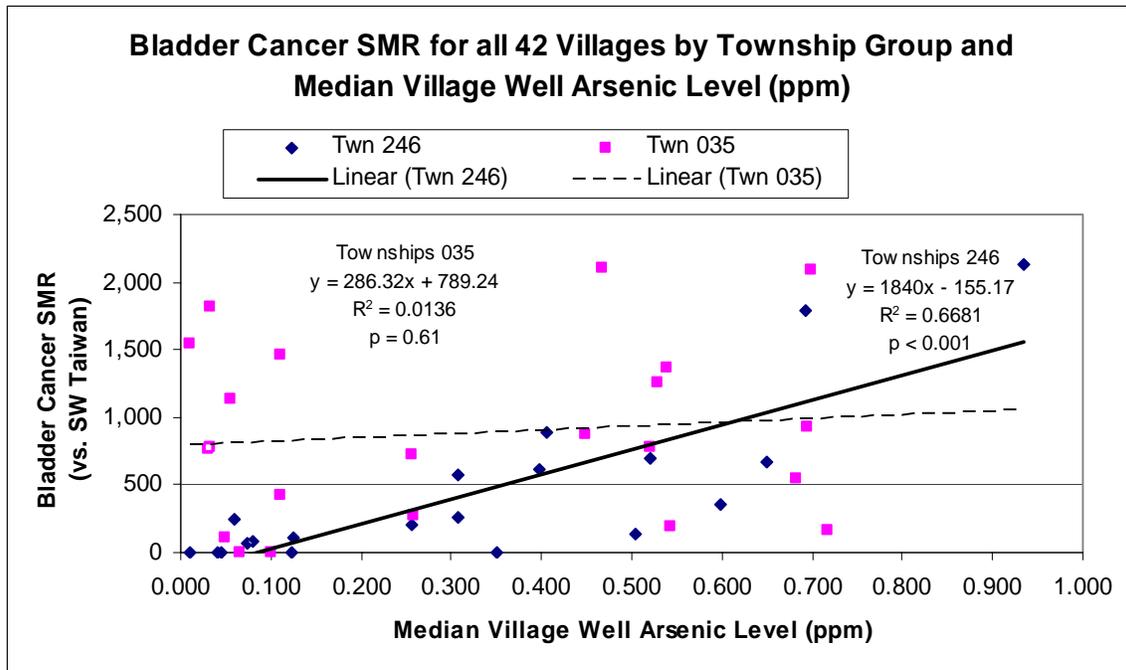


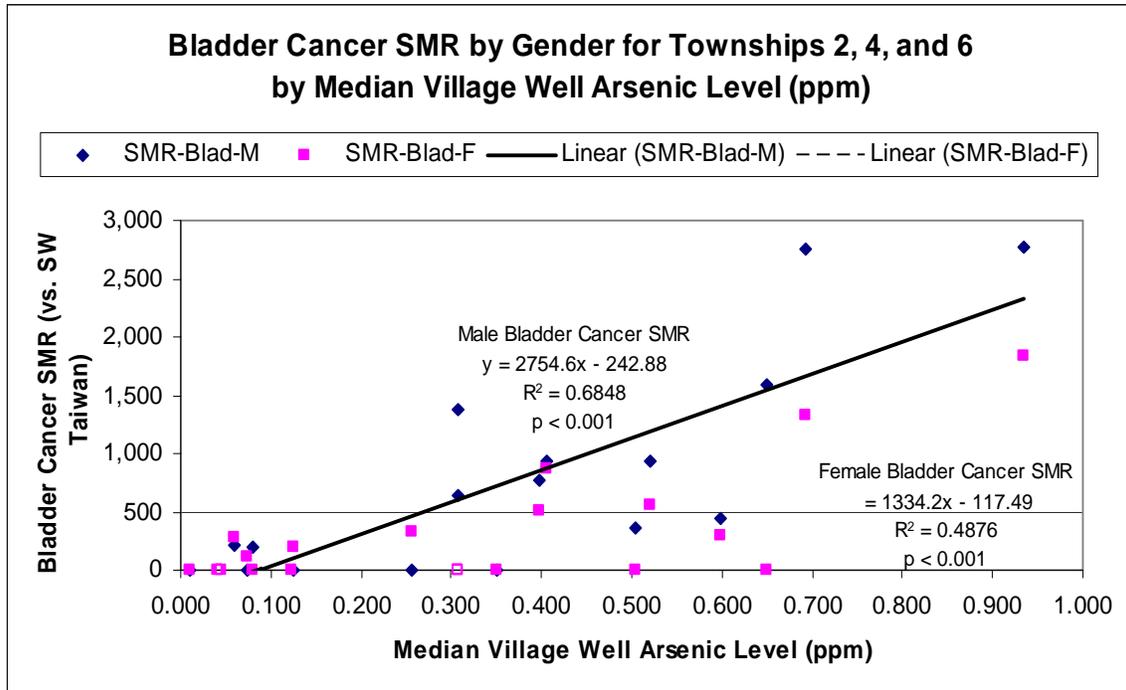
Re: Response to Statements made at the 9/13/05 panel meeting.

To: Dr. Genevieve Matanoski and panelists
From: Steven H. Lamm, MD, DTPH and CEOH
Date: September 13, 2005

This morning's meeting had a long discussion as to how epidemiology informed the issue as to whether for bladder cancer the risk followed a linear or non-linear model. We have examined that issue within the SW Taiwan dataset of interest. Earlier, we had pointed out that township was a major predictor of risk. Figure 1 demonstrates that the bladder cancer risk was (using a linear regression model) associated with the median village arsenic well level for townships 2, 4, and 6 (combined) [$p < 0.001$], but not for townships 0, 3, and 5 (combined) ($p = 0.61$). The explanatory R^2 for townships 2, 4, and 6 is 67%; while that for townships 0, 3, and 5 is 1%.

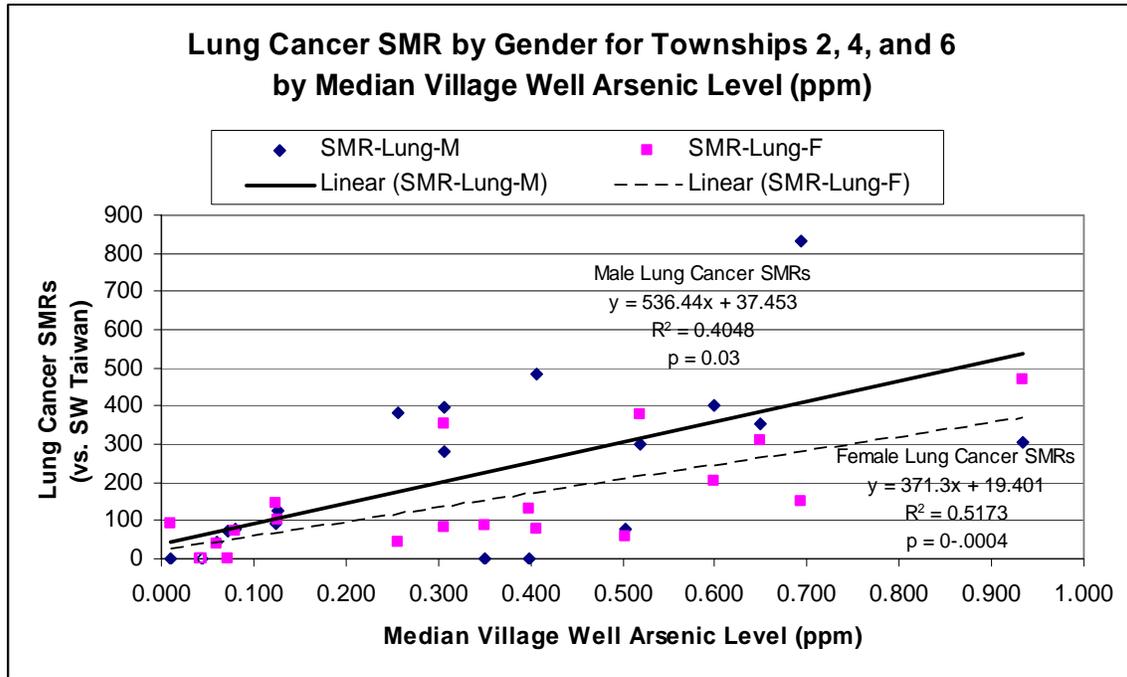


When the bladder cancer SMR data for Townships 2, 4, and 6 villages are then stratified by gender, the linear regressions (Figure 2) show for each a significant slope with an X-intercept at 0.088ppm. The explanatory R^2 s are 68 % and 49 % for males and females, respectively. These epidemiological findings would suggest that an appropriate risk model for bladder cancer and inorganic arsenic exposure is a threshold model. The X-intercept is between one and two standard deviations from the origin. It is noteworthy that replicate analyses (male; female) both show a threshold of 0.088 ppm.



The slope for the male cancers is twice that for the female cancers. This may reflect the statements that smoking prevalence was much greater in SW Taiwan for males than for females and/or that water consumption rates were greater for males than for females. Visually, it appears for the female bladder cancers that the data may more appropriately fit an upward bending model, but we leave that for the statistical modelers.

Similar analysis of the male and female lung cancer SMRs for the villages in townships 2, 4, and 6 has been performed (Figure 3). The slope for males is only 45 % greater than that for the females. Neither the male nor the female model suggests a better fit to a threshold model than to a non-threshold model.



It may be that the inclusion of smoking histories would better inform the arsenic dose-response relationship. In view of the strong effect that cigarette smoking has on lung cancer risk, the actual dose-response pattern for both male and female lung cancers may be obscured.

The apparent threshold for inorganic arsenic concentrations and bladder cancer appear to be compatible with many of the toxicological comments made at the panel meeting.

We recommend that the NE Taiwan data be examined to better characterize the inorganic arsenic dose-response relationship for lung cancer, controlling for the effect of cigarette smoking.

Cordially,

Steven H. Lamm, MD, DTPH
 Arnold Engel, MD, MPH
 Cecilia Penn, MD, MPH
 Rusan Chen, PhD
 Manning Feinleib, MD, MPH