, and in some cases statistically significantly so, when the analysis is limited to that of the 18 low-dose villages becomes statistically significantly positive when the SW Taiwan population data are additionally included as a 19th village. EPA's conclusion (page

403) that for the low-dose villages "the dose-response relationships are positive and statistically significant" is strictly a consequence of the inclusion of the SW Taiwan population as an inordinately over-influential additional village rather than as a reference population.

"Threshold" or High-end Effect

The workgroup report states (page 2) that "The EPA also evaluated whether the models were inordinately affected by the high end of the dose-response curve and found that they were not." This statement is incomplete. It may be correct for the Poisson models that also include the SW Taiwan population as an additional "village", but it is not correct for the models that use only the study village data and do not include the SW Taiwan population data.

Our April 20, 2010 letter to the workgroup on cancer risk evidence at low arsenic exposure showed that the arsenic concentration slope became negative in an iterative analysis when the median village arsenic was 100 ug/L or the maximum village arsenic was 172 ug/L.



The graph above is from our June 9, 2010 report to the workgroup (page 7) and demonstrates that the cancer slope factor is robust with respect to summary exposure metric with statistically significant positive slopes at exposures above 250 ug/L, with generally statistically significant negative slopes below 100 ug/L, and with non-positive slopes in the range of 110-172 ug/L depending upon choice of summary exposure metric.

These analyses are quite consistent with a "threshold" above 100 ug/L and below 200 ug/L which is more informative than the EPA statement that there is no evidence specifically at 400 ug/L or 150 ug/L.

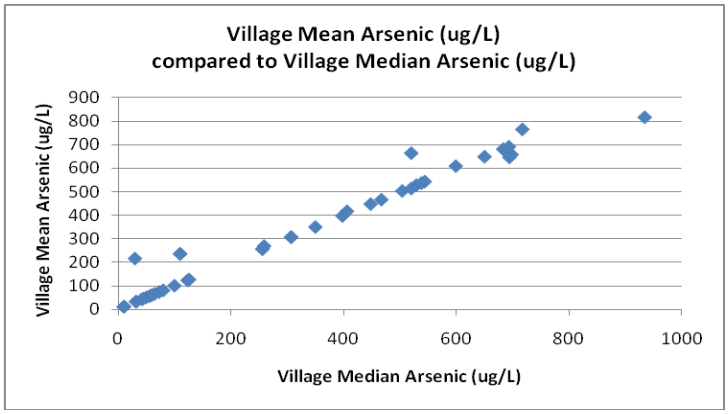
Comparison of Village Median with Village Mean

The median is not an unbiased representation of the exposures for the study villages. Historically, both the median and the mean have been used as a summary statistic of the central tendency of the exposures for the villages. Kuo TL (1968) identified exposures for villages as the mean of the arsenic concentrations, while Chen KP et al. (1962) used the median. The EPA report gives no rationale (other than historic) for the use of the median rather than the mean as the summary statistic. Nor does it examine the consequence of that use.

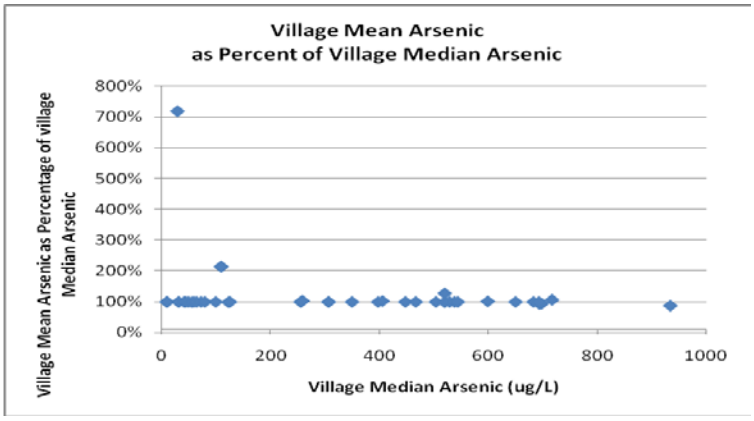
The first figure below shows the 42 study villages with their median and mean arsenic levels. For the most part they are similar, greatly because most villages have only one or two well measurements in the analysis. It should be noted, however, that a few villages of the villages with median less than 200 ug/L have means greater than 200 ug/L. These (0-G, 0-I, and 0-E) villages (all in Township 0), in fact, show high exposure levels that are not revealed by the median.

Table of Arsenic Levels for Villages with Low Medians and High Means

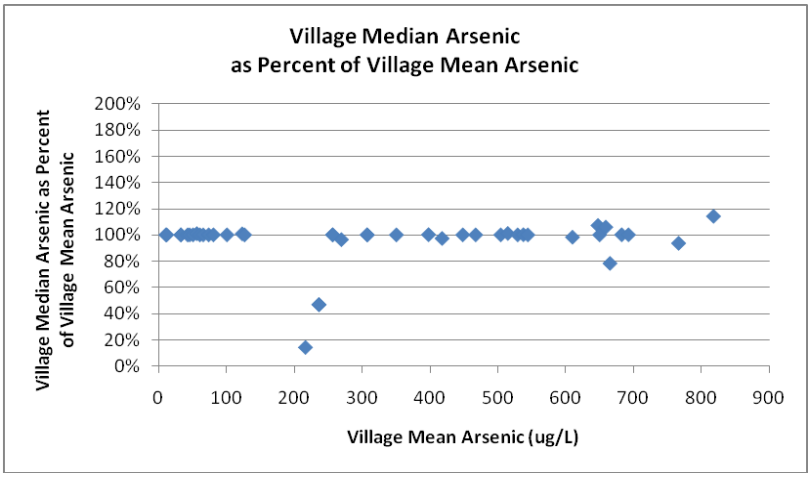
Village	Wells	Median	Mean	Maximum
0-G	5	30 ug/L	216 ug/L	770 ug/L
0-I	7	110 ug/L	236 ug/L	590 ug/L
0-E	5	110 ug/L	236 ug/L	686 ug/L



The figure above shows the absolute comparison of the village means and the village medians. The figures below show the relative comparisons – i.e., the mean as a percentage of the median and the median as a percentage of the mean.



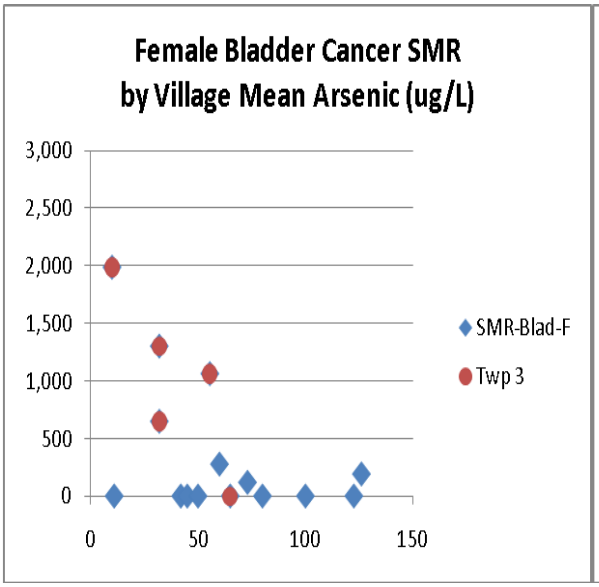
The figure below demonstrates that these villages with high arsenic exposures belong in the high exposure village group (mean > 200 ug/L) and not the low exposure village group (mean < 200 ug/L). This is a misclassification error that exists in the EPA analysis and is not revealed.

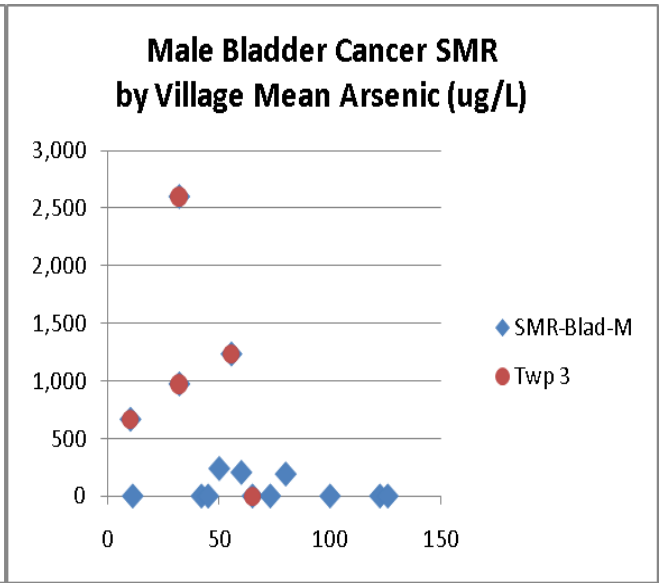


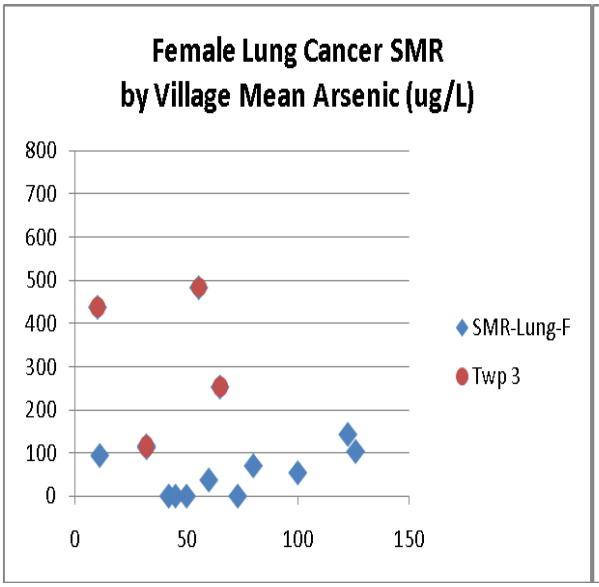
The low exposure villages are those with a village mean of 10-126 ug/L, all of whose measures are 172 ug/L or lower. The inclusion of villages with exposures above 500 ug/L in the EPA analysis prevents an examination of the risk pattern among the low arsenic exposure villages.

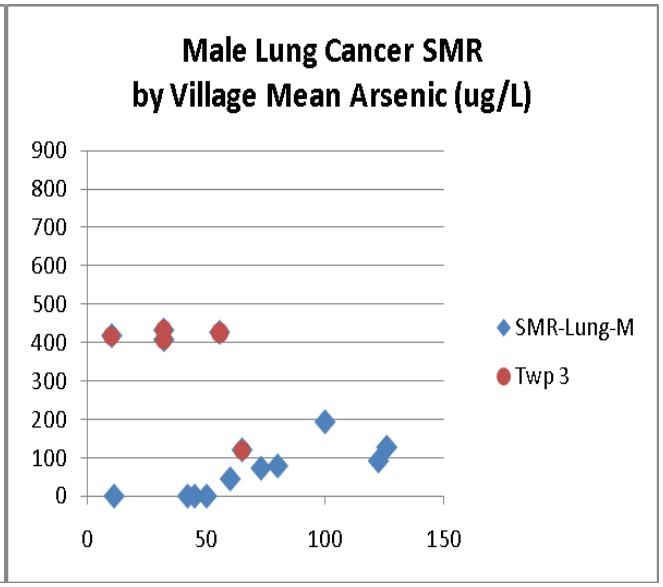
Township Analysis of Cancer Mortalityamong Low-Exposure Villages

The graphs below display the standardized mortality ratios (compared to SW Taiwan) for the low exposure study villages, separating out the villages in township 3. No dose-response increase in cancer mortality is observed for the non-township 3 villages.





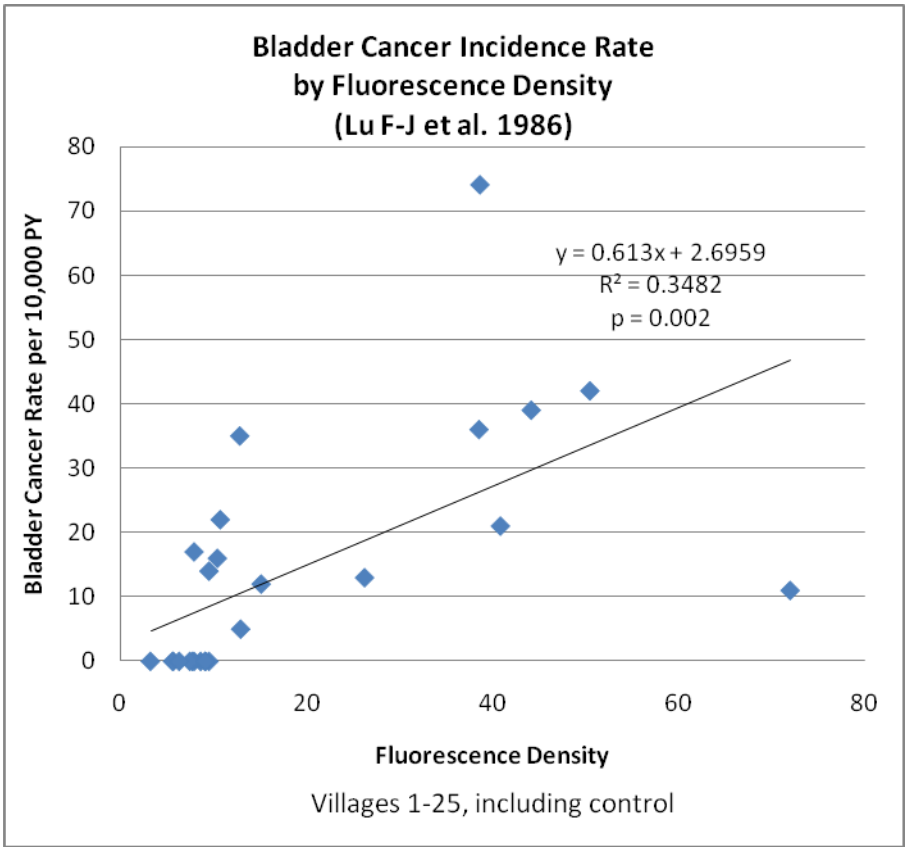




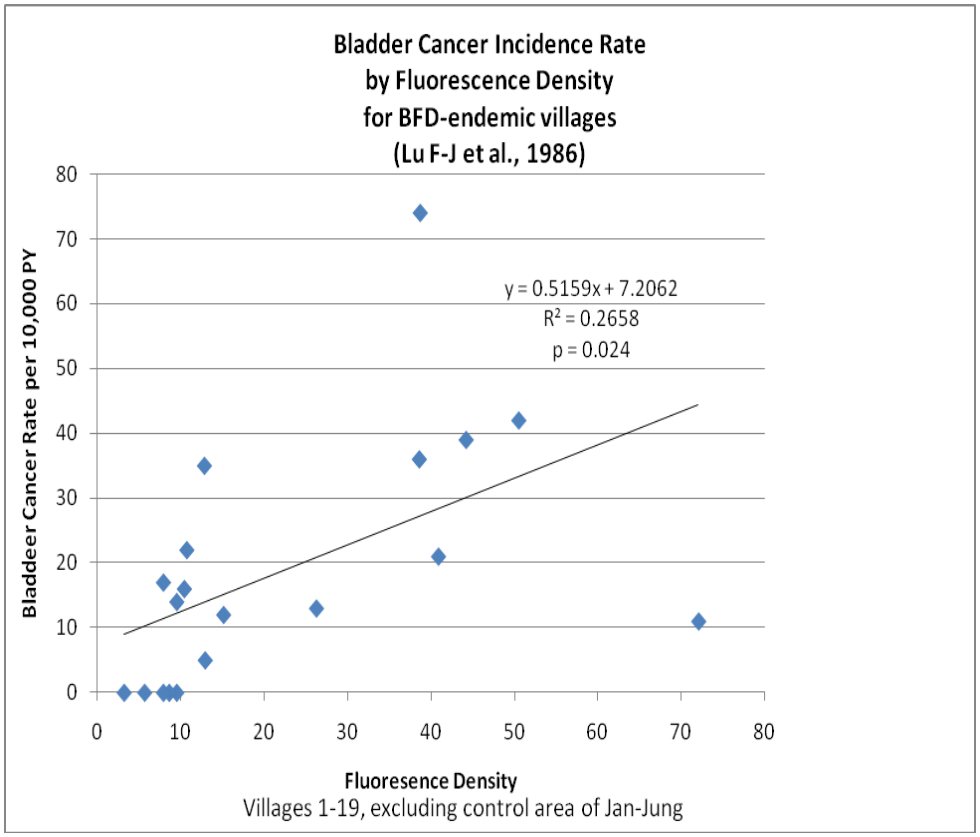
The reason that the cancer mortality risk is greater in township 3 than in the other townships and appears to be independent of the level of azrsenic is unknown. Currently studies are being carried out in the Geophysicis Laboratory of National Cheng Kung University in Tainan, Taiwan to compare the deep waters of the villages. The geochemistry and microbiology of arsenic and humic substances in the aquifer of the Blackfoot Disease area, southwestern Taiwan was presented in a symposium at the Third International Congress on Arsenic in the Environment (AS 2010) in may 2010 in Tainan, Taiwan. This symposium included a presentation on the F-J Lu et al. (1986) paper on bladder cancer incidence and fluoresence density.

Fluorescence Intensity and Bladder Cancer Incidence in BFD Area

F-J Lu et al. (1986), published in the peer-reviewed Chinese language Journal of the Chinese Oncology Society, 1986;2(3):14-23, examined the relationship between the fluorescent intensity of well water in the Blackfoot Disease (BFD) endemic area of southwest Taiwan and the incidence of bladder cancer. This is in contrast to the studies by C-J Chen and colleagues that examined the relationship between arsenic level in the well water and the mortality of bladder and other cancers.



A statistically significant positive cancer incidence slope is present both when the data from the control area of Jan-Jung are included in the analysis (25 villages) or not (19 villages). The early literature on the waters of the Blackfoot-disease endemic area focused on both the arsenic exposure and the humic substance (fluorescence density) content. The issue of the organic matter (humic substances) and its role in the health consequences of the well waters is not mentioned in the EPA report.



The regression of the bladder cancer incidence on the fluorescence density is tighter and more significant that the regression of the bladder cancer mortality on the well water arsenic levels in the Blackfoot Disease endemic area. This is neither discussed nor considered in the EPA report.

It is noteworthy that the review of the SW Taiwan data gives no consideration to the nature or etiology of the Blackfoot- disease which is a disease found uniquely here and is what brought the area to public health attention.