

Arsenic, Drinking Water, and Health

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EXECUTIVE SUMMARY

There is considerable controversy over whether chronic exposure to arsenic in drinking water at concentrations found in the United States poses a health risk. The current maximum contaminant level (MCL), 50 $\mu\text{g}/\text{L}$ [50 $\mu\text{g}/\text{mL}$ =50 parts per billion, or ppb]*, has been in place, at least as an interim limit, since 1942. A 1999 report of the National Research Council (NRC 1999), commissioned by the U.S. Environmental Protection Agency (EPA), concludes that the MCL does not achieve EPA's goal for public-health protection and advised downward revision as promptly as possible (NRC 1999). Subsequently, the EPA proposed an MCL of 5 $\mu\text{g}/\text{L}$, changed it to a final rule of 10 $\mu\text{g}/\text{L}$, and then, with the change of administration, reopened the topic to consider 3 $\mu\text{g}/\text{L}$, 5 $\mu\text{g}/\text{L}$, 10 $\mu\text{g}/\text{L}$, and 20 $\mu\text{g}/\text{L}$. The purpose of this American Council on Science and Health Report is to review issues and sources of uncertainty affecting assessment of potential health risks related to drinking water in the U.S. Some background is included on how these issues arose, as well as a review of the 1999 NRC report, to formulate a position based on the current science concerning how much of a risk of adverse health effects actually exists from arsenic in drinking water in the United States.

ACSH concludes that there is clear evidence that chronic exposure to inorganic arsenic at concentrations of at least several hundred $\mu\text{g}/\text{L}$ may cause: (1) cancer of skin, bladder, lung (and possibly several other internal organs, including kidney, liver and prostate), and (2) noncancer effects, including classic cutaneous manifestations that are distinctive and characteristic of chronic arsenic poisoning (diffuse or spotted hyperpigmentation and palmar-plantar hyperkeratoses). Noncancer effects may be multi-systemic, with some evidence of peripheral vascular, cardiovascular and cerebrovascular disease, diabetes, and adverse reproductive outcomes. Further study is needed to know if beneficial effects of arsenic in animal studies apply to humans.

ACSH concludes that there is little, if any, evidence of a detrimental health effect in humans from inorganic arsenic in drinking water at the current MCL of 50 $\mu\text{g}/\text{L}$ or below, either in the United States or elsewhere. As noted in the 1999 NRC report, "No human studies of sufficient statistical power or scope have examined whether consumption of arsenic in drinking water at the current MCL results in an increased

We use $\mu\text{g}/\text{L}$ in this document, although As concentrations and MCL are popularly spoken of in ppb.

incidence of cancer or noncancer effects" (NRC 1999, p.7). Based on our review described in this report, the American Council on Science and Health finds that the limitations of the epidemiological data available and the state-of-the-science on the mode-of-action of arsenic toxicity, including cancer, are inadequate to support the conclusion that there are adverse health effects in the United States from arsenic in drinking water below the current limit of 50 µg/L.

INTRODUCTION

Arsenic (As) is a naturally occurring element, ubiquitous in the environment in both organic and inorganic forms. Inorganic arsenic, the more toxic form, is found in groundwater, surface water, and in many foods, such as fish, rice and grains. Human exposure to inorganic As is mainly through drinking water. According to a recent FDA Diet Study, the average adult As intake from food is 53µg/day, of which about 20% (13µg) is inorganic. (For perspective, at the currently approved MCL of 50µg/L, total As intake from 2L water would be about 100µg, with the large majority of that being inorganic; at 10µg/L, total As would approximate 20µg, again mostly in the inorganic form).

In some parts of the world—Taiwan, Mexico, western South America (Chile, Argentina), Bangladesh, Inner Mongolia—As occurs at high levels naturally in drinking water, at levels ranging from several hundred to well over one-thousand µg/L. In some western states, Americans are also exposed to drinking water at higher levels than the current 50 µg/L MCL, although these levels are in the 50-100 µg/L range. These states include New Mexico, Arizona, Nevada, Utah, southern California, Idaho, and Nebraska. Most of those exposed to higher As levels are in rural areas, with Albuquerque NM as the only urban area with elevated levels.

Chronic exposure to high levels of inorganic As in drinking water—in southwest Taiwan, study populations had median exposures of 780 µg/L (Tsai 1999)—has been found to be causally associated with a variety of adverse health effects, including cancers (skin, lung, bladder) and numerous noncancer diseases.

On the other hand, some nutritional authorities believe, based on studies in a variety of animal species, that As may be an essential nutrient, with a daily requirement of perhaps 20µg per day. In certain patients who are depleted of As (e.g., chronic dialysis patients), correlation with nerve and vascular injuries has been reported (Mayer et al., 1993). Goats, minipigs, rats, and chicks, under experimental conditions of semi-

synthetic diets, have become functionally impaired on diets containing very low amounts of arsenic. They have, however, shown improved (lower) rates of reproductive abnormalities and/or growth retardation on diets supplemented with 350-4,500 ng/g of arsenic (NRC 1999, p.260).

Regulatory Chronology

The current MCL of 50µg/L has been the standard for arsenic in drinking water in the United States since 1942. The Safe Drinking Water Act (SDWA) was passed in 1974, directing the U.S. Environmental Protection Agency (EPA) to establish national standards for contaminants in public drinking-water supplies. Enforceable standards are set at levels at which no adverse health effects in humans are expected and that can be achieved with the use of the best technology available. In response to passage of the SDWA, EPA adopted 50µg/L as the interim standard for total arsenic in drinking water in 1975. An amendment to the SDWA in 1986 required EPA to set an MCL and a maximum contaminant level goal (MCLG) for arsenic by 1989. A further amendment to the SDWA in 1996 required EPA to propose an MCL by January, 2000, and to finalize it by January, 2001. EPA proposed a standard (MCL) of 5µg/L on June 22, 2000 (FR 65 38888), and invited public comments on the proposal and on 3µg/L, 10µg/L, and 20µg/L as alternatives.

On October 20, 2000, exactly one month after the deadline for submission of public comments on the proposed rule, EPA announced that additional data had been received that the Agency was considering during the development of the final regulation (FR 65 6307-63035). The new information consisted of a peer-reviewed article by Morales *et al.* (2000). This paper re-analyzed data from previously published Taiwanese studies. It also addressed risk of lung cancer, and extended the dose-response modeling for risk of bladder cancer from arsenic in drinking water that had been reported in the NRC report *Arsenic and Drinking Water* (NRC 1999) and had been essentially adopted by EPA for its proposed rule. As an ecological study, its analysis of health effects was limited by confounding factors.

Additionally, the notice made available the cost curves used to develop the costs published in the proposal of June 22. EPA invited public comments by November 20. EPA also asked the Drinking Water Committee (DWC) of its Science Advisory Board (SAB) to review its June 22 proposal, the principal task being "to consider certain technical issues raised by EPA relative to its proposed reduction of the MCL for arsenic

in drinking water from 50 to 5µg/L" (EPA 2000).

EPA published a "final" (our quotes) rule for arsenic in drinking water of an MCL 10µg/L (up from 5 µg/L in the proposed rule) and an MCLG of 0µg/L, on January 22, 2001(FR 66 6975-7066). The rule applies to both community water systems (CWSs) and non-transient non-community water systems (NCTNCWSs). On March 20, 2001, the new EPA Administrator, Christie Whitman, announced that EPA would delay the effective date for the arsenic rule for 60 days. This was in accordance with a White House memorandum of January 20 communicating President Bush's plan to ensure that his appointees had the opportunity to review new regulations in order to avoid "costly, burdensome, or unnecessary regulation"(FR 66 37620). "In order to provide safe and affordable drinking water the Administrator announced plans to seek independent review of the science behind the arsenic standard and the cost estimates used to develop the rule"(FR 66 37620). The 60-day extension was then followed by a 9-month extension making the effective date for the arsenic rule February 22, 2002, to allow time to obtain independent review of the science, cost, and benefit analyses used to support the arsenic in drinking water regulation. The compliance date for the MCL issued in January, 2001, was left unchanged. Until January 23, 2006, the MCL for arsenic is 50µg/L, which only applies to CWSs and there is no MCLG for arsenic (FR 66 37620).

On July 19, 2001, EPA requested public comments on the January 22 "final" rule and invited input on a range of MCL options for arsenic from 3µg/L to 20µg/L. The comments must be received by October 31, 2001. As described above, EPA has undertaken additional analyses of science, cost, and benefits issues, and these reports are now available. "Once the analyses are completed, EPA will consider this new information and provide for an additional opportunity for public comment on the new analyses along with EPA's preliminary conclusion about whether the January 2001 arsenic rule should be revised, and if so, what the revised standard should be. EPA will consider the public comments, as well as the record for the arsenic rule for this reconsideration, and issue a final decision on whether to revise the January 2001 rule. If EPA does decide to revise the January 2001 rule, EPA will issue a new revised rule."(FR 66 37621).

Additional analyses requested by EPA

The three reports that are referred to are an update of the National Research Council's subcommittee report on arsenic in drinking water (NRC 1999), a benefits analysis by the Arsenic Rule Benefits Review Panel (ARBRP) of the Executive

Committee of the EPA Science Advisory Board, and a report of the Arsenic Cost Working Group to the National Drinking Water Advisory Council (NDWAC). The NRC update of its report was released in September 2001, the NDWAC report had been finalized and submitted to the EPA Administrator (<http://www.epa.gov/safewater/arsenic.html>), and the ARBRP had submitted a review draft to the SAB Executive Committee (www.epa.gov/sab/drrep.htm). The ARBRP report advised the EPA to conduct a new economic analysis of any arsenic standard for drinking water, considering more factors and methodologies than were used in an analysis supporting the January rule. Among other recommendations, the NDWAC report found that "The value of existing national cost estimates is now limited by the large uncertainty associated with the estimated outcomes...new effort should be made to establish a better system [of estimating cost]..." (Executive summary of the NDWAC report).

Recent studies

The panel writing the NRC update arrived at similar conclusions to the 1999 panel, after reviewing new studies published subsequent to the earlier panel's review. These newer studies, including at least one not analyzed by the NRC subcommittee, are discussed below.

Chiou et al (2001) studied over 8,000 northeastern Taiwanese by determining incident urological cancers (kidney and transitional cell carcinoma, TCC, or bladder cancer) and relating these to individual well-water As levels. The number of new bladder cancers over a 3-year period was found to be elevated in those with prolonged exposure to As levels over 100 µg/L. However, the short period of evaluation was probably responsible for the few cases noted: there was a total of only ten TCC cases during the 3-year study period. The wide confidence index, even for the most exposed group, makes this study too imprecise to be relied upon in a quantitative risk assessment.

The Ferreccio study (2000) came from northern Chile, where the water has had very high As levels, historically in the 800-900 µg/L range until 1970 (more recently, around 40 µg/L). The Chilean group analyzed incident lung cancer cases, using a case-control method. They determined As levels from a historical municipal database of various As levels at various times; the cases (and controls) were obtained from eight public hospitals. All study patients were interviewed regarding drinking water sources, smoking, and other historical factors. The unusual control selection methods used in this study make its

conclusions—significantly elevated lung cancer risk (OR 8.9) in the most-exposed group, As level 200-400 µg/L—seriously suspect. They did find evidence of synergism between smoking and As exposure, which seems to be valid.

Kurttio et al (1999), in a case-cohort study, analyzed whether bladder and kidney cancer was related to As exposure from drinking water in Finland. The As levels in this group were quite low, but smokers exposed to As levels above 0.5 µg/L had a significantly elevated risk of bladder cancer. Interestingly, however, non-smokers in the same exposure group had a lower risk of bladder cancer—although the RR was only slightly, not significantly, diminished.

The NRC panel did not address data from a study conducted in southwest Taiwan (Guo and Tseng, 2000), which analyzed the dose-response between As in water and bladder cancer death rates in ten townships (approximately 500,000 people), and total cases reported to the National Cancer Registry from 243 townships, and 1,862 bladder cancer cases. There was no association found between bladder cancer and As levels of less than 640 µg/L in drinking water (although there was an association at higher levels).

The IMCAP (Inner Mongolia Cooperative Arsenic Project) study (Tucker et al, 2001) assessed risk of skin diseases, including cancer, in over 3,100 people who used 184 wells in three villages. Arsenic levels ranged from less than 10µg/L to 2,000µg/L. Skin cancer developed in eight residents, each of whom also had other skin disorders. Two exposure metrics were used to gauge total As burden, “peak arsenic concentration” and “cumulative arsenic dosage.” All the skin cancer cases occurred in areas whose As levels were 150µg/L or higher.

ARSENIC AND HUMAN HEALTH: OVERVIEW

We now turn to sources of uncertainty related to assessment of health risks from arsenic in drinking water in the U.S. and how they have arisen. This leads us to an overview of selected events that have made arsenic in drinking water such a prominent U.S. health concern in the past ten years and discussion of the NRC report (NRC 1999) on arsenic and drinking water, that the EPA commissioned and relied on heavily in its proposed rule (MCL of 5µg/L) of June 22, 2000, and, to a lesser extent, in its final rule of January 22 (MCL of 10µg/L). Issues aside from health effects, e.g., economics and cost-benefits, are considered by EPA in setting a rule; the NRC report addresses the science exclusively. Of course, as discussed in the chronology above, the final rule was essentially put on hold with the change of administration in Washington in January, 2001, and the topic of setting a standard for arsenic in drinking water was reopened.

Arsenic's effects on human health have been studied for centuries. Although it has a reputation as a poison, most of its uses over the past 2 centuries have been as a medicinal. The recent controversy over its adverse effects in drinking water exposures emanates from data accumulated from several countries over the last 20 years, demonstrating that As is a toxin and carcinogen when exposure to high levels for a prolonged period occurs. There is no evidence supporting its toxicity or carcinogenicity at currently approved U.S. exposure levels.

Arsenic and skin cancer

The U.S. Environmental Protection Agency produced a health assessment document for inorganic arsenic in 1984 containing a qualitative and quantitative carcinogen risk assessment for both inhalation and ingestion routes of exposure (EPA 1984). Risk estimates from arsenic in drinking water were based on a study conducted in a region of southwest Taiwan, endemic to blackfoot disease (gangrene due to vascular occlusion), that showed an association between prevalence of nonmelanoma skin cancer and ingested arsenic (Tseng 1968; hereafter the "Tseng study"). Arsenic intake was based on arsenic concentrations in wells used for drinking water—Tseng's group stated that most had As levels in the 400-600 µg/L range, although Tsai (1999) reported a mean of 780 µg/L in the same region—and on age (age was assumed to be the duration of exposure) of 40,421 persons personally examined by medical teams. A special report of the Risk Assessment Forum of EPA followed shortly thereafter on skin cancer and nutritional essentiality (EPA 1988) because "Several EPA offices raised questions about the assessment for the ingestion exposure, including: the validity of the Taiwan study and applicability of the dose-response assessment to the U.S. population, the interpretation and use of arsenic-associated skin lesions, and the role of arsenic in human nutrition (the 'essentiality' issue)" (EPA 1988, p.1). The Forum's 1988 report is described in detail in Chapter 2 of the NRC report (NRC 1999).

In particular, based on the Tseng study and other similar reports, in 1988 EPA classified inorganic arsenic a human carcinogen by the oral route. It also used the Tseng study for quantitative risk assessment of skin cancer in the U.S., although with many uncertainties. The U.S. lifetime estimate of risk was estimated as an additional 3-7 skin-cancer cases per 100,000 persons, for each µg/L of inorganic arsenic in drinking water. At 10µg/L, that would be an additional 3-7 cases of skin cancer per 10,000 lifetimes.

It is worth noting some reservations expressed in the Forum's report about risk

estimates at low exposure that remain sources of uncertainty in EPA's current (January 22, 2001) risk assessment. For example, "absent animal data or reliable human data under conditions of low exposure, the shape of the dose-response, if any, at low doses is uncertain". (EPA 1988, p.31). It is also noted that evidence of nutritional essentiality of trace amounts of inorganic arsenic would affect any interpretation of the health risks at low exposure levels. Experimental studies with rats, chicks, minipigs, and goats have suggested the "plausibility" of essentiality in humans(EPA 1988, p.31).

An additional concern, that has been at least partially addressed since the Forum's report, is the lack of information on intake of inorganic arsenic from a diet consisting principally of rice, yams, and fish, both from arsenic in the food itself and from rehydrating rice and dried yams in cooking with arsenic-contaminated water. More is known now about the arsenic content of food, both in the study area and in the U.S. The issue remains relevant to the NRC report of 1999 and to EPA's risk assessments for its proposed and final rules (June, 2000, and January, 2001) because they are based on studies conducted in the same general region as the Tseng study, i.e., the endemic region of southwest Taiwan, although not in exactly the same villages. The endpoints used by the NRC and EPA are mortality from bladder and lung cancer. Much of the data on tests for arsenic concentrations in the village wells, used to determine exposure to arsenic, appears to be from the same source as the Tseng study, but no records are available on exactly which villages and which wells were used in the Tseng study.

It is now thought that the dietary intake of inorganic arsenic from the food itself in the Taiwan study area is roughly on the order of 50 $\mu\text{g}/\text{day}$ (equivalent to drinking two liters of water per day at an arsenic concentration of 25 $\mu\text{g}/\text{L}$), compared to about 1-20 $\mu\text{g}/\text{day}$ in the U.S. (Schoof et al, 1999). The NRC report notes that some factors, such as poor nutrition and arsenic intake from food might affect assessment of risk in Taiwan or extrapolation of results to the U.S. (NRC 1999, p.8). The final EPA rule has attempted to adjust risk estimates for arsenic in food and arsenic added from cooking with arsenic-contaminated water, but accounting for arsenic in food requires some questionable assumptions. For example, nothing is known about the distribution of arsenic intake in food in the endemic area. By contrast, a U.S. study (MacIntosh, *et al.* 1997; as cited in EPA 2000, p.13)) found that dietary arsenic in the U.S. ranged from less than 1 to 123 $\mu\text{g}/\text{day}$ (mean 10.2, standard deviation 6.5, in a sample of 785 adults), with the variability apparently due to variations in diet rather than in regional differences in arsenic content of the same food items.

Even if one makes the simplifying assumptions that dietary intake of inorganic arsenic is the same for all persons in the endemic area of Taiwan (e.g., 50 µg/day) and that the biologically effective dose from food is the same as from water for equivalent administered doses, one still does not know the shape of the dose-response curve from 0 to 50 µg/day. Thus some assumption must be made, such as continuation of a linear, or uniform, extrapolation for water in arsenic at high concentrations. But it is more biologically plausible, and what is known about arsenic's effects in biological systems strongly suggests, that the shape of the dose-response curve at low arsenic concentrations is sublinear (NRC 1999, p.213). Indeed, it is possible that the dose-response to ingested As follows a threshold model, in which the risk is nil until a certain exposure level is attained; some experts hold that this is a more likely theory than the linear response assumed by the panel. Although the panel states that "the several modes of action that are considered most plausible would lead to a dose-response curve that exhibits **sublinear** characteristics at some undetermined region in the low-dose range," (page 253), the report states quite clearly that, absent clear evidence to the contrary, the "default" dose-response assumption is one of linearity.

Arsenic and internal cancers

EPA's Risk Assessment Forum report in 1988 evaluated the evidence linking ingested arsenic and the occurrence of cancers involving internal organs (EPA 1988; Appendix C). Many of the references were case reports, but two epidemiologic studies (Chen *et al.* 1985; Chen *et al.* 1986) were singled out for further discussion in the Forum's report. Tseng and coworkers (Tseng *et al.* 1977) had noted that the most common cause of death in patients who had either skin cancer or blackfoot disease (due to the very high levels of As in SW Taiwan's artesian wells) was carcinoma at various internal sites. Chen *et al.* (1985) began investigation of the population of the endemic area, the same general area that had been studied by Tseng some 15-20 years earlier, and found that the mortality rates were elevated for cancers of the kidney, bladder, skin, lung, liver, and colon. Chen *et al.* (1986) reinforced the findings of arsenic-induced cancer in the lung, bladder, and liver, based on a case-control study. The Forum's report (Appendix C) notes, however, that further details of the data were needed to assess the dose-response, specifically information on age and arsenic concentrations in the drinking water--the exposures (arsenic concentrations) were not specified beyond being grouped into four categories, (<300µg/L, 300-599µg/L, >600µg/L, and "undetermined.").

Those additional data of interest to EPA were first published in a letter to the *Lancet* (Chen *et al.* 1988). The authors noted that various cancer mortality rates were significantly higher than for the general population of Taiwan, and that a significant dose-response relationship was observed between arsenic concentrations in drinking water from artesian wells and the mortality rates for cancers of the bladder, kidney, skin, prostate, lung, and liver. Smith *et al.* (1992) extrapolated the summary data in the *Lancet* letter to the U.S. and concluded that "the population cancer risks due to arsenic in U.S. water supplies may be comparable to those from environmental tobacco smoke and radon in homes". This was cause for concern, if not alarm, within parts of the EPA community. One might say that the first shot had been fired in the controversy over risk of arsenic in U.S. drinking water.

The arsenic risks in the U.S. suggested by Smith and colleagues were considered ill-founded by some, for several reasons. For example, the cancer mortality rates for each broad range of arsenic concentrations (spanning 300µg/L in the first two groups and twice that in the last group) had to be treated as occurring at a single value in each group. The data are ecological, i.e., arsenic exposure is not known for individuals, making it subject to the "ecological fallacy". (The NRC report discusses problems with risk assessment based on ecological data (NRC 1999, p. 269)). The background population mortality rates for all of Taiwan were used as intercepts, with exposure to arsenic in drinking water assumed to be zero. The endemic area, however, is not representative of Taiwan as a whole: it is an extremely impoverished rural area where people principally survive on a diet of rice, dried yams, and fish. Some questioned the validity of applying those low-dose risk estimates to a different country or culture, such as the U.S.

These methodological issues are worth noting because they have largely persisted, to varying degrees, through the analyses of the NRC and the EPA. The EPA proposed rule (June, 2000) used the NRC analysis (NRC 1999), which was based on more detailed data (42 points from the endemic area instead of 3) and applied more conventional models for dose-response (variations on the Poisson regression and the multistage-Weibull models), but the issue of extrapolating risk estimates from high doses to low doses is common to risk assessments in general. The question of whether to use all of Taiwan for a comparison population, some other external population for comparison, or no comparison population at all, has been taken up by both the NRC subcommittee and EPA's Science Advisory Board (EPA 2000, p.4), and dose-response analysis is very sensitive to the choice.

Similarly, the appropriateness of extrapolating risk estimates from the endemic area to the U.S. has continued to receive considerable attention, largely because of the potential effects of poor nutrition, arsenic in food and in water used for food preparation, cultural/lifestyle differences including the availability and quality of health care, and the low selenium levels in Taiwan. With ecological exposure data, one can only match mortality rates in a group (the group being a village in the endemic area) to the arsenic concentrations in the wells tested in the village. One cannot adjust for confounders such as smoking, which is a well-known risk factor for bladder cancer and especially lung cancer.

After reviewing the article by Smith *et al.* (1992), the current author contacted an author of the Taiwan studies (Chen) requesting a more detailed set of data to see what a plot of the data might suggest about the shape of the dose-response curve. Chen sent data for 60 villages instead of just the original 42, containing mortality data for cancer of the bladder, liver, lung, and skin, all recorded between 1973 and 1986 and cross-classified by 5 year age intervals and 11 intervals for arsenic concentrations. Plots of the age-standardized mortality rates for female and male bladder cancer are shown in Figure 1a,b (Brown and Chen 1995a). The dotted line is the maximum likelihood estimate assuming only that the true dose-response curve is nondecreasing and it appears nonlinear. It is rather obvious that one or two of the groups at the low exposure end don't fit well with the rest of the groups and further analysis pointed to two specific villages, referred to as Villages 3-H and 3-5. Chen could find no explanation why the mortality rates would be so high in those two villages, at such low arsenic concentrations, so the villages were treated as outliers and deleted from the data. When Villages 3-H and 3-5 were omitted, the plots in Figure 1a,b changed to those shown in Figure 2a,b, which appeared more reasonable. It was apparent that data analysis, at least for this set of 60 villages, would be required in fitting any conventional parametric dose-response model to detect any villages that might have undue influence on the outcome, in either direction (checking for outliers is a common practice in statistical regression). (The NRC report, that will be discussed below, analyzes data from a smaller number of villages (42 instead of 60), but Villages 3-H and 3-5 are included (NRC 1999, A10-1). We found no indication that the NRC data had been examined for possible outliers.)

Taking the approach one step further, data for all 60 villages were used (instead of 11 groups of villages) and the individual well concentrations were examined instead of just relying on the median value for each village. There was only one well test for 24

(40%) of the villages (presumably there was just one well) and in the villages with more than one well test, the values often covered a wide range. This variability was explained as largely due to a mix of shallow wells and deep artesian wells (Brown and Chen 1995b). Later, for the data supplied to the NRC subcommittee, Chen reverted to the original 42 villages that he had reported on earlier. A plot of the well tests for the 22 villages of those 42 with more than one value is shown in Figure 3 (values are from NRC 1999, Table A10-1, which also shows the median values used by the NRC). The problem with variable well tests in a village is that the distribution of usage is unknown, so that one only knows that any arsenic-induced cancers occurred within the range of possible arsenic concentrations. This poses a problem of misclassification error of exposure. One can still demonstrate that risk of cancer tends to increase as arsenic concentrations increase (i.e., that there is a trend), but it is a limitation for the more refined task of actually estimating the magnitude of risk at specific arsenic concentrations (i.e., for dose-response assessment).

In 1996, the U.S. EPA asked the NRC to review the arsenic toxicity data base and evaluate the scientific validity of EPA's 1988 risk assessment for arsenic in drinking water (the Risk Assessment Forum's 1988 skin cancer risk assessment described above). Specifically, the NRC subcommittee was asked to (paraphrased): (1) review EPA's characterization of human health risks from ingestion of arsenic compounds in food and drinking water and the associated uncertainties; (2) review available data on cancer and noncancer health effects from arsenic in drinking water; (3) review data on the toxicokinetics, metabolism, and mechanism/mode-of-action for their implications of assessing health risks; (4) identify research priorities to fill data gaps. It is also noted that a formal risk assessment for arsenic in drinking water was neither requested nor provided (NRC 1999 p.2). Discussion of the NRC report (NRC, 1999) follows, with emphasis on how sources of uncertainty, most of which have already been mentioned above, were addressed.

The recent studies discussed above (with the exception of the Guo and Tseng study, as noted) were also reviewed by the NRC 2001 panel in their assessment of arsenic's carcinogenicity (Chiou et al, 2001; Ferreccio, 2000; Kurttio et al, 1999; Tucker-IMCAP, 2001). As these have been addressed in a previous section, we need not devote much more time to them. One further point must be made, however: the IMCAP authors state, "The dose-response curve for skin cancer is best described...by a frequency-weighted

model with a threshold at or near 150 [µg/L] or by a most likely estimate hockey-stick model with a threshold at 122 [µg/L] arsenic. These results are consistent with the threshold-model analysis of the Taiwan data set that had showed a threshold at about 120 [µg/L].” The NRC 2001 panel, shifting emphasis, stated, “The data appear to be adequately described by such statistical models; however, they are also well-described by a nonthreshold linear model” (NRC 2001, pg.51).

Based on data from Taiwan, Chile, Argentina, Finland, and Bangladesh, the NRC 1999 update panel concluded that there was enough evidence to claim that bladder cancer and lung cancer are caused by ingestion of arsenic, as well as skin cancer. Increased risk of other cancers, such as kidney and liver, have also been reported, but the evidence is not strong (NRC 1999, p.131). It is noted that with minor exception, the epidemiological evidence for cancer comes from places where populations were exposed to arsenic concentrations in drinking water of at least several hundred micrograms per liter (p.130). Inhaled arsenic is a recognized cause of lung cancer (p.100), and studies of lung cancer among workers exposed to airborne arsenicals indicate a linear dose-response relationship over a broad range of exposure(p.130).

Only a few U.S. studies are described in the NRC report. A case-control study conducted by Bates *et al.* (1995) in Utah concludes that "Overall, no association was found between bladder-cancer risk and arsenic exposure" (p.99). An EPA cohort study by Lewis *et al.* (1999), also conducted in Utah that appeared subsequent to the 1999 NRC report, extends a previous investigation by Southwick and colleagues. The results are mixed, with more outcomes significantly low than significantly high for both cancer and noncancer effects, at average exposure levels up to 191 µg/L. The rate of prostate cancer was significantly elevated in males, but bladder cancer rate was not higher in either gender, and cancer of the respiratory system and all malignant cancers, as a group, were significantly **reduced** in both genders.

Engel and Smith (1994) conducted an ecological study on arsenic in drinking water and cardiovascular mortality in 30 U.S. counties where the average arsenic concentration was greater than 5µg/L. They found no increased rate of all cancers, nor of lung cancer, in those counties with As levels over 20µg/L in their water. Of course, this was not a primary outcome measurement.

As noted above, with minor exceptions, epidemiological studies for cancer are based on populations exposed to arsenic concentrations in drinking water of at least several hundred micrograms per liter. Studies conducted in the U.S. are among those where populations are exposed to concentrations well below those levels. Of particular

concern to EPA is whether cancer (or noncancer) effects are likely to occur at the current MCL of 50µg/L. **But no human studies of sufficient statistical power or scope have examined whether consumption of arsenic in drinking water at the current MCL results in an increased incidence of cancer (NRC, 1999, p.7).** There is no evidence of As-related skin disease, which is often the most reliable early sign of As toxicity. Thus, there is no direct evidence of an arsenic health effect in the U.S.

Many aspects of the above-cited studies make them unreliable for use in a scientifically valid risk assessment. In addition, the lack of knowledge about the mechanism of As carcinogenicity (and thus the dose-response curve, especially at low exposures) make choice of extrapolation curve crucial in determining real risk. Certainly, a nonlinear model with a threshold for carcinogenicity above the current MCL is at least as plausible as the EPA default assumption of a linear dose-response. Little is known about latency of effect. There is much evidence implicating As as a human carcinogen in several organ systems at high exposure levels. **There is no clear scientific evidence to support its carcinogenicity at current exposure levels in the United States.**

NONCANCER EFFECTS—NRC 1999 REPORT

Noncancer effects resulting from chronic ingestion of inorganic arsenic have been detected at doses of 10µg/kg/day and higher (equivalent to 350µg/L per day in a 70 kg person drinking two liters/day). Initial nonmalignant cutaneous effect of chronic arsenic ingestion is diffuse or spotted hyperpigmentation, that is usually followed by palmar-plantar hyperkeratoses (p.131). (These distinctive and characteristic manifestations have been the source of diagnosing chronic arsenic poisoning, leading to discovery of high arsenic concentrations in the drinking water as the source, e.g., regions of Inner Mongolia). High levels of exposure to As over prolonged periods have been shown to be a causative factor in various noncancerous skin disorders, including hyperkeratosis and hyperpigmentation. These disorders have occurred at As levels of 200 µg/L and above; there is no reliable evidence of lower As levels as a causative factor in skin conditions.

A wide range of other noncancer effects, including diabetes, have been investigated for an association with arsenic ingestion, with varying outcomes and degrees of supporting evidence. These are discussed in the NRC report under the general headings: gastrointestinal, cardiovascular, hematological, pulmonary, immunological, neurological, endocrinological, reproductive and developmental.

Recent studies from Bangladesh (Rahman 1999) and SW Taiwan (Tseng 2000) lend further support to the causal relationship between exposure to high levels of

As in drinking water and hypertension and diabetes, respectively. In the latter study, As levels were correlated with the incidence of noninsulin-dependent diabetes several decades after exposure to water As levels in the 700-930 µg/L range. The former study linked As levels between 50 and 100 µg/L with a trend towards higher blood pressure.

Recent studies from south Asia and SW Taiwan also support prior studies linking high levels of As in drinking water (in the 500-600 µg/L range) to noncancer lung disorders such as bronchitis.

The Engel and Smith (1994) study on arsenic in drinking water and cardiovascular mortality in 30 U.S. counties where the average arsenic concentration was greater than 5µg/L (referred to above) came up with mixed results that are difficult to interpret.

Peripheral neuropathy, possibly related to vascular disease (e.g., blackfoot disease in SW Taiwan), has long been associated with high levels of As exposure. Recent studies have presented some evidence linking very high exposures (in the 1,000 µg/L area) with intellectual impairment in Thailand (Siripitayakunkit,1999).

Diseases of the liver and the hematological system have also been linked to high levels of As in drinking water in several parts of the world.

The 1999 NRC report chapter on health effects concludes that epidemiological studies are needed to characterize the dose-response relationship for arsenic-associated cancer and noncancer endpoints, especially at low doses, and that such studies are of *critical importance* [emphasis added] for improving the scientific validity of risk assessment (p.133). With respect to noncancer effects, emphasis is placed on arsenic-associated cutaneous effects, cardiovascular and cerebrovascular disease, diabetes mellitus, and adverse reproductive outcomes.

Human sensitivity/methylation

The NRC subcommittee reports that human sensitivity to the toxic effects of inorganic arsenic exposure is likely to vary based on genetics, metabolism, diet, health status, sex, and other possible factors (p.5) and that these factors can have important implications in the assessment of risk from exposure to arsenic. People with reduced ability to methylate arsenic retain more arsenic in their bodies and may be more at risk for toxic effects. Poor nutritional status might decrease the ability of an individual to methylate arsenic, resulting in increased arsenic concentrations in tissues and the development of toxic effects. There is some evidence from animal studies that low concentrations of S-adenosylmethionine, choline, or protein decrease arsenic methylation

(p.5).

Further, wide variations in the fractions of methylated forms of arsenic in urine are known to occur among populations and between individuals within the same exposed population, which suggests that genetically-coded enzymes responsible for the methylation of arsenic could be a factor (p.4). But the bottom line seems to be that "The extent to which variation in arsenic methylation affects its toxicity, including carcinogenicity, is not known" (p.4). It should be noted that articles have appeared in the literature since the NRC report suggesting that organic arsenicals are of interest as carcinogens, as well as the inorganic forms, and that while methylation aids in the elimination of arsenic from the body, it may also generate chemical species that are responsible for adverse effects in some target organs or cells (EPA 2000, p.10, with references cited).

Nutritional essentiality

The NRC report devotes much of a chapter to nutritional essentiality. The executive summary notes that arsenic has not been tested for essentiality in humans. But arsenic supplementation at very high concentrations (e.g., 350-4,500 nanograms per gram) in the diet has been shown to favorably affect growth and reproduction in minipigs, chicks, goats, and rats (p.3). Regarding nutritional essentiality, the summary and conclusions section of Chapter 9 (Essentiality and Therapeutic Uses) makes a carefully worded statement: "Data from four species indicate that semisynthetic diets with arsenic concentrations in the range of 35 to 50 ng/g or less in combination with dietary or reproductive stress result in functional impairments. Such concentrations might occur naturally in some experimental diets and are similar to those found in most human foods except seafood. The mechanisms and sequence of events leading to functional impairments are not known." This statement does not take into account body weight or amount of food consumed per day. The estimated average human daily intake of inorganic arsenic from food, by age group and gender, is provided in Table 3-6 of the report, but daily intake is not provided for experimental animals in the studies cited. It may be noted that the evidence of a protective effect against abnormal reproductive effects and reduced growth is about 1-2 orders of magnitude higher than what may be an essential level of 35-50 ng/g arsenic, and thus roughly 1-2 orders of magnitude higher than the concentrations found in human food (aside from seafood). Of course, there are no comparable data on humans.

Nutrition

Several studies have suggested that poor nutrition might increase the adverse health effects of As, although no information is available on how responses to As toxicity are modulated by the nutritional status of individual (p.238). Several dietary factors that need further study have been suggested as possibly affecting sensitivity to As, including methionine, cysteine, vitamin B₁₂, folic acid, selenium, and zinc (p.243). A study by Hsueh et al. (1995) of subjects in the blackfoot-disease endemic area in Taiwan found that high consumption of dried sweet potato, a possible indicator of undernourishment, was associated with prevalence of skin cancer (p.242). The subcommittee states that there is no question that the nutritional status of persons chronically exposed to As is **crucial** [emphasis added] to understanding the signs and symptoms of As toxicity (p.242), but it also feels that much more work is needed to draw any definitive conclusions about specific dietary factors (p.243).

With regard to selenium, "despite convincing evidence for a strong arsenic-selenium interaction in experimental animals, there is as yet no direct evidence for its health effect in humans. Such a health effect, however, resulting from the lack of adequate selenium to counteract As excesses would be consistent with the situation in the blackfoot-disease areas of Taiwan. Selenium status there should be considered a moderator of As toxicity and taken into account when the Taiwanese data are applied to populations with adequate selenium intakes" (p.240). It is noted that, as measured in both urine and serum, selenium concentrations in areas of Taiwan rank lowest in the world (p.242). The SAB review of EPA's proposed rule cites a 1989 study of the National Research Council that estimates the selenium intake in the Taiwan study area at 25% of the recommended dietary intake...and refers to studies that have documented substantial effects of smaller selenium decrements on cancer of the bladder and lung (EPA, 2000, p.30).

Arsenic in food

It is noted in the executive summary of the NRC report that As in food, as well as poor nutrition, might affect assessment of risk in Taiwan or extrapolation of results to the U.S., and the public health significance of daily ingestion of a given amount of As in drinking water will be influenced by the background levels of As consumed in food (p.8). As recommended in Chapter 5 of the 1999 report, studies are needed on the bioavailability of inorganic As in various foods, although such studies are not given high

priority (p.167). Estimated average inorganic As intakes for selected age and sex groups in the United States are included in the report (Table 3-6) and average daily intake estimates have been obtained from consumption of yams and rice grown in the blackfoot disease region of Taiwan (Table 3-8). The range of estimated daily **inorganic** As consumption from different samples of yams and rice is wide, ranging from 15-211µg per day (p.51), but even the lower value exceeds the estimated average for U.S. males or females of any age group. Water used in cooking would be an additional but indirect source of As from food for the Taiwanese. No discussion was found on how a higher intake of inorganic As in food in Taiwan might affect extrapolation of risk estimates for As in drinking water from Taiwan to the United States. The final proposal of EPA (FR 66 6975-7066) makes some adjustment for arsenic in food, and in the water used in cooking, which reduces projected estimates of risk in the U.S.

Data and dose-response assessment

The subcommittee clearly recognizes the limitations of the available data for dose-response assessment, but finds the study data on internal cancers from the endemic area of Taiwan the best choice in the absence of a well-designed and well-conducted epidemiological study that includes individual exposure assessment (p.7). But it also warns that it is important to keep in mind that the considerable variability in the As concentrations detected in multiple wells within some of the villages leads to considerable uncertainty about exposure concentrations in the Taiwanese data (p.294). Further, with reference to use of the bladder cancer data to illustrate some principles of dose-response assessment, "**...it is important to emphasize again that the results are not to be interpreted as a formal risk assessment, or as an endorsement of these data for the use of risk assessment for arsenic in drinking water**" (p.273). "Such analyses must be conducted with caution, keeping in mind the potential for measurement error and confounding to bias the results" (p.294). **Cautions and disclaimers run throughout, making it abundantly clear that the analysis was conducted to illustrate to EPA some methods and issues to be taken into account, not for definitive numerical values.**

The subcommittee felt that the cultural homogeneity of the endemic region reduces the concern for unmeasured confounding (p.7), but nothing is known about potential confounders such as the use of tobacco or other risk factors for bladder or lung cancer. That is one of the weaknesses of an ecological study.

The subcommittee found that the choice of statistical model can have a major impact on estimated cancer risks at low-dose exposures (p.8) and recommends that a range of modeling approaches be explored (p.296). It is advised that the final calculated risk should be supported by a range of analyses over a fairly broad feasible range of assumptions and sensitivity analyses conducted to ensure that the conclusions do not rely heavily on any one particular assumption (p.296). The potential effect of measurement error and confounding on the dose-response curve and associated confidence limits should be further addressed (p.7). The estimates of benefits from lowering the MCL, i.e., number of cancer avoided, depend heavily on the choice of probability model selected. “Lacking definitive data on genotoxicity, pathology, metabolism, and pharmacokinetics to help determine the shape of the dose-response curve, particularly at low doses, EPA used the multistage model to fit the data of the Tseng study and included a factor for duration of exposure.” (NRC 1999 at pg. 19).

The dose-response analysis begins with the generalized multistage (“Weibull”) model and then moves to Poisson regression, with variations on the way age (duration of exposure) and exposures (As concentration) enter the models. It was found that the best-fitting (Poisson) model yields low-dose risk estimates that are considerably higher than those from the multistage model, clearly demonstrating model sensitivity. With regard to the multistage model, with data for male bladder cancer as an example, it was found that several of the villages at low exposure concentrations appear to have higher cancer rates than would be predicted from the fitted dose-response model.

A sensitivity analysis was conducted by refitting the multistage model to different subsets of the villages. The results suggest that the risk estimates are also fairly sensitive to which villages are excluded or included (p.279). The data were also grouped according to various exposure intervals (e.g., by intervals of 100µg/L, 200µg/L, etc.) and the results varied dramatically (p.282). The multistage model was also fit to the data for villages with just one well, and for villages with multiple wells, and to the data for the five villages with the highest median As concentrations and the five villages with lowest concentrations. The differences were not large except for the five lowest villages alone, for which the excess lifetime risk of male bladder cancer was two orders of magnitudes larger than the other three cases (Table 10-8). The outcome was apparently not investigated as a possible problem with the data (e.g., outliers) in the lowest five villages. The lowest five villages include Villages 3-H and 3-5, which have abnormally high bladder cancer mortality rates in the data for 60 villages, as discussed earlier in the

section "Arsenic and bladder cancer" and illustrated in Figure 1a,b. Further data analysis, simple plots such as Figure 1a,b, and plots showing how well the model predicts the observed outcomes, are needed to determine if any specific villages are having an undue influence and may need to be treated as outliers. Such analysis is also needed to evaluate how well a model fits the data (in addition to the Akaike information criteria, the numerical indicator of fit that is used).

In the recommendations section of Chapter 10, on statistical issues, it is concluded that limited sensitivity analyses not shown in the report suggest that generalized linear models (GLMs) might be more robust [than the multistage-Weibull] and it is concluded in the executive summary that applying different statistical models to the male bladder cancer data revealed that a more stable and reliable fit is provided by Poisson regression models that characterized the log relative risk as a linear function of exposure (p.8). This conclusion was apparently enough to satisfy EPA in preparation of its proposed rule (June, 2000). According to the review of the proposed rule by the Drinking Water Committee of the Science Advisory Board, "...the panel noted its belief that EPA took the modeling activity in the NRC report as being prescriptive despite the clearly stated NRC intention that their efforts were illustrative, not actual risk assessments" (EPA 2000, p.3).

Costs

Estimating costs of As remediation presents similar difficulties to those of estimating health effects, with (at least) one more degree of uncertainty added. The NRC panel specifically did not address this issue, but the EPA commissioned a separate panel, whose report was released in December 2000 (EPA 815-R-00-026, *Arsenic in Drinking Water: Economic Analysis*). Our paper will not go into much detail on this topic; suffice it to say that the estimated costs of lowering the As MCL range from huge (est. \$792M, if the rule becomes 3 µg/L) to very large (est. \$77M at 20µg/L). These costs would be borne predominantly by the 3,000 community water systems (serving 11 million people) and the 1,100 "non-community" systems (serving 2 million) whose water systems will have to be brought into compliance via some corrective methodology. The overwhelming majority of these systems serve fewer than 10,000 Americans each. Some small system customers would see their water bills increase by up to hundreds of dollars yearly, provoking decisions among the indigent and near-indigent on which "essentials" to continue to obtain.

The EPA report points out that "national compliance cost estimates cannot be used to assess local challenges that may be faced by small water systems and their

customers. There may be small water systems and populations that will be unable to afford compliance with the arsenic rule....” The cost-analysis working group recommended that external funding resources be considered to assist such areas. The Arsenic Rule Benefits Review Panel (ARBRP) report notes that the people who would benefit from the putative reduction of health risk brought about by a new As standard would be the ones whose water bills and taxes would pay for it, and urges regulators to “try to determine whether those who receive these benefits would be willing to bear the costs...”. This analysis would “allow decision makers to evaluate a range of strategies rather than a one-size-fits-all approach.” (ARBRP, pg.13-14).

If the rule mandates a lowered MCL, many small water systems will suffer financial strains, as will the municipalities whose creatures they are. If the new MCL is stringent, thousands of small water systems may well shut down, leaving their customers to drill their own wells, exposing them to higher levels of As than previously, and (theoretically, at least) exposing them to more adverse health consequences. The newly imposed federal regulation would deny to local communities the choice of spending their scarce public-health resources on lowering As risks—if any—or spending it on other local needs: hospitals, health insurance for the uninsured poor, among many others.

Conclusion

The NRC panel indicated that its analysis was not meant to substitute for further investigation of the most appropriate method for assessing risk posed by As in drinking water (EPA 2000, p.2 of submittal letter to EPA Administrator). They stated that their evaluation of data was not a formal risk assessment, nor “as an endorsement of these data for the use of risk assessment for arsenic in drinking water.” The report went on to make recommendations seemingly oblivious to these statements and outside of their stated mandate. The highest levels of As in drinking water in America are far lower than the averages of that in the water of the populations evaluated in the Taiwanese and Chilean studies used by the NRC panel. The uncertainties involved in assessing the risk to human health from As in drinking water—the differences between the populations studied and Americans in genetic and nutritional factors, the exposure uncertainty in the populations studied (from water as well as from food), limited data analysis, (for “outlier” villages, model choices, plots indicating how well models fit the data), among other factors—support the NRC subcommittee’s own statement that “the resulting estimates of the excess lifetime risk of cancer can change...by several orders of magnitude.” (NRC, table 10-8 and page 247).

The MCL for As has been 50µg/L in the U.S. for decades. There is no compelling evidence that this level presents a health risk to Americans, nor that it contributes to the toll of cancer here. Thus, the EPA estimate of benefits from lowering the MCL should be a range of values which should include zero. A regulatory approach lowering that standard would be precautionary in nature: "Let's not take any chances." Such precautionary regulations against hypothetical or unlikely risks should be balanced against known or likely unintended consequences—trade-offs—including cost-induced reversion to unhealthy water sources, and diversion of scarce public-health financial and intellectual resources. These thoughts are truer today than they were before the disaster of September 11th 2001, as our public health efforts should now be even more targeted towards real threats to our health. The ultimate goal of regulation should be the net improvement of America's public health, not merely a narrow focus on reducing the level of a particular contaminant. A stringent regulatory standard for As will have an uncertain outcome as to its net effect on public health, with a detrimental effect—as an unintended consequence of diversion of scarce public funds—being (at least) as likely as a beneficial one.

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