

## 1. From Dr. Gary Kayajanian; September 15, 2005

Dear Tom Miller:

As I indicated by phone yesterday, I am attaching an additional commentary based on comments made by committee persons during the SAB Meeting earlier this week. No opportunity was available to me to offer these observations earlier than now. I trust these two pages will be forwarded promptly to all members of the committee.

Regards, Gary Kayajanian

I have characterized inorganic arsenic as a potent anti-carcinogen, based on a J-shaped response to exposure levels in drinking water, with the trough “around 50 µg/L.” My view is that the J-shape results from the impact of arsenic on reducing a broad range of cancers caused by other carcinogens. As the level of arsenic increases above 65 - 250 µg/L the impact of this broad anti-carcinogenic response gets overtaken by arsenic’s potency as a carcinogen. Eventually, from the Taiwan data the NAS and I have relied on, arsenic at 400 µg/L in men and 600 µg/L in women, have roughly the same carcinogenic activity as arsenic “below 50 µg/L” [i.e., 10-32 µg/L]. Under this view, if there were no background cancers to prevent, there would be no J-shaped curve – only a monotonically or strictly monotonically increasing exposure response curve.

From her public comments during the September 12-13, 2005 SAB Public Meeting, Chairlady Matanoski characterized any J-shaped exposure response curve that might exist as resulting from complex attributes of arsenic on cancers arsenic causes. She might mistake or mischaracterize cellular or tissue studies with low or no background surrogate cancer effects as supporting the view that no real J-shape curve describes arsenic’s impact on real world cancer levels. Dr. Matanoski asserted that at low dose there are too few cancers to show a threshold for a threshold carcinogen. I take this to mean, where a J-shape is claimed for arsenic, that there would be too few cancers in the trough “around 50 µg/L” for a significant decrease to be observed vis-à-vis “less than 50 µg/L.” But this is not so. First, even with fewer cancers between 42-60 µg/L than between 10-32 µg/L, the bladder and liver cancer mortality rate in each sex is lower between 42-60 than between 10-32 µg/L. Second, the range 42-60 µg/L was initially chosen to provide a baseline for the Administrator’s regulatory decision on arsenic. The trough comparison group can be extended from five villages to ten or even fifteen, with arsenic ranges expanding to 42-110 and 42-256 µg/L. The greater expansion of the trough comparison groups triple to sextuple the number of cancers in the trough to a number more than observed in the 10-32 µg/L category. Several comparisons of cancer mortality rates are reported in Table 1, below. The trough remains real, according to these broader comparisons.

**Table1**

Arsenic Range, Males:	Person Years	# Bladder Cancers; p comparison	# Lung Cancers; p comparison	# Liver Cancers; p comparison	# Bladder + Lung; p comparison	Bl. + Lung +Liver; p comparison
10- 32	23,616	11	12	16	23	39
42- 60	41,191	5; <.03	11; NS	6; <.005	16; <.01	22; <.001
42-110	84,487	12; <.03	24; NS	19; <.02	36; <.02	55; <.001
42-256	113,527	13; <.02	38; NS	37; <.05	51; <.02	88; <.01
Females:						
10- 32	21,523	14	7	14	21	35
42- 60	37,256	6; <.01	4; NS	9; <.04	10; <.003	19; <.0002
42-110	77,154	10;<.01	8; <.09	22; <.05	18; <.001	40; <.0002
42-256	103,585	18;<.01	17; NS	31; <.06	35; <.004	66; <.0006

One issue that troubled the panel was exposure uncertainty resulting from multiple wells in 22 of the villages. In the two lowest exposure five-village groupings, only two of the ten villages had a well with an arsenic level outside the group range. Below in Table 2, the 10-32 µg/L versus the 42-256 µg/L cancer mortality comparisons are made, including only those villages with wells within the range: four of the original five villages between 10-32 µg/L; thirteen of the original fifteen villages between 42-256 µg/L.

**Table 2**

Arsenic Range, Males	Person Years	# Bladder Cancers; p comparison	# Lung Cancers; p comparison	# Liver Cancers; p comparison	# Bladder +Lung; p comparison	# Bl + Lung +Liver; p
10- 32	18,228	8	9	12	17	29
42-256	103,002	7; <.02	34; NS	30; <.07	41; <.03	71; <.004
Females						
10- 32	16,662	12	4	9	16	25
42-256	94,442	13; <.006	13; NS	24; NS	26; <.006	50; <.002

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Dr. Ken Cantor fretted that the exposed population, especially in the Millard County data set compiled by Lewis *et al.*, was compromised by exposure misclassification in the arsenic-“exposed” Millard county population. Such exposure misclassification, he has argued, should diminish the significance of any difference noted between any exposure categories. However, the total cancer mortality in women in the 25-<75 µg/L exposure category *is significantly less than in each of the other categories*, whether impacted by misclassification or not. If there were exposure misclassification, the true relationship between the cancer measure in 25-<75 µg/L and other exposure categories would be even more significant. “Exposure misclassification” in a data set might not sound good, but given the character of these data, it does not undermine the significant finding Kayajanian reported.

These reactive post meeting comments are offered now, because Chairlady Matanoski would not allow them as the SAB Committee opined and I could not have developed the calculations at the meeting site.

Sincerely,  
Gary Kayajanian  
[561] 649-6629

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## 2. From Dr. Gary Kayajanian; September 17, 2005

Tom Miller:

I am sending an additional brief science comment on a low dose bladder cancer comparison from data generally described the 2004 Lamm et al. reference paper. Please pass the comment on to the Arsenic Panel members.

Regards,  
Gary Kayajanian

### Gary Kayajanian's Further Rebuttal Comments on Arsenic Matters

Most of the Panel's thinking focused on a high-to-low dose reading of data sets like those from Taiwan. I would like to examine the very low end of the arsenic exposure continuum by comparing bladder cancer mortality in two US exposure categories: Counties with arsenic levels  $< 3 \mu\text{g/L}$  [ $N = 2765$ ] with those having  $\geq 3 \mu\text{g/L}$  [ $N = 268$ ]. The number of observed bladder cancers [O] in all 3033 US counties when summed becomes the number of expected bladder cancers [E]; for the entire population  $E = O$ , and  $O/E =$  an SMR of 1. So, if all the county groupings with arsenic  $\geq 3 \mu\text{g/L}$  have an SMR  $< 1$ , then the county grouping with  $< 3 \mu\text{g/L}$  arsenic should have a SMR  $> 1$ .

Lamm *et al.* created three county sub groupings with arsenic levels  $\geq 3 \mu\text{g/L}$ . All counties in the group Lamm *et al.* analyzed [ $N = 133$ ] had one or more bladder cancer deaths and relied exclusively on groundwater; this group had an SMR = .94 with a 95% confidence range of .90 - .98. [Table 1 from Lamm *et al.*] An unanalyzed second group of 72 villages had no bladder cancers; the SMR for this group would be 0, with the upper bound unknown to this commenter. Clearly though, if these two groups are pooled the resulting SMR and upper bound each would be less than what Lamm *et al.* reported for its cohort of 133 counties. There is no reason to believe that the group of 63 villages with other water sources Lamm *et al.* excluded from their analysis would report an SMR and an upper bound any different from they reported for groundwater only sources. Then, the pooled counties with arsenic levels  $\geq 3 \mu\text{g/L}$  would have an SMR and upper bound less than 1. As a result, the SMR for the cohort of counties with  $< 3$

$\mu\text{g/L}$  would have to be  $> 1$ , more than the upper bound SMR for the pooled counties with more arsenic. In the low range of arsenic exposures found in US counties [ $0 < 60 \mu\text{g/L}$ ], the greater [ $\geq 3 \mu\text{g/L}$ ] arsenic level is associated with the lower bladder cancer SMR. [Further, according to Lamm *et al.* [their Table 1], above  $3 \mu\text{g/L}$  the SMR decreases as the arsenic in drinking water level increases.]