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

Re: Written submission for the oral public comments section at the Arsenic Review Panel meeting on September 12, 2005

Dear Dr. Matanowski,

I am writing in response to charge C2 in the final 7/25/05 charge to EPA Science Advisory Board Arsenic Review Panel:

*C2: Use of human epidemiological data from direct iAs exposure*

*Question 1: Does the Taiwanese dataset remain the most appropriate choice for estimating cancer risk in humans? What is the rationale for the response?*

*Answer: YES and NO*

**It is well known (the ecological fallacy) that it is impossible to derive a dose-response relationship from an ecological study without additional information. That additional information can be incorporated into a model which can be tested.**

**However it is a fundamental principle of scientific study that if a model does not fit a data set it must be wrong.**

**Of course, all models are wrong, but some models are useful.**

**EPA is trying to do the impossible. It is trying to argue that there is one data set which, by itself, can be used to derive all relevant information about arsenic risk. THAT DATA SET DOES NOT EXIST.**

**When the Taiwan data on internal cancers, bladder and lung, in particular, first came to my attention in 1991 (5 years after it was published by Chen et al. in 1986 and 5 years after EPA should have noticed it) I plotted the data and, as all physical**

scientists do, put the statistical error bars on the graphs to clarify the situation. Some of these plots have been published (although somewhat late!)

"Carcinogenic Risks of Inorganic Arsenic in Perspective", D.M. Byrd, M.L. Roegner, J.C. Griffiths, S.H. Lamm, K.S. Grumski, R. Wilson and S. Lai. *Int. Arch. Occup. Environ. Health* 68, 484-494 (1996).

The salient feature was that many of the plots were excellent straight line fits through the origin. The slopes were large – much larger than any regulator at that time was using - and clearly enough to mark arsenic as a major potential carcinogen. This was a red flag that should have, but was not, heeded by EPA as an immediate incentive to action.

We claim no originality: we discovered that Alan Smith had already come to the same conclusion but without the graphs.

Problems with the ecological study were clear from the start. Subsequent work has only succeeded in unequivocally demonstrating the extent of these problems.

- (1) Concentrations were badly measured, exposures derived there from correspondingly uncertain, and derived doses worse still. It is a simple mathematical result that if ANY dose-response relationship with structure (threshold, superlinear, etc) is algebraically folded with a wide distribution of possible doses the result comes closer to a linear dose-response. Therefore, all that could be derived from the data is one parameter of an assumed model – and the obvious one is a slope of an assumed linear (no threshold) dose-response.
- (2) The assumption was made, and has continued to be made, that the only uncertainty in the data is the statistical uncertainty. This is, of course, usual in the initial stages of any study. This is obviously untrue for the studies (Lamm et al.) of cancer incidence in US counties. There a fluctuation between counties of 30% standard deviation was found which exceeds the statistical error varying between 5% and 20%. Steven H. Lamm, S.H., A. Engel, M.B. Kruse, M. Feinleib, D. M. Byrd, S. Lai, and R. Wilson, (2004) "Arsenic in Drinking Water and Bladder Cancer Mortality in the USA: An analysis based on 133 U.S. counties and thirty-years of experience" But it is also probably untrue for the Taiwan data. A 30% uncertainty added to each point makes any detail less convincing. It should be naively expected that data from the Taiwan areas was (at the relevant period in Taiwan history) less likely to be well recorded. Indeed, the recent work of Lamm and collaborators clearly demonstrates these difficulties.

I have not studied the work of Lamm et al. in enough detail to judge whether the detailed conclusions are valid. But for me, the general conclusion must remain.

**ALL THAT CAN BE DERIVED FROM THE TAIWAN DATA (even 19 YEARS LATER) IS ONE PARAMETER OF A MODEL.**

Many of us were aware of these problems in 1991 and searched for areas where similar arsenic exposures might have occurred. Alan Smith found colleagues in Chile and Argentine. Again, I believe that all that can be derived from the studies in Chile and Argentine is a single parameter of a dose-response model which must be assumed in advance.

**BUT an examination of their reports suggest that THAT PARAMETER IS AS GOOD AS THE SAME PARAMETER DERIVED FROM THE TAIWAN DATA**

CJ Chen told me of the situation in Inner Mongolia. While we believe that our data on skin lesions in Inner Mongolia

"Relationship between Consumption of Arsenic-Contaminated Well Water and Skin Disorders in Huhhot, Inner Mongolia " Tucker et al peer Reviewed Report to ASTDR July 2001

are good, there are no data on the internal cancers.

Bangladesh and SE Asia have come up. Indeed, the number of skin lesions exceeds that of the other regions and boggles the mind. But there are no data so far on internal cancers. (Whether they would have been found already in spite of an anticipated 20 year latency is uncertain)

Rather than trying to get the last tiny drop of information from the SW Taiwan data, EPA should spend time now on figuring out how to get the information needed. Any further data dredging of the SW Taiwan or Chile data should be with the aim of finding tentative hypotheses to test. Making sure that:

- (A) measurements are good;
- (B) that epidemiological study plans are agreed in advance to avoid the fundamental statistical problem of asking the question after you know the answer.
- (C) Making postulates on co factors (e.g cigarette smoking, eating betel nuts)

In other areas of science where similar problems arise, e.g. high energy physics, enormous effort is undertaken, and enormous funds expended for simulation and modeling before the study is done. I do not see that here.

I see three regions where more effort on planning might pay off.

- (1) The NE Taiwan prospective study by Chen et al.
- (2) Bangladesh
- (3) US counties

I am aware of the difficulties in (2) and (3). I will address (3) not because it is the most important but because it has been neglected. (The most recent NAS report implied that such a study could not be done). The study of Lamm et al, (2004) noted above, was

limited by the assumption that the (30%) non-statistical uncertainty in the data point is independent of the arsenic concentration and is the same for each county. It seems to me that a careful look at the publicly available data might enable us to check that assumption; to find some of the causes of variability from county to county and (hopefully) reduce thereby the uncertainty from 30% to 15%. The Lamm et al. study could also be extended to other cancers (lung is even more likely to be linear than bladder) and other medical end points. Already, with the assumption stated above, the study was able to rule out the slope of the assumed linear dose-response derived by the most recent NAS committee from the Taiwan data (but not the EPA-derived slope).

An important fact here is that it is unlikely that it will be possible to derive from these data a believable dose-response slope. But it will be, and is, possible to state what the dose-response slope is not. As stated in physical science studies, to derive an upper limit.

**In conclusion, the question posed is the wrong question. It should not be asked. The very posing of the question is leading EPA in the wrong direction. EPA should clearly and publicly change its goals and admit that it can derive one and only one parameter from the each high-dose data set (which parameters happen to agree roughly between data sets) and for the data at the lower doses of interest in the USA admit it can only (but usefully) provide an upper limit or a model-dependent result. Then, it can put effort in on how, by observation and experiment, the situation might be improved.**

Yours sincerely,

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