

Written Submission to US EPA panel subpanel on arsenic
Richard Wilson
Mallinckrodt Professor of Physics, emeritus
Harvard University
Cambridge MA 02138
wilson5@fas.harvard.edu
April 1st 2010

In September 2005 the EPA Science Advisory Board asked the following question.

Does the Taiwanese data set remain the most appropriate choice for estimating cancer risk in humans? What is the rationale for the response?

My conclusion was that the question posed is the wrong question. It should not have been asked. Once asked and criticized it should have been withdrawn. The very posing of the question led EPA in the wrong direction. I have seen no sign that the EPA took any notice of the criticisms and never responded in any way to my detailed comments. This, by the way is a major failing of EPA. Unlike NRC and NASA they do not give detailed responses, or even acknowledgments, to public comments. For the person making the comments this is like sending his letter into a black hole.

I here repeat and upgrade the comments that I made 5½ years ago. Most of them still apply today.

EPA has failed to clearly and publicly change its goals. It should admit that it can derive one and only one parameter from each high-dose data set. If these parameters agree roughly between data sets, particularly in different countries, then there is some reassurance that the effect being studied is real and not an artifact - such as the famous study relating the number of brooding storks and the number of newborn babies in Germany.

In answering questions about the effects at the lower doses of interest in the USA, the EPA should admit the high dose data can only (but usefully) provide an upper limit or a model-dependent result. Once this admission is made the EPA can put effort in on how, by observation and experiment, the situation might be improved.

The data from Taiwan was an 'ecological study'. 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.

It is to be hoped that the models the EPA use are useful. But the use of each model must be specified and the limitations understood.

In emphasizing the Taiwan data as the definitive data set to derive a regulatory level the EPA was, and probably still is, trying to accomplish the impossible.. EPA was in 2005, and may still be, 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 were presented in public meetings in 1991 and have been published (although somewhat late!) in:

"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 Professor Alan Smith of UC Berkeley had already come to the same conclusion but without the graphs.

The 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, super linear, 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 of cancer incidence in US counties published in 2004. There a fluctuation between counties of 30% (standard deviation) This exceeds

the statistical error which varies 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 than more recent data. Indeed, the recent work of Lamm and collaborators clearly demonstrates these difficulties.

EPA commented on the work of Lamm et al., in 133 counties noted above on June 28th 2007. They emphasized the uncertainties. But they failed to note that despite these uncertainties, which Lamm et al. had already pointed out, the data can be used to put an UPPER LIMIT on any assumed linear dose response relationship for bladder cancer. Of course the data show nothing about the effect on lung cancer which is expected to be a bigger effect.

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. Professor Alan Smith found colleagues in Chile and

Argentina. Again, I believe that all that can be derived from the studies in Chile and Argentina is a single parameter in each case of an dose-response model which must be assumed in advance.

BUT an examination of their reports suggest that the single parameter is in agreement between Taiwan, Chile and the Argentine. This crucial agreement is lost when undue emphasis is placed on the Taiwan data.

In 1991 Professor CHJ Chen of Taiwan told me of the situation in Inner Mongolia. While we believe that our data on skin lesions in Inner Mongolia are good, there are no such good data on the internal cancers.

"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. Steven H. Lamm,Zhen Dong Luo,Ge You Zhang, Ye Min Zhang, Richard Wilson, Daniel M. Byrd, Shenghan Lai, Feng Xiao Li, Michael Polkanov, Ying Tong, Lian

Loo, Stephen B. Tucker, and the Inner Mongolia Cooperative Arsenic Project (IMCAP) An Epidemiologic Study of Arsenic-related Skin Disorders and Skin Cancer and the Consumption of Arsenic-Contaminated Well Waters in Huhhot, Inner Mongolia, China Health and Environmental Risk Assessment, 13:713-756. (2007)

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 statistical and logical problems arise, e.g. high energy physics, enormous effort is undertaken, and enormous funds (hundred million dollars or so for the Large Hadron Collider) 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 incorrectly 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%. This unfunded study could well be extended to lung cancer to derive an upper limit for the assumed linear slope for lung cancer caused by ingested arsenic..

Thus 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, the data may be used to derive an upper limit.

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But please: abandon the scientifically illogical approach of the EPA as exemplified in the 2005 report and think the problem through from scratch.