



MEMORANDUM

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U.S. Environmental Protection Agency, 1200
Pennsylvania Ave., NW., Washington, DC 20460

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SUBJECT: **Review of 2010 USEPA "Toxicological Review of Inorganic Arsenic (in Support of IRIS)**

INTRODUCTION

The discussion below evaluates EPA's February 2010 profile entitled "Toxicological Review of Inorganic Arsenic" (EPA, 2010), drafted to support endpoints in the Integrated Risk Information System (IRIS). The document is a redraft of earlier profiles on arsenic (EPA, 2005), principally to provide a more detailed review of existing epidemiological studies, discuss the mode of action (MOA) of arsenic, and address recommendations made by the National Research Council and the EPA's Scientific Advisory Board.

It is our view that the document is fundamentally flawed, as the combined weight-of-evidence show:

- a) the data from the underlying study (Morales et. al., 2000), for which the human exposures to arsenic are "assumed" (based on village location and well water concentration), do *not* adjust for the confounding variable of cigarette smoking,
- b) studies conducted in the same country (Taiwan) on [Blackfoot] diseased individuals use the "<10 µg/L" category as the "referent" (no effect) dose, thus obviating the usefulness of predicting increases in cancer rates at concentrations that are below the current MCL for arsenic,
- c) at least four studies show evidence that smoking and oral arsenic exposure act synergistically, supporting occupational studies and *in vitro* evidence that arsenic acts as promoter or co-carcinogen, and
- d) that low levels of arsenic in drinking water (<10 ug/L) do *not* induce bladder or lung cancer in any of the studies conducted on U.S. populations.

SUMMARY OF MORALES ET AL.

The toxicity profiles use information taken from human data published in a seminal risk assessment by Morales et al. (2000). Both the 2005 and 2010 EPA profiles use the Morales data set, originally obtained from Taiwanese population data that was published by previous peer-reviewed studies as the basis for deriving the current cancer slope factor (CSF). These original data came from 42 villages in an arseniasis-endemic area in a poor region of southwestern Taiwan (emphasis added to discern another Taiwan study below). What this means is that, in the past, arsenic in drinking water was so elevated that most of the population is diseased, showing frank symptoms of Blackfoot Disease (dry gangrene, hyperkeratinosis, skin lesions, etc.). The amount of literature reviewed by EPA in the current (2010) toxicological review is voluminous, including retrospective U.S. studies that showed no association between low levels of arsenic in drinking water (<10 ug/L) and cancer. Despite U.S. and European data that show contrary evidence regarding exposure to arsenic in drinking water resulting in lung or bladder cancer, EPA has decided to hold on to using the original Taiwanese data (they have not wavered from using these data since the early 1990s).

The 2010 risk assessment is an updated IRIS risk assessment of the 2005 IRIS Toxicity Profile. The update is based on recommendations by the both the NRC and the SAB. The 2010 version uses data obtained from Morales et al. (2000), which was the key document that drove the MCL for arsenic from 50 $\mu\text{g/L}$ to 10 $\mu\text{g/L}$. EPA's original (and still "current") CSF posted on IRIS (1.5 mg/kg-day-1) was based on the incidence of skin cancer in this population.

EPA's 2005 "draft" toxicological profile changed the measurement endpoint from skin cancer to mortality due to lung and bladder cancer "because they are the internal cancers most consistently seen and best characterized in epidemiology studies (EPA, 2005)". This change of endpoint resulted in an increase of the CSF by a factor of approximately 3 (this CSF was never posted as EPA requested the SAB review mentioned above).

The current 2010 toxicity profile increases the CSF by an additional factor of 6 (for a total difference of 18). The majority of this increase (about two thirds, as these authors interpret it) is based on the fact that EPA "adds" bladder cancer and lung cancer deaths, EPA adjusts U.S. intake of water to account for the use of Taiwanese drinking water rates in Morales et al., and, EPA estimated the lifetime cancer incidence in U.S. populations by using a "modified version" of the "BEIR IV" relative risk model (the same model was used for assessing radon risk, and the subsequent risk assessment of radon is highly controversial).

SUMMARY OF COMMENTS ON TOXICOLOGICAL REVIEW

Cancer Studies

Section 4.2.2 (Cancer Bioassays) of the Review states that "Cancer bioassays with inorganic arsenic have obtained negative results with mice, rats, hamsters, rabbits, beagles, and Cynomologus monkeys..." Additionally, no human ecological or epidemiological studies have shown "low dose" (<10 $\mu\text{g/L}$) drinking water concentrations to be carcinogenic. Further confounding the assessment of

the carcinogenicity of arsenic, the Review states that “mechanism of action” for arsenic has yet to be developed because all of the animal models tested are negative.

Similar to other EPA documents, it appears that positive data are the only data given credence, and “negative” data or studies are denigrated. Studies using low dose arsenic exposures in drinking water (e.g. in New England, where arsenic observed more frequently in residential groundwater) are deemed “equivocal”:

“Although dose-response relationships have been observed for the majority of cancers noted in areas with high levels of arsenic in their drinking water, results for low-level arsenic epidemiologic investigations (primarily from the United States and Europe) have been equivocal in the relationship between these cancers and arsenic exposure.”

This appears to be written to downplay negative studies, and, based on these authors review, the word “negative” should have been using in place of the term “equivocal”. In summary, this critique of the current IRIS toxicity cannot discern how EPA can promulgate a CSF that would require arsenic to be regulated at levels that occur below concentrations observed in the naturally occurring water, soil or sediment. These authors believe that EPA should second guess the use of particular assumptions and models it used, as the current MCL for drinking water was developed because it is at the current limit of “best available treatment” technology.

Additionally, because trace levels of arsenic are ubiquitous in food and water, intake of low levels of arsenic would clearly show a “threshold”, above which it would start to accumulate in the body (i.e. the amount converted by the liver and excreted from the body is exceeded by amount taken in via food and water). Based on a careful review of the EPA 2010 document, it is clear, from the effects data presented, that this “threshold” is above 10 µg/L for drinking water.

Arsenic Acts Synergistically with Smoking

The toxicity profile indicates that, both *in vivo* and *in vitro*, arsenic can act as a co-carcinogen or co-mutagen (meaning arsenic alone has no effect, but combined with another agent, it will cause cell transformation and/or cancer). Additionally, contrary to traditional epidemiological protocol, the EPA analysis uses Taiwanese data that does NOT adjust for smoking. This is particularly disturbing, given that tobacco smoking is *the* primary risk factor for both lung and bladder cancer. More importantly, the EPA 2005 toxicity profile cites four peer-reviewed studies from four different countries that clearly show that arsenic intake, combined with smoking, results in a “synergistic” effect (i.e. 2 + 2 = 8). The following studies are cited in the EPA 2010 toxicological review:

- The 2004 Taiwanese study of Chen *et al.* states that “The etiologic fraction of lung cancer attributable to the joint exposure of ingested arsenic and cigarette smoking ranged from 32% to 55%.” This result is virtually identical to a meta-analysis of a range of other studies addressing occupational arsenic exposure (Hertz-Picciotto *et al.*, 1992) which found a synergistic effect associated with cigarette smoking and arsenic on lung cancer, in which 30% to 54% of lung cancer cases were attributable to both exposures. This means, for smokers, up to half of the Taiwanese population lung cancer rate may be attributable to the combined effect

of oral arsenic exposure and smoking, neither of which would be caused by exposure to oral arsenic or smoking alone.

- A 1995 cohort study by Tsuda *et al.* on 454 people who drank arsenic polluted water in Japan showed that, “for lung cancer, there was evidence of synergistic effects between arsenic exposure and smoking history”.
- In a case-control study conducted in Chile by Ferreccio *et al.* (2000), found that synergism between arsenic and smoking was seen in person’s drinking water containing more than 200 ug/L. An odds ratio of 13.1 was expected if the effect was additive, but they determined an odds ratio of 32.0 and, for those who never smoked, the odds ratio in the >200 ug/L range was only 8.0.
- A study on 6,669 residents in Wisconsin by Knobeloch *et al.* (2006) found that “tobacco use was also associated with higher rates of skin cancer and appeared to synergize the effect of arsenic on the development of skin cancer”.

The 2010 study completely ignores the fact that this synergism would strongly bias the calculation of a higher CSF because the cancer death rates used in the exposed population in southwestern Taiwan were contrasted against to those in an unexposed “comparison” population (either southwestern Taiwan or the whole country) and just assumes the increase in cancers in the exposed population is solely due to arsenic in drinking water.

Uncertainty about Arsenic Dose-Response Relationship

This contrasting Taiwanese study also used a human exposure of <10 $\mu\text{g/L}$ as the “referent” (baseline) exposure, and there was no increase in the “standardized mortality ratio” (i.e. observed cancers/expected cancers) for any drinking water concentrations below 100 $\mu\text{g/L}$.

These authors, as well as other authors cited in both EPA reports, believe the dose-response relationship in the data as very “noisy” (e.g. no obvious dose/response relationship; note in Morales *et al.* (2000) that the lifetime risk at 1,500 $\mu\text{g/L}$ is approximately the same as the risk observed at 50 $\mu\text{g/L}$). The original paper of Morales *et al.* (2000), from which EPA obtained its data, states “...it is likely that a variety of factors, including cigarette smoking, use of bottled water, and dietary intake of inorganic arsenic, could influence or even confound the model” and that it is “important to consider this and other sources of uncertainty when interpreting the results.” It also appears that the authors of the 2010 EPA Toxicological Review “guessed” at the background dietary intake of arsenic, which is most likely, based on the incidence of arseniasis, higher than they cite (e.g. it appears they did not take into consideration the tradition of chewing betel nuts that are wrapped in chewing tobacco).

Analysis of the Taiwanese data by Lamm (2003, 2006) and Kayajanian (2003) found that the dose-response relationships used for the EPA 2010 review are inconsistent. Lamm found that this was particularly true when arsenic in village wells fell below 151 ug/L. EPA defends their study by stating that both of those studies (which were published in well respected journals) have “severe limitations”. But EPA then states that “it is important to recognize the complexity and limitations of the Taiwanese

data set”, that “most population groups have zero cancer deaths”, and that “the data are very ‘noisy’”. So, EPA denigrates the exact same data set on which the 2010 EPA CSF was derived!

They also state that the “use of simpler models (linear regression, for example) can (and did) produce misleading results”. This is interesting, given that NRC also used linear regression modeling in its previous assessment of arsenic toxicity. In other words, their choice of the [BEIR IV/Poisson] model, as well as some of the other conservative assumptions they used (e.g. normalizing the U.S. water ingestion rate to the “tropical” Taiwanese ingestion rate), was somehow more superior to what was published in several other peer-reviewed journals.

Although the SAB concluded that the Taiwanese database is still the most appropriate source for estimating bladder and lung cancer, they also “noted considerable limitations within this data set” and suggested that that “one way to mitigate the limitations of the Taiwanese database would be to include other relevant epidemiological studies from various countries.” From these author’s perspective, the EPA comprehensively reviewed other studies, but completely dismissed the negative studies (particularly in the US and Europe) and focused on the positive studies to bolster their argument. It would be impossible for one reviewer to go through all these papers in detail but, according to EPA’s reports, the weight of evidence is that high levels of arsenic in drinking water may cause bladder cancer, and that levels below 10 $\mu\text{g}/\text{L}$ (the current U.S. MCL) cannot discern any adverse effect in humans.

Given the shortcomings of the Taiwanese data and study, the 2005 analysis made the “decision” (which was also used in the 2010 report) that has no citation or basis in regulatory policy (from what we could discern):

“It has been decided that the oral slope factor will combine the lung and bladder cancer results. Because cause of death is listed as only from one cause (e.g., either lung or bladder cancer), there is no double counting; therefore, combining the two cancers will account for deaths from both types of cancer.”

These reviewers disagree with this risk management strategy. Tumorigenesis via environmental agents is typically “organ-specific”, i.e. the mechanism for bladder cancer would not be the same as the mechanism for lung cancer. There are a whole host of agents that cause both bladder cancer and lung cancer (most of them being reactive metabolites of cigarette smoke). There are few, if any, toxic agents that cause lung cancer following oral exposure. If EPA had conceived a common “mechanism of toxicity”, the above statement could be justified....but they cannot and do not.

Modeling

It is also unclear why EPA deviates from the use of the Benchmark Dose model (e.g. BMDS software) to determine the point of departure (POD) for the benchmark response (they cite the documentation but do not mention or address its use in the derivation of the CSF). The BMDL (lower confidence limit on the benchmark dose) is typically used as the basis for the POD for linear low-dose extrapolation, which is the general dose–response assessment approach applied to most carcinogens. The selection of the

BIER IV model is not presented in a transparent fashion, nor is the derivation of the CSF using this model.

SUMMARY

These authors conclude that the EPA 2010 Toxicological Review is, at best, inaccurate because it relies on a dataset that does not correct for smoking. This is truly hard to believe, given that it was known, well before EPA's first draft Toxicological Review (2005), that a synergistic effect was evident between arsenic and tobacco smoking (and, given EPA's opinion on the carcinogenicity of second hand cigarette smoke, their use of a data set that does not correct for smoking appears disingenuous). It is not necessary to criticize the absence of the BMDS model or the use of the highly controversial Bier IV model because the data going in to the model is fundamentally biased.

A recent paper by Celik et al. (2008) conducted a systematic review of the literature examining the association between arsenic in drinking water and the risk of lung cancer in humans. They found that "only one of the ecological studies presented results adjusted for potential confounders other than age", that "different study designs carried out in different regions provide support for a causal association between ingesting drinking water with high concentrations of arsenic and lung cancer", but that lung cancer risk at "lower exposure concentrations remains uncertain". This critique is in full agreement with that assessment, and recommends that EPA recognize the "severe limitations" of their current estimation of the CSF. We also recommend that EPA only use ecologic data for persons who have been exposed to arsenic in drinking water but have not used any form of tobacco (including the traditional practice of chewing betel nut combined with tobacco).

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