Cancer Risks from Arsenic in Drinking Water: Implications for Drinking Water Standards

Allan H. Smith, Mary Lou Biggs, Lee Moore, Reina Haque, Craig Steinmaus, Joyce Chung, Alex Hernandez, Peggy Lopipero

ABSTRACT

The current drinking water standard for arsenic in the U.S. and much of the world is 50 μg/L. The WHO has recommended lowering permissible concentrations to 10 μg/L, and the U.S. EPA to 2 μg/L, in each case based on extrapolation of skin cancer risks from a population in Taiwan with high levels of arsenic in their drinking water. Evidence from studies in Taiwan, Argentina and Chile is presented in this paper to show that, more important than skin cancer which is usually non-fatal, ingestion of inorganic arsenic in drinking water is also a cause of several internal cancers. For lifetime consumption of inorganic arsenic in drinking water containing around 500 μg/L, it is estimated that on the order of 10% of all deaths in adults would be attributable to ingestion of arsenic, mainly as a consequence of lung and bladder cancer. This extremely high cancer mortality risk estimate is based primarily on investigations in Region II of Chile, but is also supported by studies of other exposed populations, particularly Taiwan. Linear risk extrapolation from 500 μg/L to lifetime consumption of water with an arsenic concentration of 50 μg/L, the current drinking water standard, results in cancer mortality risk estimates reduced by a factor of ten to around 1 in 100 adult deaths being attributable to arsenic. Consideration is given to evidence for possible sub-linearity in the dose–response relationship which would make this estimate excessively high. The evidence is mixed, but neither human epidemiological studies, nor consideration of potential carcinogenic mechanisms, give assurance that the dose–response relationship would be significantly sub-linear in the dose range resulting from consumption of water between 50 and 500 μg/L arsenic in water. Even if marked sub-linearity were present, and risks at 50 μg/L were ten times lower than predicted from linear extrapolation, risk estimates would still be roughly of the order of 1 in 1000 persons dying due to arsenic in drinking water. Since such high cancer risks are unacceptable by any yardstick, it might be thought that the drinking water standard should be drastically reduced, even to lower concentrations than the 2 μg/L suggested by the U.S. E.P.A. However natural food sources become the predominant source of inorganic arsenic ingestion once water arsenic concentrations are reduced to about 10 μg/L and below. It is concluded that although much more research on arsenic is needed, the need for such research should not be used as an excuse to delay implementation of an inorganic arsenic drinking water standard considerably lower than the current 50 μg/L.

Keywords: arsenic, drinking water, epidemiology, cancer, risk assessment
INTRODUCTION

The purpose of this document is to summarize information pertinent to setting arsenic drinking water standards. The current standard in the U.S. has been 50 μg/L since the 1940s (U.S. EPA, 1988). The World Health Organization recently recommended a standard of 10 μg/L (WHO, 1993). Some countries have introduced new arsenic water standards including 25 μg/L in Canada and 7 μg/L in Australia. The U.S. E.P.A. proposed for consideration a standard of 2 μg/L. Both this standard, and that recommended by WHO, were based on skin cancer studies in Taiwan and a risk assessment published by the U.S. E.P.A. ten years ago. In this paper, the evidence that arsenic causes several internal cancers in addition to skin cancer is summarized. Cancer mortality risk estimates for high levels of exposure found in various parts of the world are presented. Consideration is then given to potential cancer risks at lower concentrations of arsenic such as those occurring at the current standard of 50 μg/L. The potential for sub-linearity in the dose–response relationships is also discussed. Finally, recommendations are made for standard setting which include consideration of non-water sources of inorganic arsenic in the diet.

ARSENIC INGESTION AND CANCER: SUMMARY OF RECENT HUMAN EVIDENCE

Until recently, the evidence that ingestion of arsenic is a cause of various cancers other than skin cancer came mainly from studies in Taiwan (Chen et al., 1985, 1988; Chiu et al., 1995; Guo et al., 1997; Wu et al., 1989) and to a lesser extent from two studies in Japan (Teuda et al., 1990, 1995). A review published in 1992 concluded that these studies strongly suggested that ingested inorganic arsenic causes cancers of the bladder, kidney, lung and liver, and possibly other sites, but that confirmatory studies were needed (Bates et al., 1992). Since then several studies have provided strong additional evidence that arsenic ingestion does indeed cause internal cancers, in particular cancers of the bladder and lung.

A threefold increase in bladder cancer mortality (SMR 3.07; 95% CI 1.01–7.3) was reported after further follow-up of a cohort of 478 patients treated with Fowler’s solution (potassium arsenite) in England (Cuzick et al., 1992), strengthening the bladder cancer evidence previously reported for this cohort (Cuzick et al., 1982). With one exception, the bladder cancer cases had received cumulative doses of less than 2000 mg of arsenic. This is a relatively low cumulative dose, equivalent to drinking 2 liters per day of water with an arsenic concentration of 100 μg/L for 30 years. No overall increase in lung cancer was found (SMR 1.00; 0.5–1.7) but a weak dose–response trend for respiratory cancer with cumulative arsenic dose had previously been reported in this cohort (SMRs 0.8, 1.1, 1.4, 1.8, p = 0.16) (Cuzick et al., 1982). The most recent publication did not provide comparative respiratory cancer data.

No overall increased risk in bladder cancer was found in a study involving low arsenic exposure levels in the state of Utah (Bates et al., 1995). However among smokers, there were increased trends in time window latency analyses especially in the period 30–39 years prior to cancer diagnosis. Arsenic water levels ranged from 0.5 to 160 μg/L. It was concluded that smoking might potentiate the effect of arsenic on the risk of bladder cancer. Since the risk estimates obtained were higher at these low levels of exposure than predicted from the results of the studies in Taiwan, the investigators concluded that confirmatory studies were needed.

A mortality study in the arsenic exposed region in Cordoba, Argentina, showed increased risks of bladder cancer among both men and women during the study period 1986 to 1991 (Hopenhayn-Rich et al., 1996a). The standardized mortality ratios for the low, medium, and high exposure counties were 0.80, 1.42, 2.14 for males (p value test for trend 0.001) and 1.21, 1.58, 1.82 for women (p = 0.04), respectively. The high exposure counties also showed increased mortality from lung and kidney cancer, but the findings for liver cancer were equivocal with increased risks in all counties (Hopenhayn-Rich et al., 1996). Evidence was
presented showing that smoking did not contribute to the increased risk of deaths from these cancers. The crude estimate of the average concentration of arsenic in drinking water among the water sources containing more than 40 μg/L tested 50 years ago was about 180 μg/L.

Dramatically increased mortality from bladder (SMRs about 7 and 8) and lung cancer (SMRs about 3–4) in Region II of Chile for the period 1989–93 has recently been reported (Smith et al., 1998). Kidney cancer mortality was increased to a lesser extent, but no increases were found for liver cancer. Increased mortality was also reported for skin cancer. Approximately 5–10% of all deaths among adults over the age of 30 were attributable to arsenic; chiefly to lung and bladder cancer. There was no increase in deaths from all other causes combined. Evidence indicated that smoking had not contributed to the increased cancer mortality in the Region. The arsenic levels in drinking water in the peak exposure period from about 1965 to 1980 averaged between 500 and 600 μg/L.

The studies in Argentina and Chile were conducted with a priori hypotheses that internal cancers, in particular bladder, lung, kidney and liver cancer would be increased, based mainly on findings in Taiwan. Given the a priori hypotheses, the results concerning lung and bladder cancer, and to a lesser extent kidney cancer, strongly support the evidence in Taiwan that ingestion of arsenic in drinking water is a cause of these cancers. The findings do not support liver cancer as an outcome. In retrospect, it is noteworthy that liver cancer in the Taiwan studies was associated with lower relative risks among the arsenic-exposed than bladder, lung and kidney cancer. It is possible that arsenic does cause liver cancer, but co-factors such as those associated with high liver cancer rates in Asia may be required.

**CONCLUSION REGARDING BLADDER CANCER**

There is sufficient evidence from several studies in several countries to conclude that ingestion of arsenic is a cause of human bladder cancer. Beyond the findings in Taiwan, the strongest additional evidence comes from large population studies in Chile and Argentina, each conducted with the a priori hypothesis that bladder cancer risks would be increased. Both studies found that the highest relative risks for internal cancer mortality associated with arsenic exposure were for bladder cancer. These ecological studies are supplemented by studies with individual data, in particular in Taiwan and in the Fowler's solution study in England. There is therefore ample evidence to conclude that inorganic arsenic ingestion is a cause of human bladder cancer.

**CONCLUSION REGARDING LUNG CANCER**

Recent studies add to the evidence that ingestion of inorganic arsenic causes increased risks of lung cancer. Clear increased risks were found in ecological studies in both Argentina and in Chile. Confounding due to smoking could be excluded as the explanation in both populations. Increased lung cancer risks had already been reported in a small study in Japan involving drinking water. As yet there are no large studies with individual exposure data. However, the findings in Argentina and especially in Chile where arsenic exposures were higher, provide evidence that the ingestion of arsenic most probably causes increased human lung cancer risks. Biological plausibility that arsenic from ingestion might increase lung cancer risks is strengthened by the fact that it is a confirmed lung carcinogen by inhalation. Taking this into account, there is now sufficient evidence to conclude that ingestion of inorganic arsenic is a cause of human lung cancer.

**CONCLUSION REGARDING OTHER INTERNAL CANCERS**

While recent studies add to the existing evidence and make it probable that ingestion of arsenic can cause kidney cancer, the findings are not as strong as for bladder and lung cancer. The evidence concerning liver cancer has actually been weakened by recent studies.
POPULATION RISK ESTIMATION FOR HIGH LEVELS OF EXPOSURE

Smith et al. (1998) showed that 5–10% of deaths occurring in adults in Chile were attributable to arsenic exposure chiefly due to bladder and lung cancers. In this population, arsenic in water contributed more to mortality than did cigarette smoking.

Other studies, particularly in Taiwan, are consistent with the very high population risk estimates calculated for Chile. For example, the bladder cancer relative risk estimates in Chile were around 7 and 8 for relatively short exposures (around 15 years) averaging between 500 and 600 μg/L. In Taiwan, the highest exposed populations drank water containing an average of 800 μg/L for longer periods and the relative risk estimates were on the order of 30–60 (Chen et al., 1988; Smith et al., 1992). Lower bladder cancer relative risks on the order of 2 were found in Argentina in association with much lower exposures, probably averaging around 180 μg/L.

Regarding lung cancer, relative risks were again higher in Taiwan where exposures were higher and of longer duration than in Chile. Lower relative risks were found in Argentina where exposures were lower. Population relative risk estimates for bladder and lung cancer thus show a consistent pattern. Since the exposures in Chile were much less than lifetime, with the highest levels occurring over only 15 years, a conservative rough estimate of lifetime mortality from drinking water containing inorganic arsenic at around 500 μg/L, might mean that 10% of adult deaths could result, predominantly due to cancers of the lung and bladder.

The consistency of this estimate derived from Chile with ecological studies in Taiwan can be seen by comparing the estimation of cancer risks for consumption of 1 liter per day of 500 μg/L. A risk assessment in 1992 used linear extrapolation to estimate that consumption of 1 liter per day of water containing 50 μg/L of arsenic might result in 13.4 per 1000 deaths when U.S. background cancer rates were incorporated into the analysis (Smith et al., 1992). Using the same methods, the estimate for 500 μg/L would be 13.4% which is consistent with the 10% estimate derived from Region II of Chile.

DOSE–RESPONSE RELATIONSHIPS: LINEAR OR SUB-LINEAR?

Clear dose–response data are still lacking in epidemiological studies of populations exposed to arsenic in their drinking water. Most studies have employed ecological groupings rather than individual exposure data. The highest priority for arsenic health effects research should be to add to the currently available information concerning dose–response relationships between ingestion of arsenic in drinking water and the risk of various outcomes, including cancer. However, quite extensive dose–response data are available for inhalation of inorganic arsenic and lung cancer risks.

THE DOSE–RESPONSE BETWEEN ARSENIC INHALATION AND HUMAN LUNG CANCER MAY BE LINEAR OR SUPRALINEAR

It is reasonable to propose that the shape of the dose–response curve for lung cancer caused by arsenic inhalation would be similar to that for lung cancer and other cancers caused by ingestion of inorganic arsenic. As far as inhalation is concerned, a reasonable question is whether or not the dose–response relationship might be supralinear or linear (Hertz-Picciotto and Smith, 1993). There is no evidence to suggest sub-linearity in the dose–response relationship. The findings using air measurements of arsenic inhalation were consistent with supralinearity in six studies conducted in three countries. One possible explanation is consistent overestimation of exposure at high air concentrations due to work practices to avoid exposure. This explanation is supported by one study which found supralinearity using air measurements for exposure, but linearity when urine measurements of arsenic were used (Enterline et al., 1987). Urine arsenic concentrations reflecting absorbed dose may
TABLE 1
Arsenic in drinking water cancer risk extrapolation to 50 and 10 μg/L. Estimates of lifetime cancer mortality.

<table>
<thead>
<tr>
<th>Water arsenic concentration (μg/L)</th>
<th>Actual risk or linear extrapolation</th>
<th>10 times less than linear extrapolation</th>
<th>100 times less than linear extrapolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>1 in 10</td>
<td>1 in 1,000</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>50</td>
<td>1 in 100</td>
<td>1 in 5,000</td>
<td>1 in 50,000</td>
</tr>
<tr>
<td>10</td>
<td>1 in 500</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

give a better estimate of inhaled dose than measurements of air concentrations using fixed samplers. This would occur if workers tended to avoid the most dusty environments as much as possible during their workday. We are of the opinion that this is the most likely explanation, and that the true dose–response relationship between inhaled arsenic dose and lung cancer risks is linear in the observable range, rather than supralinear. Since detailed dose–response data with individual exposure estimation for arsenic ingestion are still lacking, the studies of arsenic inhalation are important in that they do not provide any evidence for sub-linearity in the observed dose range in which lung cancer relative risks increased from less than 2 to more than 5.

EXAMINATION OF EPIDEMIOLOGICAL EVIDENCE FOR A THRESHOLD OR SUBLINEARITY CONCERNING ARSENIC

Two ecological analyses have suggested that the relationship between arsenic water concentrations and cancer occurrence in Taiwan is sub-linear or has a threshold. Brown and Chen (1995) reanalyzed the Taiwanese data and concluded that there could be a threshold or sub-linearity in the arsenic and cancer dose–response relationships. However, the reanalysis appears to have involved re-classifying village exposure and deleting villages according to post hoc criteria.

A further ecological analysis has been presented for bladder cancer incidence data in Taiwan (Guo et al., 1997). The investigators used a novel method for ecological data analysis. Superficial examination of the results suggests a threshold for arsenic water levels and bladder cancer. However, the unusual methods used were not accompanied by any results allowing the comparison of findings with other studies in Taiwan. Indeed, they would appear to be in conflict with them. For these reasons, this study provides little, if any, evidence for non-linearity in dose–response relationships for arsenic-induced bladder cancer, let alone evidence of a threshold.

In contrast to these unusual ecological analyses of data from Taiwan, results of other epidemiological studies, including further studies in Taiwan, demonstrate that it is unlikely that there is marked sublinearity and provide no evidence for a threshold. Skin cancer prevalence in Taiwan increased according to duration of residence in the area, duration of consumption of high-arsenic artesian well water, average arsenic water levels, and cumulative dose (Hsueh et al., 1995). Similar findings have been reported for lung and bladder cancer (Chiou et al., 1995). Although variables were for the most part categorized into three levels, the findings generally demonstrated a monotonic dose–response relationship for both cancers by duration of exposure, average arsenic concentration in drinking water, and cumulative exposure.

Apart from two unusual ecological analyses of Taiwanese data, there are no data supporting sub-linearity nor a threshold. This does imply that the results of these analyses
should be excluded. However, in the absence of data supporting them, it is important to note that findings in various ecological studies, and limited findings with some individual data studies, support a monotonic dose–response relationship in the ranges of exposure considered thus far.

MECHANISTIC EVIDENCE

The mechanisms for arsenic carcinogenicity are unknown and there appear to be almost as many theories as there are investigators. Because arsenic does not cause point mutations in experimental systems, some investigators have postulated that these results are consistent with theories of sub-linearity for arsenic dose–response relationships. However, inference of sub-linearity from simple toxicological considerations is at best speculative without support from empirical data from human studies. Since there may be several mechanisms involved, multiple interactions with other factors both extrinsic and intrinsic, and variations in genetic susceptibility, inference from in vitro experiments and mechanistic theories cannot predict the shape of dose–response relationships for incidence rates of long latency diseases with complex multistage and multifactorial etiologies such as cancer. In addition, no information has been produced to identify the range of arsenic exposures in which meaningful sub-linearity might occur for any postulated theoretical mechanisms.

As with other major causes of human cancer, it is not likely that mechanisms allowing for valid predictions of dose–response relationships for low levels of arsenic will be identified in the foreseeable future. Indeed, mechanistic theories to date do not even predict why such high rates of bladder cancer would occur in humans exposed to arsenic at levels not much higher than the current drinking water standards. Until they do, it is futile to even begin to use such theories to postulate what might be happening below the as yet detectable effect levels in humans. This is not to say that mechanistic research is not important. However, this research involves a long term investment which may take decades and as such will not provide the methods for determining permissible exposure limits for arsenic in drinking water in the near future. It is also noteworthy that for many established causes of human cancer, the dose–response relationships found in epidemiological studies are more or less linear, whether or not point mutations are caused by the particular agents involved.

There is quite extensive human evidence concerning dose–response relationships for arsenic methylation. As discussed in a previous review, there is substantial evidence that inorganic arsenic was present in urine in approximately similar proportions to methylated forms at all levels of exposure from very low to very high (Hopenhayn-Rich et al., 1993). Subsequent studies have confirmed these findings. The largest human study examining methylation patterns in humans as reflected in urine profiles was in a population in the North of Chile. This study showed that the percentage of inorganic arsenic in urine was only slightly greater in the high exposure compared to the low exposure population (Hopenhayn-Rich et al., 1996b). These results were confirmed by an intervention study among highly exposed persons who were provided with arsenic-free water for two months. Total urinary arsenic averages fell from 636 µg/L to 166 µg/L whereas the percentage of the inorganic form changed very little, from 17.8% to 14.6% (Hopenhayn-Rich et al., 1996c). Another study reported very low levels of the metabolite monomethylarsonic acid (MMA) in urine in an isolated population in Argentina, but the levels of inorganic arsenic were similar to those reported in other populations (Vahter et al., 1995). Taking all the evidence into account, it can be concluded that some sub-linearity in cancer dose–response relationships could be supported by the human methylation data if inorganic arsenic is the main carcinogenic agent. However, the sub-linearity would be very slight, and there is no evidence from methylation patterns that would support a threshold below which there would be no cancer risks.
While extensive evidence is now available for urinary arsenic patterns of methylation, a biomarker of exposure, the information to be derived from studies using biomarkers of effect is more limited. A bladder cell micronucleus study in the North of Chile measured micronuclei in exfoliated bladder cells for persons residing in two towns with either high or low exposure (Moore et al., 1997a). Water levels in the high exposure town were on the order of 600 μg/L while actual exposure assessed by measuring urinary arsenic varied over a wide range. Increases in micronucleus prevalence were associated with urinary arsenic levels less than 700 μg/L. Above that level, micronucleus prevalence returned to background levels, perhaps as a result of cytotoxicity. When the population was divided into quintiles according to urinary arsenic concentrations, increased micronucleus prevalence was found at urinary arsenic concentrations on the order of 100 μg/L (range 54–137 μg/L) where there was a doubling of the prevalence of micronuclei (prevalence ratio 2.1, 95% confidence interval 1.4–3.4). An intervention study in a highly exposed sub-set of participants provided further evidence supporting these findings (Moore et al., 1997b). Although confirmatory studies are needed, the aforementioned results suggest that ingested inorganic arsenic might have genotoxic effects in bladder cells at low levels of exposure.

EXTRAPOLATION OF CANCER RISKS TO THE CURRENT DRINKING WATER STANDARD

A major risk assessment undertaking concerning arsenic in drinking water was published in 1992 with linear extrapolation to 50 μg/L (Smith et al., 1992). In the same year, investigators in Taiwan conducted risk extrapolations which produced results of a similar order of magnitude (Chen et al., 1992). It should be noted that the extrapolations are over a short range, much shorter than is usually the case for environmental exposure to carcinogens. Ecological evidence in Taiwan suggests a detectable increased risk in villages with average water levels around 170 μg/L (Chen et al., 1988). In Argentina, the highest exposure counties average estimate was about 180 μg/L where bladder cancer risks were clearly increased. (Hopenhayn-Rich et al., 1996a). Bladder cancer risks were also increased in counties classified as having medium exposure. The relative risks were 1.42 for men and 1.58 for women. It would appear then that detectable increased bladder cancer risks have already been found for levels of arsenic in water only 3 to 4 times that of the current drinking water standard. Of course, in ecological studies it is possible that effects are due to a small proportion of persons having much higher exposure than the average. Even if this were true, it would surely be accepted that there are real effects at 500 μg/L. If this were so, the extrapolation to 50 μg/L only involves a factor of 10.

Another way of considering these risks is in safety factor terms. If approximately 10% of people will die with a given exposure level, and it is not yet clear what the lowest detectable effect in epidemiological studies will be, what safety factor might be appropriate? We might start by allowing a factor of 10 because further epidemiological studies will certainly find effects below exposure levels causing deaths in 10% of people. We might then say we want a safety factor of 10 from that level, plus another factor of 10 to allow for variations in human susceptibility, and sensitive sub-populations. This would bring us down from the 500 μg/L level at which around 10% of people might die from the exposure to 0.5 μg/L. This safety factor approach is presented here because it again demonstrates what a small extrapolation is being made from 500 μg/L to 50 μg/L in the above risk estimation.

IMPLICATIONS OF NON-WATER SOURCES OF ARSENIC

Based on either traditional methods of risk extrapolation, whether using linear or sub-linear models (Table 1), or by considering safety factors, it is apparent that proposed drinking water standards for arsenic would be very low, presumably less than 1 μg/L. Reaching such a standard would involve treating almost all sources of drinking water. Perhaps fortunately,
there is good reason to reject such a low drinking water standard without resorting to an assessment of the costs involved.

Arsenic is present everywhere in the earth's crust, in soil, in vegetables, fruits, and meats (IARC, 1987). In fact, it is present in all food sources. Even if all arsenic were removed from water, we would still have food intake which could not be prevented. For this reason, any consideration of human risks at low water concentrations needs to consider risks from all pathways, in particular from food. Increasing data are becoming available on food sources of inorganic arsenic, but the best source of information involves urinary levels of inorganic arsenic and its metabolites in persons whose water has very low arsenic concentrations. Unfortunately, detailed studies of urinary concentrations in persons drinking very low arsenic containing water have not been conducted, and there are considerable uncertainties in trying to base estimates on calculations using food concentrations since only limited data are available. Based on what we know so far however, it is reasonable to conclude that when water arsenic levels are below 10 μg/L, food becomes the main source of intake of inorganic arsenic. If so, there is little to gain from reducing water levels below 10 μg/L when food intake cannot be altered.

Based on the above considerations, revision of the current drinking water standard warrants urgent consideration. A prudent approach might be to make the permissible concentration 10 μg/L, as recommended by WHO, although as noted without technical justification. This would considerably reduce cancer risks which might occur with consumption of water containing 50 μg/L, and perhaps even prevent these risks altogether if there is a threshold or marked sub-linearity in dose–response. Finally, a limit of 10 μg/L would result in a major reduction in human exposure in spite of food sources of inorganic arsenic, something which could not be said about any proposal to reduce the water standard much below 10 μg/L.

SUMMARY RECOMMENDATIONS REGARDING DRINKING WATER STANDARDS

1. Any proposed drinking water standard should take into consideration potential cancer mortality risks due to lung and bladder cancer. At high levels of exposure, arsenic in drinking water results in the highest known population cancer mortality, other than that occurring among cigarette smokers.
2. While there may be sub-linearity in the dose–response relationship, even marked sub-linearity would result in unacceptably high cancer risks at the current drinking water standard of 50 μg/L.
3. The theoretical benefits of an extremely low drinking water standard is offset by the inevitable intake of inorganic arsenic from food. When drinking water levels are below 10 μg/L, food becomes the main source of exposure, so there is little to gain by reducing drinking water levels much below 10 μg/L.
4. While further research is needed concerning variation in individual susceptibility, interactions with other exposures, more precise estimates of the dose–response relationships, and the possibility that arsenic is an essential nutrient, etc., this need should not be used as an excuse to delay prudent public health action, based on what we already know.

REFERENCES


