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Via E-mail

Angela Nugent, PhD (nugent.angela@EPA.gov)
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Dear Dr. Nugent,

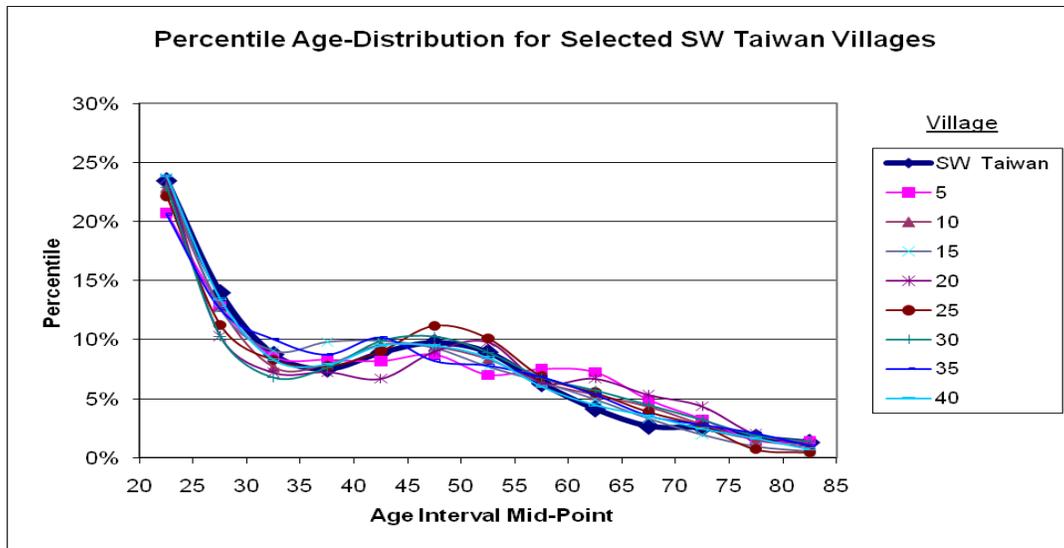
This report on the Toxicological Review of Inorganic Arsenic (February 2010) is submitted by Consultants in Epidemiology and Occupational Health, LLC. (CEOH) on its own behalf as a scientific contribution. We have been active contributors to the epidemiological analysis of the human health risks, including cancer, from arsenic exposure for over 30 years. We hope that this document will be viewed as contributing to the deliberative scientific process.

The Toxicological Review has based its quantitative risk analysis of the oral carcinogenic potency of arsenic on the Wu et al. (1989) SW Taiwan data base and has concluded that their results are (a) “robust” and (b) demonstrate “significant positive associations between arsenic exposure and cancer risks for all of the endpoints analyzed, even in low-exposure groups [Page F-7].” This is only a consequence of their parsimony in modeling and in analysis.

The only parameters in their dose-response risk model are age, age², and dose (median) [Page 127]. No other parameters have been tested. The core assumptions that the Toxicological Review makes are (1) that the only sources for variability in village cancer risks are age-distribution and arsenic exposure and (2) that the median is the informative and representative metric of the village well arsenic exposures. Their findings are not robust but, rather, are a consequence of their assumptions.

Model Variables:

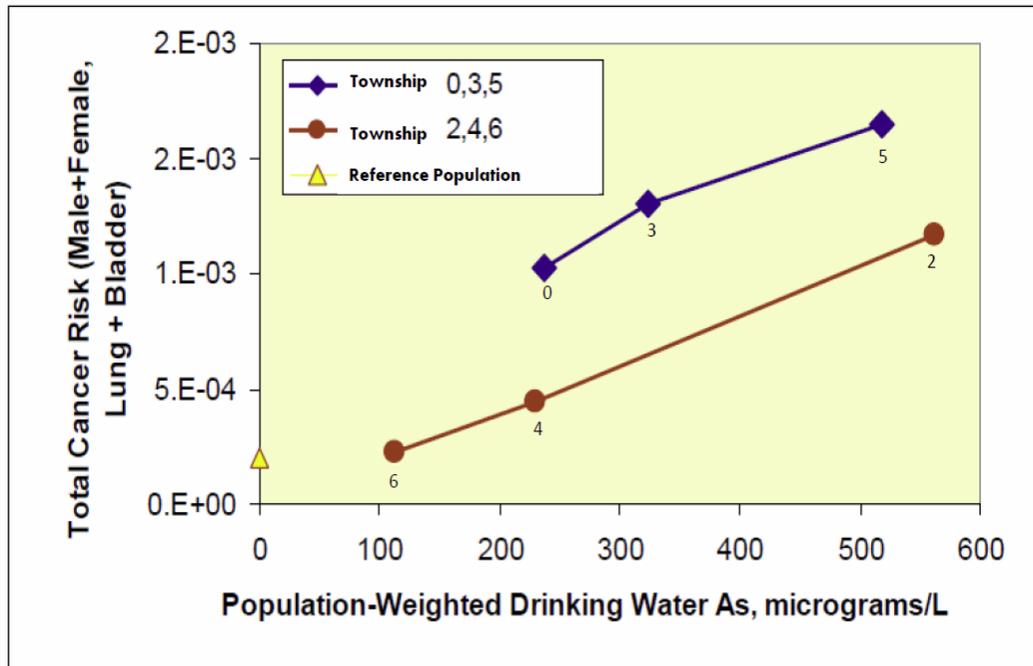
1. The age distributions vary little among the villages and differ little from the comparison population. While age is clearly a risk factor for mortality and for cancer mortality, there is little to suggest that age variability is significant among the study villages and thus as a risk factor.



2. The NRC data set (corrected) contains a number of factors that might be examined as explanatory variables, and were not.¹ Foremost are the factors that led to the selection of the study villages. The study area was chosen because of the occurrence of Blackfoot Disease (BFD), a disease unique to SW Taiwan. No case has been seen anywhere else in the world, in spite of chronically high exposure levels. While the Tox Review consistently refers to the study area as the BFD-endemic area, it does not point out the uniqueness of this disease and how its presence might be a marker for some other etiological agent or factor. The analytic findings are not robust with respect to the endemicity of Blackfoot disease.

3. The villages in the study were selected because they were located in one of six BFD-endemic townships and Figure F-1 (Corrected) [page F-4] in the Tox Review clearly demonstrates that the cancer risk varies both by township and by arsenic exposure. The data for Figure F-1 come from the 42 study villages in the six selected townships and from the SW Taiwan reference population. Chen et al. (1985) showed the differences in cancer risk by township. The publication (Lamm et al., 2007) that presented the arsenic dose-responses by township has not been cited in the Tox Review. "Township" should be examined in the model as an explanatory variable and is not. The analytic findings are not robust with respect to the inclusion of site or township in the model.

¹ The Table A-10-1 in the "Clarifications on the Draft 2010 Toxicological Review of Inorganic Arsenic..." is incorrect. The column titles have been corrected but not the data errors.



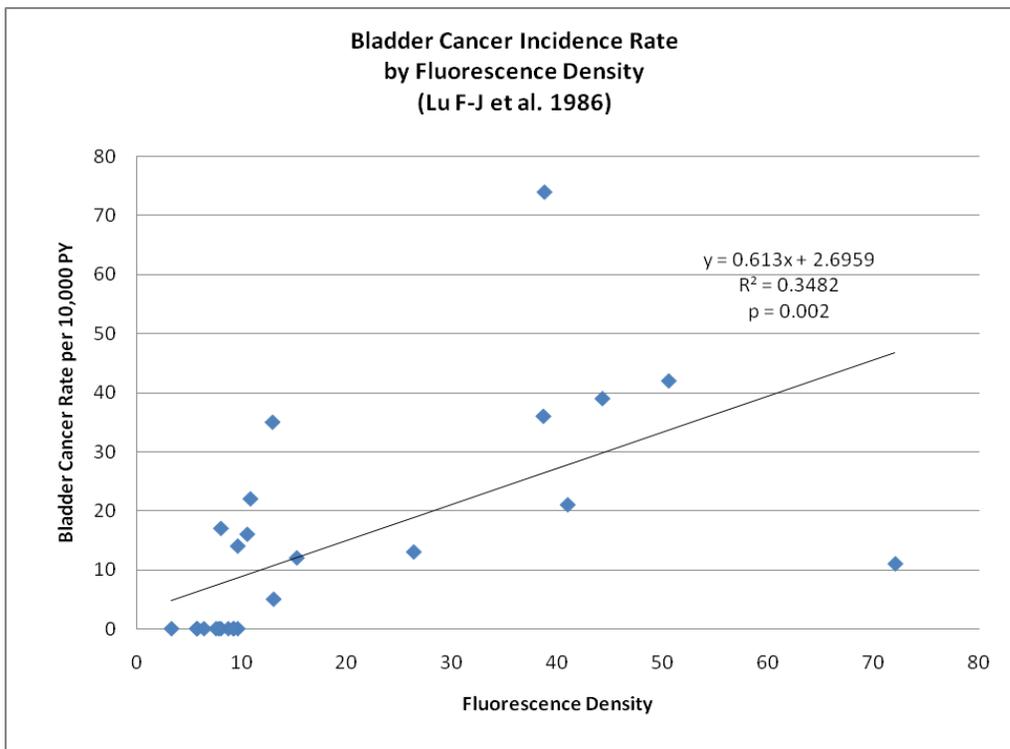
- The water supply for the BFD-endemic area came from two aquifers, with differences in pumps, appearances, and water quality. The differences were known to the residents, to the early epidemiologists (Chen, Wu, and Wu, 1962), and to the hydrologists and geochemists. The shallow aquifer had low arsenic levels both in the endemic area (median 40 ug/L) and in the non-endemic areas (median 30 ug/L). The deep (artesian) aquifer had high arsenic levels both in the endemic area (median 780 ug/L) and in the non-endemic areas (median 380 ug/L). The analytic findings are not robust with respect to the water source or aquifer.

The Tox Review has assumed that the arsenic level in the drinking waters of SW Taiwan outside of the BFD-endemic areas is zero ug/L. This is contrary to the published literature of Chen, Wu and Wu (1962) that is again acknowledged by both C-J Chen (1985) and MM Wu (1989).² The arsenic levels in the surface well waters in the non-endemic areas (n = 61) had a range up to 250 ug/L and a median of 30 ug/L. This median of 30 ug/L would have served as a reasonable data-based estimate for the water arsenic exposure in the SW Taiwan region rather than the Tox review assumption that the comparison area drinking water had zero ug/L arsenic. The analytic findings would not be robust to the use of the 30-40 ug/L level, particularly for the low-dose villages.

- Wu et al. (1989) note that, besides arsenic, the high-arsenic well water contained “ergotamine, organic chlorides, and fluorescent substances. There is an entire literature on the humic substances in the well waters of the BFD-endemic area that the Tox Review has taken no notice of. While a PubMed search for “Taiwan Humic” in 2006 yielded 39 references, a similar search in 2010 yields 132 references. The Third International Congress on Arsenic in the Environment recently in Tainan, Taiwan (As2010) held a full section on arsenic and humic substances in the aquifers of the Blackfoot Disease area. Humic substances have been considered to be a possible

² It should be noted that the Chen and Wu of the 1962 literature (KP Chen, HY Wu, and TC Wu) are not the same as the Chen and Wu of the late 1980s literature (CJ Chen and MM Wu).

risk factor for BFD and are therefore an important risk factor for health considerations in this area. The word “humic” does appear in the Tox Review, and the word “fluorescent” only appears with respect to microscopic assays. The extensive research work on fluorescent substances in the BFD-endemic area waters by Professor FJ Lu is not even cited. The Lu et al. 1986 study demonstrated a stronger correlation coefficient (R^2) for fluorescent intensity and bladder cancer incidence than that shown in Wu et al. (1989) for arsenic and bladder cancer mortality. It has not been mentioned. Fluorescence appears to be a risk factor for bladder cancer, whether it is an independent risk factor has to be considered.



6. The Tox Review has not considered the nature of the arsenic in the drinking water. Wang et al. (2003) had demonstrated that only half of the arsenic was As_2O_5 and that nearly 50 % of the arsenic in the drinking water was humic acid-bound. Whether both fractions contributed equally to the carcinogenicity has not been considered. The Tox review is deficient in that it has considered the specificity of the outcome variable (which cancer, which gender) and issues on toxicological mechanism, but it has not considered the specificity of the exposure. The expertise of the Agency in exposure description and explanation has not been brought to bear on the risk assessment for SW Taiwan study.
7. The validity of the arsenic measurements has not been addressed in the Tox Review, nor has their suitability for risk inference at low arsenic concentrations. The major paper addressing these issues (Brown and Chen, 1995)³ has not been cited.

³ Brown KG and Chen C-J (1995) reported that the data do not appear suitable, however, for the more refined task of dose-response assessment, particularly for inference of risk at the low arsenic concentrations found in some U.S. water supplies. The problem lies in variable arsenic concentrations between the wells within a village, largely due to a mix of shallow wells and deep artesian wells, and in having only one well test.

The Toxicological Review has not sought to determine the toxicological nature of the high arsenic well waters other than to attribute the toxicity solely to the arsenic content without specifying the nature of that arsenic content. The initial report on internal cancers from the BFD-endemic area (Chen et al., 1985) presented graphic analyses by township, by BFD-endemicity, and by water source.⁴ All three of these exposure variables are missing in the Tox Review. The Tox Review does not consider whether the quantitative level of arsenic in the well water is a measure of its carcinogenicity or a marker of it. Are the factors in these well waters that uniquely cause Blackfoot disease the same as those that cause internal cancers?

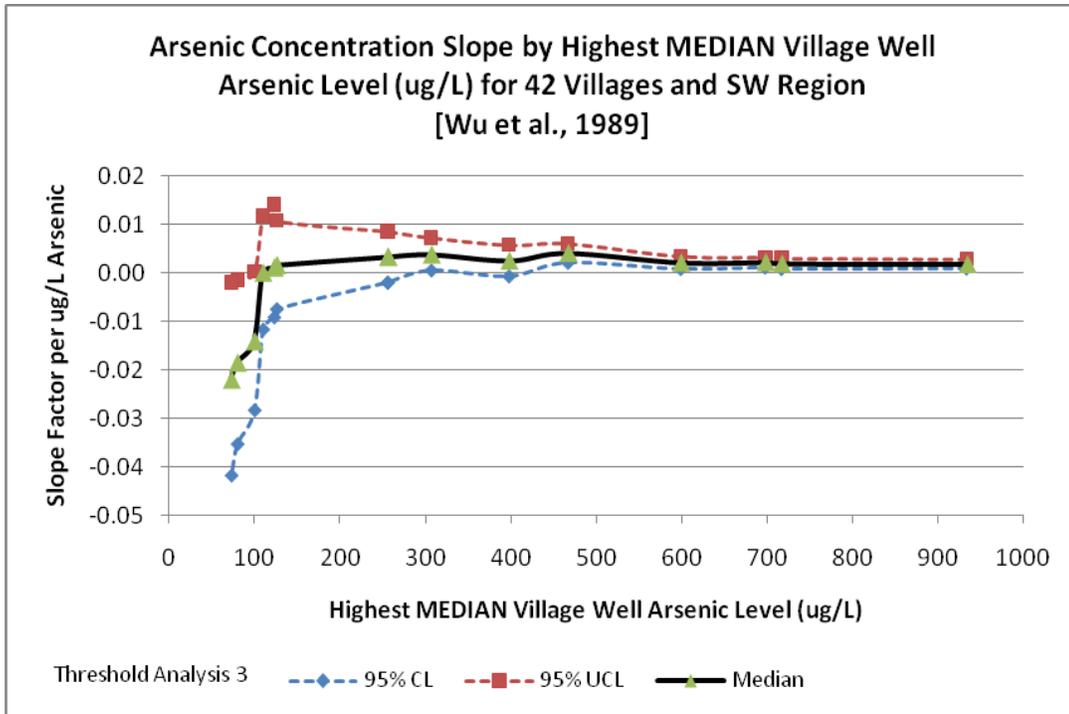
Arsenic Exposure Measures and their Analyses:

The analysis in the Tox Review is limited to the use of the median as representative metric for the village arsenic exposure. Brown and Chen (1995) have already addressed this. While we will continue our discussion using the median, we will later examine the differences in findings that might have occurred with using either the mean or the maximum as the summary exposure metric.

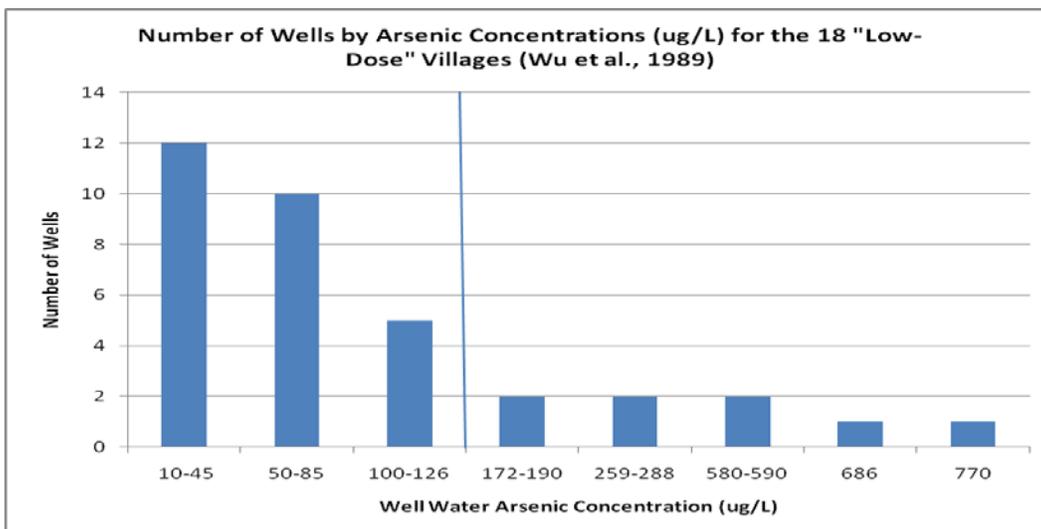
The Tox Review concludes (Page 575) that “the Taiwanese data show robust and significantly positive associations between arsenic exposures and cancer risks for all the endpoints analyzed, even in low exposure groups. No evidence was found that either 400 ppb or 150 ppb represent “threshold” arsenic measurements in drinking water below which cancer risks are not increased. Likewise, the analyses do not support the existence of a “village effect” related to the degree of dependence on artesian versus shallow wells.” These statements are incomplete.

1. The term “low exposure group” is both undefined and unclear and appears to be distinguished from “low-dose” group. In previous literature, low dose has meant the villages with a median arsenic level less than 150 ug/L. In more rigorous toxicological terminology, dose would be designated in mg/kg/day and exposure would be designated in ug/L. Most of the document refers to the “low-dose” group and intends to contain the 18 villages with a median well water arsenic level of less than 150 ug/L.
2. Using the median metric, it is correct that no “threshold” is found at either 150 ug/ or 400 ug/L. However, if the range below 150 ug/L had been examined, a “threshold” effect would have appeared at < 100 ug/L. [See Lamm et al. April 20, 2010 letter to Dr. Elaine Faustman for details.]

⁴ Chen C-J et al. (1985) reported (1) “A dose-response relationship was observed between SMRs of the cancers and blackfoot disease prevalence rates of the villages and townships in the endemic area.” And (2) SMRs of cancers were greater in villages where artesian wells were used as the drinking water source than in villages using both artesian and shallow wells, and even greater than in villages using shallow wells only.”



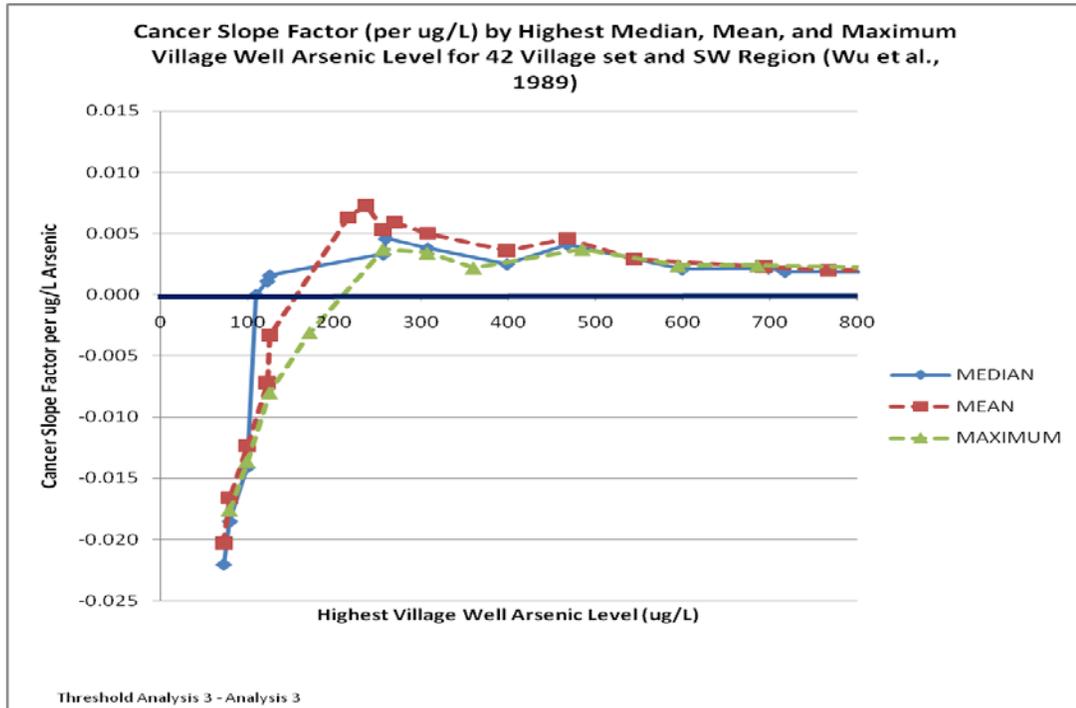
- It appears that “low exposure group” means the residents of the “low-dose” villages, i.e., median well water arsenic measurement < 150 ug/L. However, the residents of some of the “low dose” villages have high exposure wells. The 18 “low-dose villages” are not the 14 or 15 “low-exposure villages.” Eight of 35 wells (23%) are at > 150 ug/L. Inclusion of the residents of the villages with those wells is incorrect in an analysis of “low exposure groups.”



- Three summary arsenic exposure metrics for the villages are the median, mean, and the maximum. The median is a measure of central tendency with no consideration given to more extreme levels. The mean is a measure of central tendency that includes some consideration of more extreme levels. The maximum is a measure of distribution that

incorporates the excision of extreme values, as would the minimum. The analysis by mean or by maximum take into consideration the presence of the high exposure wells in the “low-dose” villages. The analytic findings will not be found to be robust to the choice of summary exposure metric.

The graph below shows the cancer slope factor over the exposure range and how it differs depending on choice of summary exposure metric.



The graph shows that the slope is robust with respect to summary exposure metric at exposures above 250 ug/L, showing statistically significant positive slopes. The slope is also robust with respect to summary exposure metric at exposures below 100 ug/L, showing generally statistically significant negative slopes.

In the range of 100 ug/L to 250 ug/L (the upper range of interest for low exposures), the slope is not robust with respect to summary exposure metric. The exposure level at which the model indicates a positive slope is at 110 ug/L for the median, at 216 ug/L for the mean, and at 256 ug/L for the maximum. Non-positive slopes are seen at 100 ug/L for the median, 126 ug/L for the mean, and 172 ug/L for the maximum. Thus, the examination of the cancer slope factor regarding village arsenic exposure and cancer mortality is markedly affected in the mid-range by the choice of the summary exposure metric.

The level at which a “threshold effect” is demonstrated from this data set is affected by the choice of summary exposure metric. These are the findings that develop from this particular dataset. No implication on mechanism of action is proposed. This analysis is being presented specifically for this data set and is not meant to demonstrate the findings of any other dataset.

5. The Tox Review (Page 575) stated that “Likewise, the analyses do not support the existence of a “village effect” related to the degree of dependence on artesian versus shallow wells.” No analysis is presented for grounding that statement. The Tox Review in Figure 1 does show a township effect (mis-labeled as a village effect in the Tox Review. Both Chen et al. (1985) and Lamm et al. (2003) have presented their evidence of a “village effect related to the degree of dependency on artesian vs. shallow wells.”

The NRC, EPA, and SAB have had a great concentration of attention on translating the Taiwan data so that it could subsequently be analyzed with respect to the US population. We would propose that the data first be analyzed for Taiwan on the basis of ug/L exposure rather than trying to convert them to a mg/kg/day basis. The modeling of the risk from arsenic in drinking water in ug/L in Taiwan would not need an assumption of either body weight or water consumption. Once the modeling for the ug/L drinking water was complete, then adjustment for non-drinking water arsenic ingestion could be demonstrated.

In summary, the risk analysis in the Toxicological Review of Inorganic Arsenic (February 2010) is deficient in its exposure analysis, both in its consideration of exposure confounders and its choice of summary exposure metric.

Cordially,

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Reference List

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