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August 19, 2005

Genevieve Matanowski, MD, MPH  
Chair, SAB Arsenic Review Panel  
USEPA Science Advisory Board

Re: Arsenic Discussion: submission requested at 8/11/05 Teleconference

Dear Dr. Matanowski,

Attached are the three papers I was asked at the Panel's teleconference to submit and what follows is a summary and extension of the comments I made during the Public comment section of that teleconference. The three relevant papers that we have published and discussed at the teleconference are Lamm et al. (2003)<sup>1</sup>, Lamm et al. (2004)<sup>2</sup>, and Lamm et al. (2005)<sup>3</sup>.

1. Lamm (2003) is based on the same data set from the Wu et al. (1989)<sup>4</sup> study of ingested arsenic and mortality from internal cancers in the Blackfoot-endemic area of Southwest Taiwan used by NRC, EPA, and Morales et al. (2000)<sup>5</sup>. Lamm (2003) has added water source as a second explanatory exposure variable in the analysis. Water source (artesian vs. shallow) had been an explanatory exposure variable in the earlier epidemiological studies of Chen and Wu (1962a)<sup>6</sup> and of Chen et al. (1985)<sup>7</sup> but was not in the Wu (1989) study.<sup>8</sup>

2. Lamm (2004) is a new study developed within an NCI/EPA public dataset that tried to develop a US-replicate of Wu (1989) using US residents and US exposures. The use of exposure levels and water sources to which US residents are exposed would reduce the number of inherent assumptions in any subsequent risk analysis

3. Lamm (2005) in an examination of four recent studies of inorganic arsenic ingestion and bladder cancer – the two ecological studies above from Lamm's group and two case/control studies from Allan Smith's group in California. The two papers from Allan Smith's group are Steinmaus et al. (2003)<sup>9</sup> and Bates et al. (2004)<sup>10</sup>. All five papers are attached as .pdf files.

### **Review of Our Findings and Recent Literature on Bladder Cancer and Inorganic Arsenic Ingestion**

1. Morales (2000) had shown no dose-response increase in bladder cancer mortality in the range of 0-400 ug/L arsenic. Lamm (2003) concurred in this observation and extended this analysis, providing as a likely explanation that the critical distinction

might have been water source (artesian) rather than arsenic level directly. That is, Lamm (2003) showed a strong dose-response relation between arsenic level and bladder cancer mortality for those living in villages dependent on artesian well water (i.e. all wells with medians > 325 ug/L arsenic) and no dose-response relation for those having access to shallow well water (i.e., wells with medians < 325 ug/L arsenic).

2. Lamm (2004) demonstrated from a study of 133 US counties that no dose-response relationship for arsenic level and bladder cancer mortality was seen over the range of 3-59 ug/L arsenic. The risk analysis was sufficiently strong to exclude the risk estimate determined by NRC (1999). This study was structurally similar to the Wu (1989) study - Wu (1989) used median village arsenic level of 42 villages with 14-year mortality observation; Lamm (2003) used median groundwater level of 133 US Counties with 30-year mortality observation.

3. Steinmaus (2003) found overall no increased risk with arsenic exposure and a significant increased risk only for ever-smokers with > 80 ug/day arsenic exposure and a 40 year lag. Steinmaus reported that “the overall risks were below those predicted using data from highly exposed populations in Taiwan”, referring to analyses based on the Wu (1989) study.

4. Bates (2004) found “no evidence of associations with exposure estimates based on arsenic concentrations in drinking water.” Their only significant finding was an increased risk in ever smokers who had used well water 51-70 years prior to interview and from wells whose arsenic status was unknown.

5. Based on the findings and analyses of these four studies, Lamm (2005) concluded that there was no evidence that the ingestion of inorganic arsenic was a carcinogenic exposure for the bladder at exposure levels generally experienced by US residents. An increased risk was only observed at very high exposures or in the presence of other factors, such as cigarette smoking. We proposed that these analytic results were “consistent with both co-carcinogenesis and high-exposure (hundreds of ug/L) as dependence models of toxicological mode of action.” We proposed that these dose-response relationships “should influence prioritization in the remediation of arsenic-contaminated drinking water supplies.

Having reviewed the recent publications that I spoke of and submitted, I would like to extend the discussion on some of the studies.<sup>11</sup>

### **Further Explanation**

#### Exposure classification

The major criticisms of Lamm (2003) and its re-analysis of the Wu (1989) study relate to the addition of the “water source” variable.

- Water source had historically been a distinguishing characteristic in the exposure description, as either artesian or shallow (or surface), and has been highly correlated with outcome of bladder cancer. The differences between them included the geological strata in which they were located, subsequent well type used, and potential for contamination and microbial growth. Chen KP et al. (1962b)<sup>12</sup> documented the differences in inorganic characteristics of the waters, and Lu et al. (1975; 1990)<sup>13</sup> focused on the organic contents of the waters (i.e., fluorescent substance; humic and fulvic substances).
- Chen and Wu (1962a) had separated the villages into those whose wells were artesian wells only, both artesian and shallow wells, and shallow wells only. They reported that all of the Blackfoot disease (BFD) cases either came from artesian well only villages or only used artesian wells in villages with both well types.

**Table 1: Arsenic Levels in BFD Non-Endemic and Endemic Areas by Well Type<sup>14</sup>**

Authors	BDF - Non-Endemic Arsenic Levels (ug/L)		BFD - Endemic Arsenic Levels (ug/L)	
	Artesian Wells	Shallow Wells	Artesian Wells	Shallow Wells
KP Chen et al. (1962b) <sup>15</sup>	150-540 (median 380)	<50 (median 25)	350 - 1,140 (median 780)	<200 (median 40)
Chen (1985)			350 - 1,140 (median 780)	0 - 300 (median 40)
Wu (1989)			350 – 1,140	0 - 300

- Table 1: Shows the arsenic levels in BFD non-endemic and endemic areas by well type. We see that this depiction shows that arsenic levels in artesian wells is much higher than that of shallow wells. Indicating that water source is an important variable in assessing arsenic exposure levels.
- The 1985 study of CJ Chen et al. also separated their study villages by water source into the same three categories and showed that the cancer mortality rates (particularly bladder cancer) were highest in the villages that only had artesian wells, mid-range in the villages with both well types, and lowest in the wells without artesian wells.
- Wu (1989) determined the median arsenic level in well water for each of the 42 villages they studied and aggregated the villages into those with medians less than 300 ug/L, those with medians of 300-590 ug/L, and those with medians of 600 ug/L or more. Wu (1989) gave no further specification of the arsenic levels.
- Two further analyses of this data set for the purpose of risk analysis were published. Chen et al. (1992)<sup>16</sup> separated the lowest group into two strata - < 100

ug/L and 100-290 ug/L – and developed an Armitage-Doll multistage modeling of risk. Morales et al. (2000) presented both an SMR analysis stratified by village median well arsenic level in 100 ug/L strata (with a cut also at 50 ug/L) and a GLM (or MSW) risk model using the disaggregated village data by median level. Neither of these analysts provided the village specific arsenic data.

- The National Research Council, in its 1999 report<sup>17</sup> on Arsenic and Drinking Water, included in its appendix a table that listed the arsenic level for each well in each village, the village median, and the cancer mortality<sup>18</sup>.

Lamm (2003) used the data in this table [Lamm (2003), page 357] as the basis for assigning an assumed water source to each well and then a classification of water sources for each village.

- As an operational definition and as a working assumption, using the descriptions of Chen (1985) and Wu (1989), Lamm et al. (2003) defined “artesian well” as one with a level greater than 325 ug/L. We used the data from the NRC Appendix (1999)<sup>19</sup>. We then classified villages in “all artesian, some artesian, and no artesian” based on whether the well’s arsenic levels fit this definition and proceeded with our analyses. We sought to re-introduce the water source variable into the exposure classification (description).
- It may be argued that the use of the term “artesian well” for the more precise label of “wells with arsenic concentrations > 325 ug/L” introduces a misclassification; However, that is quite consistent with the data first reported by Chen (1962b) for a study said to have been conducted in the BFD-endemic area. It may also be that the determination of which village is in the endemic area has changed over time.
- The original impetus for the Lamm (2003) analysis was the observation of a discontinuity in the graphic presentation of the dose-response data for bladder cancer mortality. The SMR data are from Figure 5 (Appendix A) of the Morales et al. (2000) paper with the 95% confidence limits in the figure calculated on the basis of the Poisson distribution about the number of observed cases (Appendix: Figure 5).
- Based on the graphic presentation in Figure 5, it appears that there are two groups of data. There is little change in the risk presentation of the data in the first five exposure strata (< 400 ug/L). The risk for exposures in the upper three strata ( $\geq$  400 ug/L) appears to be greater than that at lower levels, and the relative risk between these two groups is a factor of 3-4. It is also noteworthy that the relative risk at baseline appears to be 5-10 for those who live in the BFD-endemic area (independent of the arsenic concentration) compared to the general Taiwan reference population. It is strange that analyses, have focused on the smaller 3-4 fold relative risk within this study population even though the 5-10 fold relative risk that this population appears to demonstrate is independent of the arsenic

exposure. A revision of this graph using SW Taiwan as the reference population might be worthwhile.

Nonetheless, it was a re-read of the historical literature on the health studies from SW Taiwan that led to the observations that previous literature to the Wu (1989) study had included water source as an explanatory exposure variable and the subsequent studies did not. The re-introduction of the water source variable and its effect on the analysis has been shown above.

### Population classification

- An additional re-read of the Wu (1989) is most revealing in terms of its study population. The Wu et al. (1989) study population is comprised of two groups of villages. Twenty-seven of the villages were from the townships of Peimen, Hsuechia, Putai, and Ichu and had been reported in the earlier cancer mortality study of Chen et al. (1985); Fifteen of the villages were added and came from the neighboring townships of Yensui and Hsiaying. It is not clear that both of these two additional townships are in the historic BFD-endemic area. An alternative explanation may be that these two sets of villages are different and the risk pattern might not appear similar if they were separately analyzed. If we had the information on which villages were from which townships, we would then be able to explore the heterogeneity to possibly explain the appearance of two populations.
- We do not know which of the 42 villages came from each group, though I have recently requested that information from Taiwan. The bladder cancer graph (Appendix A) already shows that there is geographic heterogeneity in the bladder cancer mortality of this area.

### **A Fresh Approach**

The primary concern above relates to – what exposure characteristics should be applied to the population of each of the study villages? Prior literature has suggested BFD-endemicity, water source, Artesian well use duration, and arsenic level. The published data (NRC, 1999) shows that the 42 study villages had from 1 to 47 wells each. Wu (1989) and the analyses derived from it have each used the village median well arsenic level as the representative exposure metric. This may lead to exposure misclassification, since one has no information as to which well(s) actually served as the villagers' drinking water source(s). As an example, village O-G had five wells with arsenic concentrations of 0.010, 0.010, 0.030, 0.256, and 0.770 ppm. For this village, the median (and representative) exposure level used was 0.030 ppm.

This is a problem that was recognized by the NRC, stating “arsenic concentrations detected in multiple wells varies considerably within some of the villages, leading to uncertainty about the exposure concentrations assigned to each village [page 292].”

One method to avoid misclassification and focus on the arsenic level as the exposure metric would be to perform a subset analysis on those villages that had only one well. While we have no way of dealing with any historical issues of measurement error, this method does eliminate the common sources of exposure misclassification. It reduces the size of the analytic data set but it removes a major source of uncertainty.

Twenty of the 42 villages [NRC (1999), A-10] had only one well. We have calculated for each of those villages the crude bladder cancer mortality rates (per 1,000 PY) and show these graphically in Appendix D. This has the advantage because for these villagers there is no apparent alternative drinking water source.

Appendix D gives the impression that there are two groups of well-water arsenic levels, which is not surprising since Wu (1989) had in this original paper pointed out that the well water sample arsenic levels had two cluster, “at levels of 0.05-0.25 ppm and 0.45-0.65 ppm [page 1126].” Among the one-well villages, the ranges for the two clusters are 0.010-0.126 ppm and 0.256-0.544 ppm.

For each cluster of well arsenic levels, a linear regression has been performed to examine the dose-response relationship. For those in the low group, the slope is negative and the  $R^2$  is 0.20. For those in the high group, the slope is positive and the  $R^2$  is 0.026.

We would point out that the arsenic levels in the low group are those that are most relevant to the exposure levels experienced in the US. It is not necessary to make any assumptions about the water sources, locations of these villages, or the nature of co-contaminants in order to observe that the dose-response relationships differ in the two groups previously distinguished by Wu. Furthermore, it might be noted that the patterned observed for the bladder cancer mortality rates in one-well villages in the Wu (1989) study with exposures up to 0.126 ppm (126 ug/L) is not dissimilar from that seen in the US study of bladder cancer mortality in 133-US counties with median arsenic water exposures of 3 to 59 ug/L.

These patterns summarize the epidemiological data and should be further investigated with regards to the mechanism or mode of action for the carcinogenicity of ingested arsenic.

### **Summary**

In summary, we have submitted and discussed some of the major findings and inclusions that distinguished our studies in reference to past studies. In addition, we have also provided further explanation of our studies, some issues pertaining to them, and an alternative approach to the data. However, the most salient points that we wish to bring to the SAB panel's attention are as follows:

- In the Taiwan data, arsenic exposure is associated with water source, which is completely confounded by its association between arsenic and bladder cancer. In

addition, to the extent that the data is presented in the Taiwan study, we found no association between arsenic level and bladder cancer when stratified by water source. We suggest that there is an independent modifier on bladder cancer.

- Even in the low-level arsenic exposure strata, there is still a 5-10 fold increase in risk of bladder cancer (Appendix A: Figure 5). It is a major void that there is no explanation for the difference in bladder cancer risk in the BFD-endemic area that appears to be independent of the arsenic exposure.
- It is likely that EPA has more detailed information in its progress reports or other documentation in the early years of the Wu et al (1989) study and that the SAB could obtain it from them. We would propose that a more detailed study on this data set or a new study is needed to look at individual level exposures, smoking habits, etc. We would suggest that EPA seek this information, make it available, and provide a re-analysis that separates out the data from the two groups of villages.
- Finally, we flag to your attention the pattern of bladder cancer mortality among the one-well villages of the study in terms of the issues that the panel is dealing with. These data

We hope that you will find our comments worthwhile and useful to you.

Cordially,

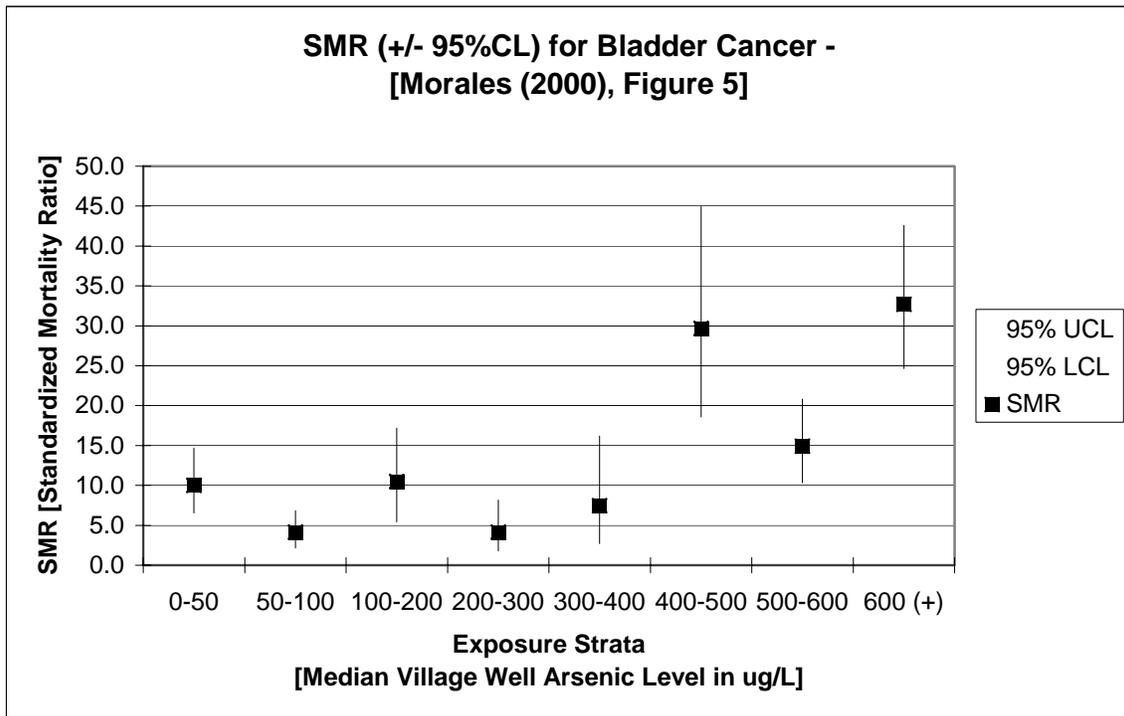
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## Appendices

Appendix A:

*Standardized Mortality Ratios for Bladder Cancer by Arsenic Exposure Strata (Median Village Arsenic Well Concentration) [Developed from Morales et al. (2000), Table 5]*



Appendix B:

*Arsenic Concentration in ppb by Kind of Well, derived from Chen et al. (1962a)*

<b>Arsenic Concentration (ppm) by Kind of Well</b> <b>[Modified from Chen et al. (1962); Table 2, page 123]</b>				
Area	Endemic		Non-Endemic	
<u>Kind of Well</u> <u>ppm</u>	<u>Artesian</u> <b>(AE)</b>	<u>Shallow</u> <b>(SE)</b>	<u>Artesian</u> <b>(AN)</b>	<u>Shallow</u> <b>(SN)</b>
0.0-0.04		10		60
0.05-0.09		1		
0.10-0.14		2		
0.15-0.19		1	1	
0.20-0.24			2	
0.25-0.29			1	1
0.30-0.34			1	
0.35-0.39	2			
0.40-0.44	2		1	
0.45-0.49	1		1	
0.50-0.54	4		3	
0.55-0.59	1			
0.60-0.64	2			
0.65-0.69	2			
0.70-0.74	3			
0.75-0.79				
0.80-0.84	3			
0.85-0.89	3			
0.90-0.94	3			
0.95-0.99	1			
1.00-1.04	4			
1.05-1.09				
<u>1.10-1.14</u>	<u>3</u>			
Total (n)	34	14	10	61
Median	0.78	0.04	0.38	0.025

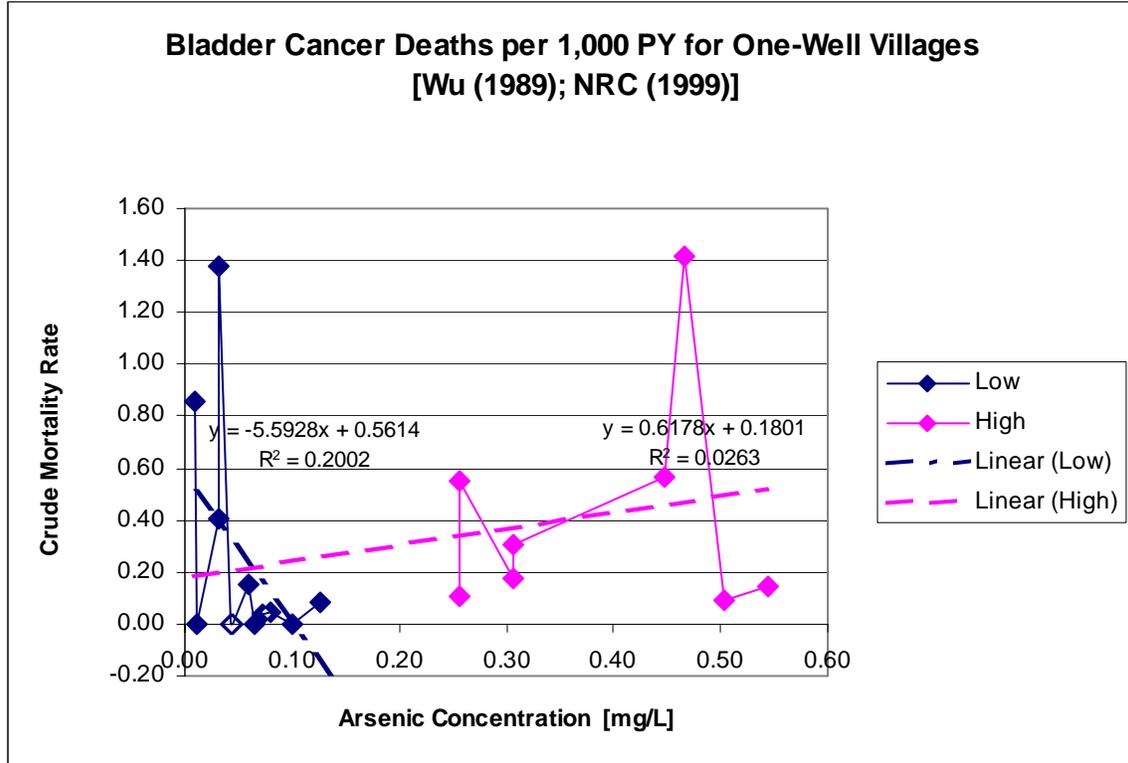
Appendix C:

*District or Township Specific Distribution of Wells by Water Source [Chen and Wu (1962a), Table 1], Blackfoot Disease Prevalence [Chen and Wu (1962b), Table 1] and Male Bladder Cancer Standardized Mortality Rates [Chen et al. (1985), Chart 2]*

<b>Artesian Well Status of Villages</b>							
<u>[Modified from Chen and Wu (1962a) Table 1], and Chen et al. (1985) Chart 2</u>							
	<u>Only</u>	<u>Some</u>	<u>None</u>	<u>Total</u>	<u>% Only</u>	<u>BFD Prev.*</u>	<u>Blad Ca SMR*</u>
<u>Initial Areas</u>							
Peimen	12	2	4	18	67%	5.6	35
Hseuehchia	11	11	6	28	39%	3.9	30
Putai	13	6	4	23	57%	2.0	16
<u>Ichu</u>	<u>2</u>	<u>10</u>	<u>13</u>	<u>25</u>	<u>8%</u>	<u>0.6</u>	<u>5</u>
Sum	38	29	27	94	40%	2.5	
Percent	40%	31%	29%	100%			
						* per 1000	*Male (1968-92) (estimated)
<u>Additional Areas</u>							
Hsiaying	1	1	13	15	7%	0.1	
Yensai	-	-	-				

Appendix D:

Crude Bladder Mortality Rates (per 1000 PY) for One-Well Villages by Well Water Arsenic Level [NRC (1999), A-10 derived from Wu (1989 and Chen (1992)]



## Endnotes

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- <sup>1</sup> Lamm SH, Byrd DM, Feinleib M, and Lai SH. (2003). Bladder Cancer and Arsenic Exposure: Differences in the Two Populations Enrolled in A Study in Southwest Taiwan. *Biomed Environ Sci*, 2003;16:355-368
- <sup>2</sup> Lamm SH, Engel A, Kruse MB, Feinleib M, Byrd DM, Lai S, and Wilson R. (2004). Arsenic in Drinking Water and Bladder Cancer Mortality in the United States: An Analysis based on 133 U.S. Counties and 30 Years of Observation. *J Occup Environ Med*, 2005;46:298-306.
- <sup>3</sup> Lamm SH and Kruse MB. (2005). Arsenic Ingestion and Bladder Cancer Mortality – What do the Dose-Response Relationships Suggest About Mechanism?, 2005 April;11(5):433-450.
- <sup>4</sup> Wu MM, Kuo TL, Hwang YH, and Chen CJ. (1989). Dose-Response Relation Between Arsenic Concentration in Well Water and Mortality from Cancers and Vascular Diseases. *Am J Epidemiol* 1989;130(6):1123-1132.
- <sup>5</sup> Morales KH, Ryan L., Kuo TL, Wu MM, and Chen CJ. (2000). Risk of Internal Cancers from Arsenic in Drinking Water. *Environ Health Persp*, 2000 July;108(7):655-661.
- <sup>6</sup> Chen KP and Wu HY (1962a). Epidemiologic Studies on Blackfoot Disease: 2. A Study of Source of Drinking Water in Relation to the Disease. *J Formosan Medical Assoc.* 61:611-618.
- <sup>7</sup> Chen CJ, Chuang YC, Lin TM, and Wu HY (1985). Malignant Neoplasms among Residents of a Blackfoot Disease-endemic Area in Taiwan: High-Arsenic Artesian Well Water and Cancers. *Cancer Res*, 1985 Nov;45:5895-5899.
- <sup>8</sup> Note that KP Chen and HS Wu, investigators from the Institute of Public Health, National Taiwan University, in the early 1960s are different individuals from CJ Chen, HY Wu, or MM Wu, investigators from the Institute of Public Health, National Taiwan University, in the late 1980s.
- <sup>9</sup> Steinmaus C, Yuan Y, Bates MN, and Smith AH (2003). Case-control Study of Bladder Cancer and Drinking Water Arsenic in the Western United States. *Amer J Epidemiol*;158(12):1193-1201.
- <sup>10</sup> Bates MN, Rey OA, Biggs ML, Hopenhayn C, Moore LE, Kalman D, Steinmaus C, and Smith AH. (2004). Case-Control Study of Bladder Cancer and Exposure to Arsenic in Argentina. *Amer J Epidemiol*;159(4):381-389.
- <sup>11</sup> US EPA (2005). Issue Paper: Inorganic Arsenic Cancer Slope Factor, Final Draft July 23, 2005. Pages 7-9.
- <sup>12</sup> Chen KP, Wu HY, and Wu TC (1962b). Epidemiologic studies on Blackfoot Disease in Taiwan. 3. Physicochemical characteristics of drinking water in endemic Blackfoot disease areas. *Memoirs Coll Med Nat Taiwan Univ*, 1961 Oct;8:115-129.
- <sup>13</sup> Lu FJ, Yank CK, and Ling KH (1975). Physico-chemical characteristics of drinking water in blackfoot endemic areas in Chia-ui and Tainan Heiens. *J Formosan Med Assoc* 74:596-605 and Lu FJ (1990). Blackfoot disease; Arsenic of Humic Acid? *Lancet* 336(8707):115-116.
- <sup>14</sup> Table 1: Shows the arsenic levels in BFD non-endemic and endemic areas by well type. We see that this depiction shows that arsenic levels in artesian wells is much higher than that of shallow wells. Indicating that water source is an important variable in assessing arsenic exposure levels.
- <sup>15</sup> Chen KP, Wu HY, and Wu TC (1962). Epidemiologic studies on Blackfoot Disease in Taiwan. 3. Physicochemical characteristics of drinking water in endemic Blackfoot disease areas. *Memoirs Coll Med Nat Taiwan Univ*, 1961 Oct;8:115-129.
- <sup>16</sup> Chen CJ, Chen CW, Wu MM, and Kuo TL. (1992). Cancer Potential in Liver, Lung, Bladder, and Kidney due to Ingested Inorganic Arsenic in Drinking Water. *Br J Cancer*, 1992;66:888-892.
- <sup>17</sup> National Research Council (NRC) (1999). *Arsenic in Drinking Water*. National Academy Press, Washington, DC, 1999.
- <sup>18</sup> NRC (1999). Op cit. Addendum to Chapter 10. Table A10-1 Internal Cancer Data from Arsenic-Exposure Studies Conducted in Taiwan Region Endemic to Blackfoot Disease. Pp. 308-309
- <sup>19</sup> NRC (1999). Op cit. Addendum to Chapter 10. Table A10-1 Internal Cancer Data from Arsenic-Exposure Studies Conducted in Taiwan Region Endemic to Blackfoot Disease. Pp. 308-309.