April 20, 2010

Dr. Elaine Faustman, Chairman
Arsenic Workgroup
Science Advisory Board
US Environmental Protection Agency
Washington, DC

Re: Cancer Risk Evidence at Low Arsenic Exposure

Dear Dr. Faustman,

Thank you for the opportunity to address the workgroup and then to participate as an observer at their meeting on April 6-7, 2010. At that time I had commented upon data quality and data selection issues that we had expected to be on the agenda. I was surprised at the meeting, however, to see the workgroup asked to opine on issues that went further. We wish to address some of those.

We would like to focus the workgroup's attention on the fundamental model whose analytic results were under discussion. We think the workgroup was asked to generate opinions from the model that went beyond the ability of the model (as used) to answer. We suggest that the model and the analyses performed with it were inadequate to answer the questions. We propose a more generic approach that may provide significant analytic insight based on the total body of data in the SW Taiwan study.

We propose a generic Poisson analysis for the distribution of bladder and lung cancer cases in the Wu et al. (1989) SW Taiwan study using the SW Taiwan regional data as a reference group. The model uses the data from SW Taiwan regional data, the model uses as dependent variables age and age-square and village well water arsenic level, plus the interaction between age and arsenic level, and non-well-water-arsenic-level village factors. We allow in our model that the bladder and lung cancer mortality in the study villages may be affected by factors related to the well water arsenic level (dose) and to factors not related to the well water arsenic level (ND).

The model follows:

Events = a1 + b1 x age + b2 x age-squared + b3 x dose + b4 x age x dose + b5 x ND

- with person year as exposure, where ND is a binary variable with the 42 villages codes as 1 and SW Taiwan population coded 0.

In contrast to the EPA model, we use arsenic concentration as the exposure metric of ug/L rather than the estimated daily dosage of mg/Kg-day. Our model is thus not dependent upon assumptions of magnitude of non-water arsenic exposure, body weight, or daily water consumption. Our model seeks the behavior pattern of "b3" for the main effect with respect to dose rather than the behavior pattern for the interactive or multiplicative term "b4". As a first pass, we present the analysis for bladder and lung cancer mortality combined.

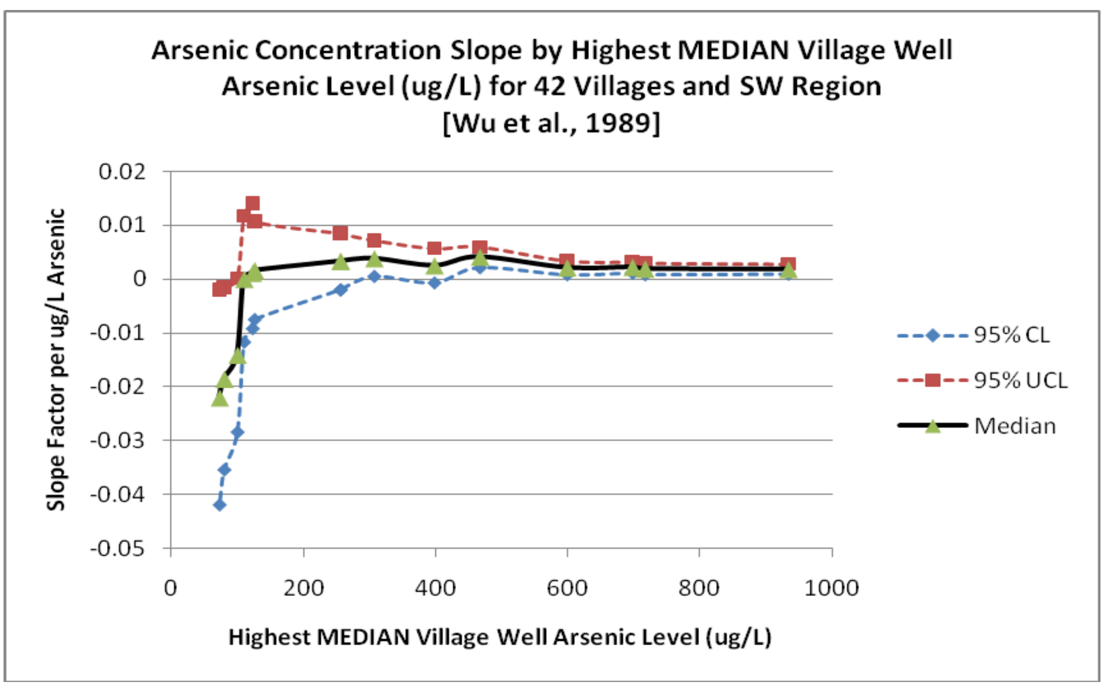
Each village data set enters the model weighted by its person-years of observation and using the village median. It is recognized that using the village median is problematic for examining the coefficient of exposure at low levels because the use of the median obscures the fact that several low-dose villages are known to contain high exposure level wells. This problem can subsequently be remedied by entering the villages by their highest (maximum) known well arsenic level.

In all of our analyses, we found the non-arsenic-level BFD area term to be statistically significant. We leave the interpretation of the non-arsenic-level term open. It may include non-drinking water arsenic and/or other unspecified factors. Known differences between the study villages and the region include the occurrence of Blackfoot-disease and the historical use of artesian wells. The distinction between an arsenic-level and a non-arsenic-level term for cancer mortality analysis of the study area villages is consistent with the findings of the Tsai et al. (1999) paper submitted to the workgroup on April 7th, 2010. That paper demonstrated an overall cancer excess with a proportional cancer excess for specific cancers thought to be related to arsenic exposure (bladder and kidney, skin, and respiratory).

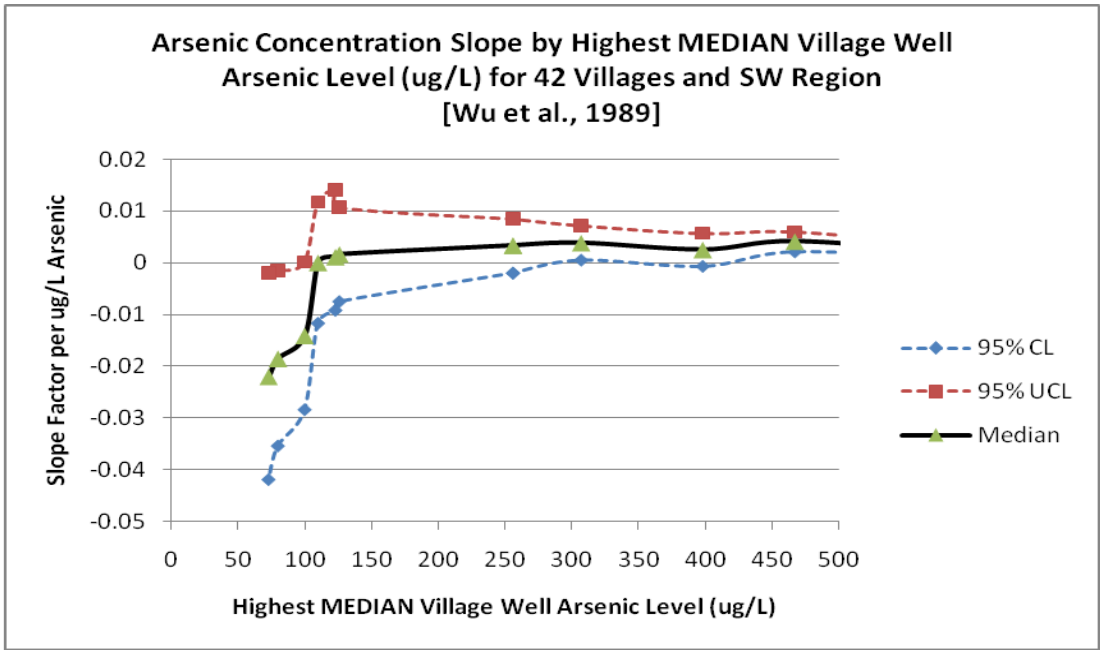
We confirm EPA's finding - when the analytic data set includes all 42 villages and the regional reference population, the co-efficient for arsenic is statistically significant. Specifically, with median dose for each village at each age group as predictor in the above equation, the estimated co-efficient from Poisson regression is 0.0018. This is equivalent to an odds ratio of 1.0018, indicating that an increase of 1 ug / L in arsenic exposure is related to about 0.18% increase in the combined lung and bladder cancer rates. The estimated coefficient for the binary variable ND is 0.829. Therefore the odds ratio is Exp (0.829) = 2.29, showing that the black foot area had an increased risk of cancer relative to SW Taiwan population. The results using mean and maximum of the dose for each village also show positive relation between arsenic exposure and cancer rates for the 42 villages.

The EPA has asked the workgroup to confirm that there is no evidence of a threshold (particularly at 150 ug/L or 400 ug/L) and that the coefficient is both statistically significant and robust. Towards that end, we have performed the following analyses.

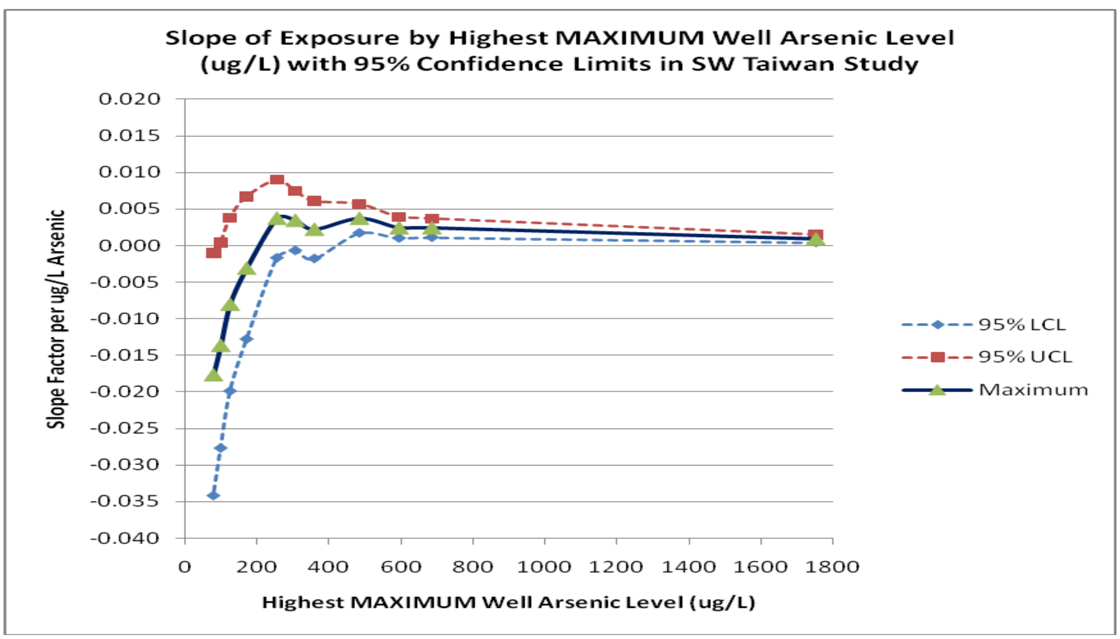
We have performed that assessment by sequentially truncating the dataset at lower medians and repeating the analysis.



Seen more closely, the graphs of the medians and the analytic results below (Table 1) show a zero slope at 110 ug/L and negative slopes at 100 ug/L and below



Refinement of this analysis entering each village on the basis of its highest well arsenic level (maximum) yields the graph below.



In the above graph of the maxima, statistical significance is lost below 400 ug/L and the slope is negative at 172 ug/L and below. The pattern is similar in all the analyses.

Thus, the interpretation that the significantly positive slope is a robust finding is a consequence both (1) of not examing the median below 150 ug/L (the slope turns negative at median = 100 ug/L) and (2) of not examing by the village well water arsenic maxima, which ignores the high exposure wells in the low-dose villages, (the slope turns negative at maximum = 172 ug/L).

These analyses indicate that the cancer mortality risk observed in the high exposure villages is not predictive of the cancer risk in the low exposure villages with different behavior below the 100-200 ug/L range than above.

The data do not support the conclusions in the final paragraph of the Toxicological Review of Inorganic Arsenic (page 575; page F-7) that "the Taiwanese data show robust and significant positive associations between arsenic exposures and cancer risks,..even in low-exposure groups" or that "No evidence was found that…represent "threshold" arsenic concentrations in drinking water."

We suggest that the workgroup give further consideration to the analysis of the SW Taiwan data.

Cordially,

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Appendix A

Table 1
Analytic Table for MEDIAN Analysis of Wu et al. Study

High ug/L	Villages	PYR Total	**MEDIAN**	95% CL	95% UCL	p
934	42	486,959	0.0018	0.0009	0.0028	0.0002
717	41	470,276	0.0019	0.0008	0.003	0.0004
698	40	459,584	0.0022	0.0011	0.0032	0.0001
599	35	411,261	0.0021	0.0008	0.0034	0.0011
467	28	327,465	0.0041	0.0021	0.006	<0.0001
398	25	301,810	0.0025	-0.0007	0.0057	0.1218
307	23	288,490	0.0038	0.0005	0.0072	0.0249
256	20	262,251	0.0033	-0.0020	0.0085	0.2189
126	18	236,396	0.0016	-0.0075	0.0107	0.7283
123	17	228,314	0.0011	-0.0092	0.0141	0.8344
110	16	202,493	0.0000	-0.0117	0.0117	0.9984
100	14	193,493	**-0.0141**	-0.0284	0.0002	0.0541
80	13	171,854	**-0.0185**	-0.0354	-0.0015	0.0326
73	12	147,150	**-0.0220**	-0.0419	-0.002	0.0308

Table 2
Analytic Table for MAXIMUM Analysis of Wu et al. Study

High ug/L	Villages	PYR-Total	**MAXIMUM**	95% LCL	95% UCL	p
1752	42	486,959	0.0009	0.0004	0.0015	0.0016
686	31	357,607	0.0024	0.0011	0.0037	0.0003
595	29	340,540	0.0024	0.0010	0.0039	0.0010
485	24	286,500	0.0037	0.0017	0.0057	0.0004
360	20	252,762	0.0022	-0.0018	0.0061	0.2813
307	19	245,234	0.0034	-0.0007	0.0075	0.1039
256	18	235,365	0.0037	-0.0017	0.0090	0.1825
172	15	203,799	**-0.0031**	-0.0128	0.0067	0.5377
126	14	190,512	**-0.0080**	-0.0199	0.0038	0.1853
100	13	182,430	**-0.0136**	-0.0277	0.0004	0.0574
80	12	160,791	**-0.0176**	-0.0342	-0.0010	0.0375