CRITICISM OF THE TOXICOLOGICAL REVIEW OF INORGANIC ARSENIC (CAS No. 7440-38-2)

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Cancer risk assessment at EPA has classic origins: first, find a significant increase in a cancer measure at high dose of a suspect chemical – this allows the Agency to classify the agent as a hazard; second, use a strictly monotonic (default) extrapolation from that high dose value to zero dose that likely overstates the health benefit of lowering actual exposure levels from a low value to a lower one; finally, set the standard for modeling the cancer data so high that no modeling – the Agency's or alternatives – can meet it … so the Agency default model has to prevail, even though it may have less to recommend it scientifically than an alternative. What EPA regulators fail to grasp (or want to ignore) is that extrapolation modeling has no utility in the face of significant contradictory data. In the present case, relying on a default model is harmful and costly, and fails to describe arsenic as beneficial or anti-carcinogenic at levels around 50 ppb in drinking water.

THE ADMINISTRATORS' CHARGE

EPA has endorsed the Taiwan data set as presented by Morales, Ryan et al. by relying on it multiple times, without self criticism, to claim a strict monotonically increasing relationship between arsenic levels in drinking water wells and bladder cancer over a range from 0 to 934 ppb arsenic. There was never a need for Agency regulators to extrapolate from 934 down to 0 ppb, because there were significant contrary data in the same table Morales, Ryan and EPA employed at the most relevant, 60 to 0 ppb arsenic exposure range. Morales, Ryan and then EPA did not find the significant contrary data. When Administrator Browner first asked, and Administrator Whitman later re-asked, Agency scientists whether the arsenic standard in drinking water should be lowered from 50 ppb or not, they established the most relevant exposure range to the scientific inquiry. When examined the bladder cancer rate in the five villages with the lowest arsenic exposure [10 to 32 ppb -- the surrogate for "lower"] was about four-fold and significantly higher than the rate in the five villages with the next lowest arsenic exposure [42 to 60 ppb – the surrogate for "50 ppb"] both in men and women. The same pattern of higher cancer rates at the lowest exposure range also held for liver and lung cancers among men and women. The significance of these finding for the three cancer types, taken together is $p < .001$ in men and $p < .001$ in women.

In the Millard County data set collected and published on by EPA scientists, the same pattern of cancer reduction of all cancers is associated with arsenic in drinking water levels between >25 to 75 ppb compared to arsenic levels between 0 to 25 ppb. The cancer observation is hugely significant in the women. [Heart disease deaths are significantly reduced in the men at arsenic levels between >25 to 75 ppb.] The weak excuse that a few cancers being misclassified would overturn these findings fails on the significance of these findings. A good statistician would tell EPA regulators that if misclassified data were found significant, the properly classified data likely would be more significant, contrary to Dr. Cantor's pro-Agency pronouncement.

The Agency regulators and others fancy themselves skillful in grouping the Taiwan villages so that the lowest exposure category [0 to 100 for EPA, 10 to 126 for Lamm] subsumes the "50 ppb" and "lower" categories, forcing modeling by extrapolation from higher exposure levels. They ignored the on-point mandate from two Administrators. When Morales, Ryan et al. used a narrower grouping of villages [0 to 50, >50 to 100, … ppb], a visual inspection of their data table 5, clearly revealed a higher mortality rate associated with the "0 to 50 ppb" villages than with the ">50 to 100 ppb" villages. Too bad, their two lower end exposure groupings failed to comply with the Administrators' charge and resulting groupings, and they missed the significant findings I found. The instant technical document might have greater value and relevance to regulatory decisions if data evaluations are keyed to the Administrators' regulatory charge.

THE BEST EVIDENCE

The best evidence of arsenic's behavior is the most relevant evidence. Relevant to what: to the Administrators charge, professional standards and common sense; to humans, over the arsenic-in-drinking-water range from 0 to around 50 ppb. Agency regulators are mistaken to settle on a single epidemiology study for their cancer claims; instead, they should seek out cancer data associated with arsenic exposures ranging from 0 to ~50 ppb in well-conducted studies. They should look for associations and dose response curves that are strong, specific and, above all, consistent within that range. ["Best evidence" is really a higher manifestation of the "weight-of-the-evidence" practice EPA claims to follow.] I would suggest the Millard, Utah data set, collected by and published on by EPA scientists, but disregarded by EPA regulators as an appropriate second data set. If Agency regulators have problems with the outside reference source in this study [the rest of the state of Utah] as having cancer rates upwardly confounded by too much drinking and smoking and too many minorities, then they should use the 0 to 25 ppb segment of the Millard population as the reference for the >25 to 75 ppb segment, which acts as the surrogates, respectively, for the new 10 ppb and for the old 50 ppb arsenic in drinking water standard.

Regulators should not transition from one "critical study endpoint" to another even if the process occurs over time and can be sold as a natural shift. (See the first bullet point on page 117.) Instead, one should seek significant data on the fullest sound set of endpoints for hazard determination and risk assessment purposes – like the grouping of six cancers and, better yet, "total cancers" from the Millard County data set. (See, Kayajanian, G. (2003), Arsenic, Cancer and Thoughtless Policy, Ecotox. Environ. Safety 55, 139-142.)

The best evidence is not animal studies, physiological, pharmacological or other chemical based reports. While these lesser studies may explain how or why epidemiological results are the way they are, or generate hypotheses about what epidemiology data might show, lesser studies can only support, never supplant well done human studies. [The technical document is very deficient in relating data in these lesser studies to the best evidence.]

THE TAINTED ARSENIC REVIEW PROCESS

In it historic review of arsenic risk assessment (§ 5.3.1, beginning on page 112 of the Draft), document authors recite a process in which EPA regulators adopted Ryan's extrapolation modeling of the Taiwan data with minor tweaks from the journal paper she co-authored. [Ryan was the more credentialed American author, as a professor at Harvard.] Ryan then sat as member of the NRC panel, to review, in effect, her own work product disguised as an EPA work product. That original NRC panel and a subsequent one, called at the behest of Administrator Whitman, were deferential in her presence to her specific expertise on the Taiwan data set and her analysis of data in it. Later, when the SAB Drinking Water Committee reviewed the EPA and NRC work products, Dr. Ryan sat at the table with Committee members and made an extended presentation of the NRC's work product. The arsenic review process, elements of which Dr. Ryan dominated, resulted in the Agency's acceptance of it favorite high-to-low dose modeling, from which now the Agency is unwilling to deviate. As for Dr. Ryan, good scientists know better than to review their own work, because doing so taints the review process and destroys the value and conclusions of the review.

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