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Role of Epidemiologic Studies in Deriving Drinking Water Standards for Metals

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Epidemiological investigations are shown to have contributed in a significant way to our understanding of the potential adverse health effects of drinking water with elevated levels of several metals. Particular emphasis is given to an assessment of the epidemiological investigations concerned with characterizing the health effects of exposure to elevated levels of arsenic and sodium in drinking water.

Introduction

In 1914 the United States Public Health Service (PHS) first adopted drinking water standards to protect the health of the traveling public. The original PHS drinking water standards were designed to regulate interstate water carriers so that people traveling on boats, buses, and trains would be assured a safe water source. Intrastate or community drinking water sources were not under federal control (*1*).

In the years since 1914, the PHS modified its standards on a number of occasions, including 1925, 1942, 1946, 1956, and 1962, in light of advances generated from technical and health-related research. During the initial decades subsequent to the development of the first drinking water standards, the main goal was to prevent the occurrence of diseases such as typhoid and cholera. However, in more recent years, that is, since World War II, there has been an increase in awareness of the toxicity of chemical pollutants in drinking water and the need for regulations. Thus, the derivation of drinking water standards represented an initial concern with the control of bacterial contamination followed by the gradual recognition of toxic heavy metals, radiation and now pesticides and other organics (*1*).

In addition to a growing recognition of new hazards in drinking water, it was also realized that regulations for exposure limits should be equally applied to intrastate drinking water supplies. Consequently, even though the federal government was not directly involved with the regulation of intrastate drinking water quality, many states did adopt their own programs to ensure drinking water safety. However, the first major federal legislation that included regulation of community drinking water was the Safe Drinking Water Act of 1974, one of whose goals was the establishment of National Drinking Water Regulations (*1*). The intention of this paper is to review and assess the role of epidemiological evaluations on the derivation of the current EPA national primary drinking water standards for metals.

It must be stated at the outset that the health criteria upon which drinking water standards are based include the integration of knowledge obtained from both toxicological and epidemiological studies. Both the toxicological and epidemiological research methodologies have their inherent strengths and weaknesses and it is necessary for regulatory officials to carefully and legitimately utilize both types of information in deriving health criteria to support standard development.

Currently there are nine nonradioactive elements and/or ions which are regulated by primary drinking water standards: arsenic, barium, cadmium, chromium, fluoride, lead, mercury, selenium and silver (*2*). It is important to realize that exposure to most of these metals occurs from multiple sources including the air, food and drinking water. Frequently, little enthusiasm has been directed toward conducting epidemiological studies focusing on exposures associated with drinking water since the assumed percentage contribution of drinking water is often considered quite small compared to all other sources (*1*).

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Extensive epidemiological studies for several of these metals such as lead, cadmium and mercury have been reported and have helped to establish dose-response relationships. Based on such studies it has been possible to identify exposure levels which could result in adverse health effects. These studies have typically concerned unfortunate episodes where populations have been exposed to intoxicating levels of pollutants from contaminated food in the cases of cadmium and mercury. As for lead, numerous epidemiological studies exist which have addressed the impact of consumption of lead based paint on clinical outcomes and the influence of airborne lead levels on blood lead levels and behavioral outcomes (*2*). In many instances the role of drinking water as a contributor has either not been specifically addressed or noticeably deemphasized.

Several epidemiological studies however, have considered the direct impact of elevated levels of arsenic and fluoride in drinking water on biomedical parameters. The findings of these studies have played a major role in the derivation of EPA drinking water standards (*2*). In addition, since the establishment of the primary drinking water standards, EPA has sponsored several major epidemiological investigations on the health effects of elevated levels of several inorganics, including arsenic, barium, selenium and sodium.

This presentation reviews the contribution of the epidemiological perspective to our understanding of the influence of arsenic and sodium in drinking water on human health.

Arsenic

The adverse health effects of exposure to arsenic compounds have been subject to epidemiological investigations for nearly a century. Data have been gathered and analyzed from a variety of sources, including patients given prescribed medicinal arsenic compounds and several occupational groups, as well as populations exposed to high levels of arsenic in drinking water supplies (*3*). Although arsenic exposure has been associated primarily with skin cancer as a result of these studies, associations with other cancers, cardiovascular dysfunctions and a peripheral vascular disorder known as "blackfoot" disease have been found.

Several epidemiological investigations in Europe (*4*), several South American countries (Argentina, Chile) (*5-7*) and Taiwan (*8, 9*), have suggested an association between the effects of chronic exposure to high levels of arsenic in drinking water and the occurrence of a variety of skin disorders including skin cancer. The most significant of these reports was published by Tseng et al. (*8, 9*) who not only correlated an extremely high prevalence of skin cancer and blackfoot disease with arsenic content of drinking water supplies in Taiwan but also reported a dose-response relationship between skin cancer, blackfoot disease, and duration of water intake based on a detailed house to house medical survey of approximately 40,000 individuals out of a total exposed population of about 100,000 individuals. The inhabitants of the endemic area began using their artesian wells, which have the high arsenic levels, about 45 years before the study of Tseng et al. (*8*). The inhabitants were generally engaged in farming, fishing or salt production with a socioeconomic state considered poor. Their diet was considered to be low in animal protein and fat and high in carbohydrates. Their habits and customs were not considered different from those of persons living in other parts of Taiwan. The overall prevalence rates for skin cancer, hyperpigmentation and keratosis were 10.6, 183.5 and 71.0/1000, respectively.

A similar medical survey of 7,500 persons living in a low arsenic area with drinking water values for arsenic ranging from less than 1 ppb up to 17 ppb served as the control population. Approximately ⅔ of the control group (i.e., about 5000) lived on the nearby island of Matsu and were mostly fishermen; the remaining members of the control group were from villages near the endemic area and consisted of farmers and salt workers. The control group, which displayed a similar sex and age distribution as the exposed group, did not have a single case of melanosis, keratosis or skin cancer.

The levels of arsenic in the drinking water supplies of the "exposed" inhabitants were quite elevated, with greater than 45% of the wells having arsenic levels in excess of 400 ppb as compared with the EPA national standard of 50 ppb. Attempts to establish a dose-response relationship compared those consuming water with arsenic levels <300 ppb vs. 300-600 ppb vs. >600 ppb. There was a definite ascending gradient or prevalence from the low to high arsenic groups for both sexes in three different age groups. Table 1 compares the skin cancer prevalence rates for the three age groups in the different arsenic exposures.

Three recent epidemiological studies in the U.S. did not find a positive relationship between excess levels of arsenic in drinking water and adverse health effects. A survey of over 200 residents in Fairbanks, Alaska, exposed to mean ar-

Table 1. Prevalence rates of skin cancer per 1000 in combined male and female groups exposed to markedly different levels of arsenic in drinking water.[a]

Age group	Arsenic level	Skin cancer rates per 1000
20-39 yr	Low	1.3
	Middle	2.2
	High	11.5
40-59 yr	Low	4.9
	Middle	32.6
	High	72.0
>60 yr	Low	27.1
	Middle	106.2
	High	192.0

[a]Data of Tseng et al. (*8*).

senic drinking water levels of 224 ppb displayed no increases in skin disorders, although the longest exposure in the study population was only ten years (*11*). Similarly, Morton et al. (*12*) did not note any increase in the incidence of skin cancer between 1958 and 1971 in Lane County, Oregon, where the arsenic content of the drinking water supplies was relatively high, although only 5% of the arsenic levels of the county drinking water supplies exceeded 100 ppb. More recently, a study in Utah by Southwick et al. (*13*) compared the health status of 145 persons consuming drinking water with arsenic levels averaging approximately 200 ppb as compared to a matched control group of 105 participants from a neighboring community where drinking water arsenic levels averaged 20 ppb. The investigators did not find any cutaneous manifestations of arsenic toxicity. In addition, cancer incidence and death rates did not reveal an excess of cancer in the exposed community.

There are several possible explanations for the apparently conflicting studies discussed above. The difference in the arsenic levels of the drinking water supplies surveyed is striking; the average arsenic content of the drinking water supplies in Taiwan greatly exceeds those of the U.S. communities studied. Duration of exposure and amount of arsenic ingested was probably much less in the American studies than in the Taiwan studies, where personal mobility is greatly reduced. Lack of adequate nutrition and exposure to other environmental pollutants may have exacerbated the effects of arsenic exposure in Taiwan. The differences in exposure to sunlight between Taiwan and Alaska may have been a factor in the observed absence of skin disorders in the Fairbanks study (*11*). With the exception of the Alaska (*11*) and Utah (*13*) studies, none of the investigations attempted to determine which arsenic compounds were present in the drinking water supplies surveyed. Since, arsenic toxicity varies from compound to compound, this may have been a factor in the conflicting results of the different studies.

Unfortunately, the Taiwan studies did not include the results of any analyses of other constituents in the drinking water besides arsenic levels between the water sources of the exposed and control groups. This lack of assessment reduces the extent of a potential causal connection between arsenic levels and observed skin cancer. This is particularly relevant, since Lu (*14*) recently reported the presence of other contaminants in the Taiwan well water associated with blackfoot disease to be ergot alkaloids, which may cause symptoms similar to blackfoot disease. Other methodological questions may be raised about the Taiwan study such as possible observer bias in knowing which was a high or low area or the verification of only about 30% of the skin cancers by biopsy. To what extent these factors may affect the interpretation of the findings is uncertain.

The case of arsenic regulation presents several difficult issues for EPA. First, animal studies with arsenic have generally not indicated that it is carcinogenic (*2*). It is always of great value when epidemiologic associations are supported with animal studies. Second, humans were estimated to consume about 900 μg/day from food (*10*). In light of these two factors plus the association of skin cancer with high levels of arsenic in drinking water, EPA established a drinking water standard of 50 μg/L which would ensure that not more than 10% of the total ingested arsenic would come from drinking water. Since the time EPA proposed the arsenic standard, there has been a profound reduction in the estimate of dietary arsenic consumption from 900 to about 70 μg/day (*15*). Since EPA's stated 1976 rationale (*2*) is to keep the arsenic exposure from drinking water at 10% of total ingested arsenic, the newly recognized reduced dietary exposure may force EPA to revise their standard accordingly or develop a new methodology.

An important related issue is that EPA has decided to consider carcinogenic effects as occurring according to a nonthreshold dose-response relationship. Consequently, there is no safe exposure level to a carcinogen. Various biostatistical models have been used to predict risk of cancer occurrence when human exposures are much lower than those in the observable range for which dose-response relationships are known. This type of downward extrapolation was applied

to the Taiwan data by EPA's Carcinogen Assessment Group using a conservative model. They predicted that the lifetime risk of skin cancer from drinking water with only 2 ppb (or 25 times less than the federal standard) would be 1 per 1000 (*16*). If biological reality conformed to this prediction of their biostatistical model, we would have an epidemic of drinking water-induced skin cancer since the average level of arsenic in drinking water in the U.S. is about 2 ppb. To what extent EPA and other regulatory agencies rely on biostatistical models to predict cancer risks and establish criteria from which national standards are based is one of the major issues of the 1980s. At this time, OSHA's carcinogen policy rejects the use of quantitative assessment in standard setting because of large uncertainties (*17*), while FDA has used quantitative risk assessment to establish an acceptable risk of 10^{-6} for exposure to DES in certain foods (*18*) with EPA employing it for the derivation of a standard for trihalomethanes (THMs) in drinking water (*19*) but apparently rejecting it with arsenic. This inconsistent utilization of quantitative risk assessments between agencies can only create confusion in the general public and further erode the credibility of our national agencies regulating carcinogenic agents. Finally, any approach to re-evaluating the present arsenic standard must address the issue of its essentiality in man. Essentiality has been shown in the rat, chick, guinea pig and goat. In fact, based on extrapolation of animal data to man, 25-50 μg of arsenic per day has been suggested as a possible daily requirement (*15*).

Sodium

Attempts to derive a sodium standard as a result of the National Safe Drinking Water Act of 1974 have been hampered by a dearth of definitive human population studies demonstrating the effects on health of sodium in the drinking water. For this reason, the U.S. Environmental Protection Agency did not propose a maximum concentration limit for sodium in drinking water (*20*). The American Heart Association (*21*) implied that a limit of 20 mg/L be adopted as a standard in order to afford protection to those individuals with heart or kidney ailments who require a low sodium diet. Similarly, in 1979, the EPA recommended that a level of 20 mg Na/L be a goal for public health water systems, while proposing a requirement for monitoring of sodium levels in water supplies (*22*).

Nearly all of the previous studies of the relationship between hypertension and sodium intake have considered the contribution of sodium from food rather than from water. This is understandable in light of the fact that water contributes from less than 0.5% to 9.0% of the total sodium an individual consumes with the important exception of persons on a restricted salt diet (*21, 23*).

The next section represents a brief summary of the past four years of research which we have conducted at the University of Massachusetts which has been designed to assess whether elevated levels of sodium in the community drinking water could bring about an increase in the blood pressure (BP) levels of elementary and high school students.

Blood pressure distributions among third and tenth grade students in two geographically contiguous Massachusetts communities similar with regard to size, income, education, and recent rate of growth were compared (*24, 26*). One community had low levels of sodium in the public drinking water while the other had considerably higher levels at 8 and 107 mg/L, respectively. These differences in sodium levels have existed for the past 19 years.

While detailed descriptions for the methodology are given elsewhere (*24, 26*), both studies involved approximately 300 students from each school system with about a 75% participation in the tenth grade study and a 90% participation in the third grade study. Screenings were conducted equally in mornings and afternoons in both towns to take into account possible diurnal variation. Nurses taking blood pressure were highly skilled and carefully standardized. Each student had his blood pressure taken three times, each time by a different nurse who was blind to previous readings. Pulse was recorded at the first reading. Each participant filled out a detailed questionnaire on factors relating to the blood pressure prior to having the blood pressure measured.

The tenth grade students of the high sodium community showed the hypothesized upshift along their entire blood pressure distribution when compared to the low sodium community students. The upshifted distribution, which occurred for both systolic and diastolic blood pressure and was consistent for both sexes, although more pronounced for females. The difference between the two groups of females for both mean systolic and diastolic blood pressure was 5.1 mm Hg, a difference statistically significant at the $p < 0.001$ level. The difference in mean systolic and diastolic blood pressure between the two male groups was 3.6 and 2.7 mm Hg, respectively. Both

of these differences were statistically significant at $p < 0.001$.

Statistical analyses designed to evaluate the possibility of confounding revealed no variables which were statistically significantly different between the tenth grade groups from the two communities which were also statistically significantly related to blood pressure within the population.

Other statistical analyses which were designed to adjust mean blood pressure simultaneously for any differences between the communities' student groups in regard to eighteen variables on the pupil questionnaire were carried out. Although minor changes in the mean values occurred as a result of these statistical analyses, the fundamental findings of the study were supported.

A statistically significant difference in mean blood pressure between the two communities for both the third grade boys and girls for systolic and diastolic blood pressure also occurred. The mean difference in systolic and diastolic blood pressure for boys from the high and low sodium communities was 3.3 mm Hg ($p = 0.001$) and 2.6 mm Hg ($p = 0.032$). The differences in mean systolic and diastolic blood pressure between the girls were 2.6 and 3.6 mm Hg and were statistically significant at $p = 0.023$ and $p = 0.002$, respectively.

As with the tenth graders, the upshifts occurred along the entire distribution of systolic and diastolic blood pressure for the third graders from the high sodium community relative to the low sodium community third graders for both boys and girls. The upshift was least marked for systolic blood pressure for girls and more distinct for systolic pressure for boys. However, the pattern was completely consistent for all four comparisons. Statistical adjustment for differences in the confounding characteristics resulted in an adjusted difference in mean blood pressure between the two towns which was even greater than when these factors were uncontrolled.

Data on liquid consumption collected indicated that the third grade pupils consumed about one liter of tap water from all drinks per day, obtaining 110 mg of sodium per day from this source. If the sodium obtained from water is added to both communities' total dietary intake, then about one quarter of the total excess sodium intake in the high sodium community is derived from this source.

Evaluation of the drinking water for heavy metal constituents known to affect blood pressure did not reveal any consistent difference of biological significance other than the originally defined differences in sodium values.

Bottled Water Study: Preliminary Findings

Methods

An experimental study was initiated to provide a more comprehensive test of the hypothesized relationship of water Na levels to blood pressure (*27*). Specifically, drinking water sodium levels were reduced in a population of fourth graders for a 3-month period to see if this would result in a decrease in blood pressure levels.

Participation was solicited from the families of the fourth grade children in the high sodium community whose parents had consented to their participation in the previous year's study among the third graders. For 3 months the cooperating families were instructed to regularly use the bottled water for all of the children's drinking water and for the preparation of foods and beverages. Additionally, bottled water was provided in the classrooms to serve the drinking needs of the children while at school. No control was exerted over the preparation of school lunches.

Children were matched by triads on the basis of sex, school, and baseline blood pressure. The members of the triads thus formed were then randomly assigned to the three water groups with one member of each triad per water group. Participating children and their families, the school personnel, and the nurses recording blood pressure were blind as to the type of bottled water being used by each child.

The three water groups were: (1) those receiving water taken directly from the public distribution system of their own high Na (110 mg/L) community; (2) those receiving water taken directly from the public distribution system of the low Na community (8 mg/L) with NaCl added to the 110 mg/L level characteristic of the high Na community water and (3) those receiving water taken directly from the public distribution system of the low Na community (8 mg/L). These three groups made it possible to assess whether any reduction in blood pressure was related to differences in sodium levels or to differences in other unknown characteristics of the waters.

Monitoring blood pressure occurred on a biweekly basis. A baseline blood pressure was obtained the week before water use was changed and was used for the initial matching of triads. Six subsequent screenings followed, at 2-week intervals, for the 12-week duration of the project.

Screening procedures were standardized as previously described. In addition to regularly monitoring blood pressure, 2-day diet records were collected before beginning the bottled water usage, and monthly thereafter for the 3 months.

Figure 1 illustrates the results for the 25 triads of girls. In this graph, pairs of biweekly values were averaged as monthly values. For both systolic and diastolic pressure, the LO sodium water group shows a consistently greater decline in blood pressure when compared to the other two high Na groups. In contrast, the response of boys was nil as can be seen in Figure 2 with monthly averages.

With respect to the girls, the low sodium group had the consistently higher blood pressure decline in all follow-up periods, ranging from 1.7 to 2.3 mm Hg for systolic blood pressure and 3.4 to 4.6 mm Hg for diastolic pressure. All the p values for the difference of means test were significant at $p < 0.10$. In the case of the six follow-up periods over half the p values were significant at $p < 0.10$. But the likelihood of all six follow-up period readings being consistently lower was 0.0156.

The final statistical procedure was a two-way analysis of covariance for repeated measures controlling for the confounders weight and pulse for girls. If six follow-up periods are used, the p for systolic blood pressure was 0.05 and for diastolic 0.01. For the combined three follow-up periods the p for systolic blood pressure was 0.08 and for diastolic pressure 0.01.

In regard to other potential confounders, there were no significant differences between boys and girls or among water groups within sex categories. Dietary data are still being coded and are not yet available.

In summary, the female data seem to indicate a sensitivity to blood pressure reduction when small amounts of Na are removed from the drinking water. However, the male data do not show a similar effect.

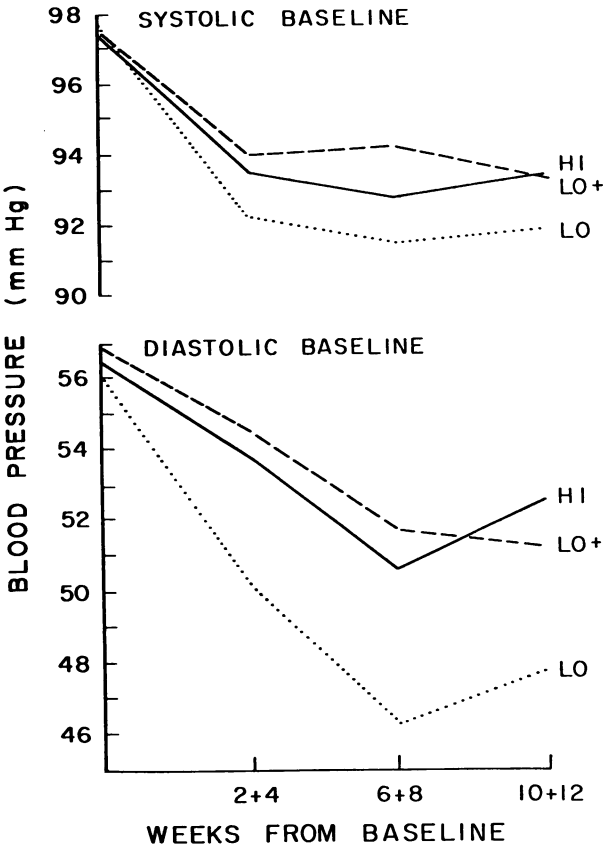

FIGURE 1. Systolic and diastolic blood pressure of 25 trios of girls at baseline and at combined follow-up weeks, adjusted for weight and pulse, by treatment group. HI: high Na community water (110 mg/L); LO+: low Na community water plus Na (110 mg/L); LO: low Na community water (8 mg/L).

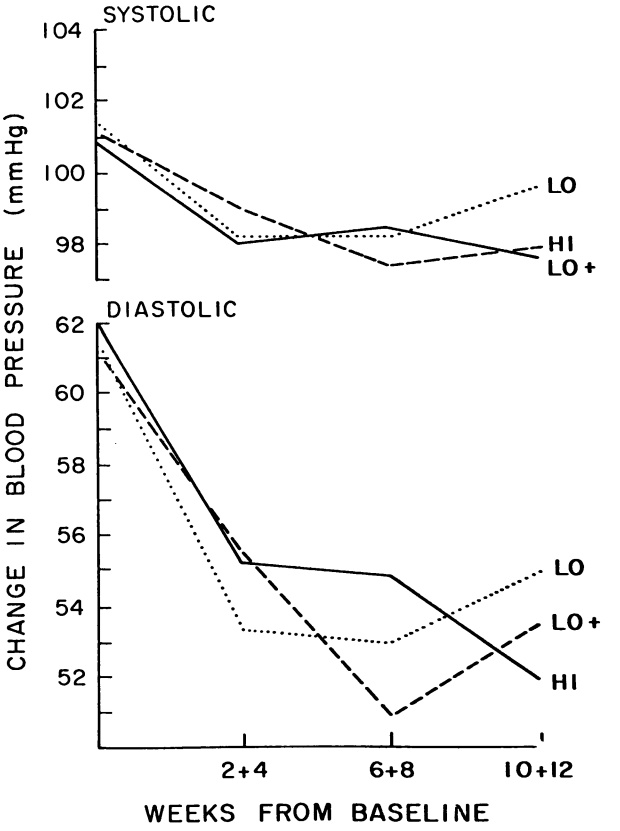

FIGURE 2. Systolic and diastolic blood pressure of 26 trios of boys at baseline and at combined follow-up weeks, adjusted for weight and pulse, by treatment group. HI: high Na community water (110 mg/L); LO+: low Na community water plus Na (110 mg/L); LO: low Na community water (8 mg/L).

Future Studies

Subsequent investigations have continued to evaluate the link between elevated levels of sodium in drinking water and increased blood pressure in several ways. Recent findings in our laboratory have revealed that low sodium vegetables cooked in drinking water with elevated levels of sodium showed a marked increase in total sodium content. Consumption of the three vegetables in common amounts per day after being cooked in water with 100 ppm or 250 ppm would contribute an additional 40 and 96 mg Na/day, respectively. If a commonly recommended cooking method of adding salt to the water were followed, the total amount of sodium taken up would be 1000 mg (*28*).

We are presently attempting to evaluate whether consumption of sodium from drinking water differentially affects blood pressure in adolescents as compared with a similar quantity of sodium from food.

Finally, the original "high" sodium community is planning to reduce their current sodium levels of approximately 110-120 mg/L to about 30 mg/L. This offers a truly unique opportunity to evaluate the effects on the community of such an intervention and should provide extremely valuable information concerning the effects of elevated levels of sodium in drinking water on human health.

Summary

It has been shown that epidemiological research has contributed in an important manner to our present understanding of the effects of several metals on human health. The major restraint in conducting epidemiological research on the effects of metals in drinking water on human health is the view that drinking water usually contributes only a small percentage of the total daily exposure to the substance. Potential investigators may often assume that it is not worth their effort to initiate epidemiological studies in this area. Such disregard for the water factor was driven home to me at a recent symposium on salt and hypertension in which a major intervention research project to identify factors needed to reduce blood pressure did not include a monitoring of sodium levels in drinking water despite the occurrence of widespread usage of water softening in that area.

The general conclusion that drinking water may contribute but an insignificant component of the daily exposure to heavy metals was challenged by Moore et al. (*29*). They reported that drinking water may be contributing much more lead to the total daily exposure than previously thought. Cooking vegetables and noodles in water with lead at the WHO standard would result in drinking water being able to contribute well over 50% of the total dietary exposure. Rowan and Calabrese (*28*) obtained similar though less dramatic effects with sodium uptake into three different types of fresh vegetables as previously noted. Other investigators have revealed that silver (*2*) and fluoride (*30*) may be markedly taken up by foods cooked in water with such substances.

The contribution of drinking water to the total daily exposure is usually calculated as the number of milligrams per number of liters of drinking water consumed each day which is assumed to be two. Rarely is the cooking process considered. Market basket surveys for metals are assessed prior to cooking. Thus, a possibly significant contribution of drinking water to the total daily exposure may be overlooked.

I would like to encourage environmental epidemiologists to apply their methodologies to attempt to identify and quantify the impact of various biological factors which may enhance or reduce metal toxicity. For example, consumption of low levels of several dietary minerals (e.g., calcium and iron) are thought to markedly affect the uptake and/or retention of lead and cadmium based predominantly on animal model research (*31*). Such animals studies are in dire need of epidemiological validation.

In addition, arsenical induced liver toxicity in humans has been found to be markedly reduced by administration of diets high in the sulfur containing amino acids, methionine and cystine (*31*). Thus, to what extent could the occurrence of arsenic-induced adverse effects as seen in the Taiwan study (*8, 9*) be influenced by inadequate nutritional status? Interestingly, the authors of that study specifically stated that the people in the endemic area subsisted on a diet low in animal protein and fat with carbohydrates being the main part of the diet.

Thus, I would like to leave you with four conclusions.

1. Several EPA drinking water standards are based primarily on animal models (*1*). Such animal research needs to be confirmed via epidemiological studies; if possible, national standards should not be based predominantly on animal studies due to the limitations of extrapolation processes. Conversely, additional burdens of proof should be placed on epidemiological derived data in the standard setting process when there is a lack of supporting data from animal models as in the case of arsenic.

2. Drinking water studies must be viewed as part of a multimedia approach. Lack of sufficient consideration of all other sources of exposure must be avoided.

3. Recent studies suggest that drinking water may be contributing considerably more to the total daily exposure to certain metals than previously thought as a result of uptake during cooking.

4. Application of the epidemiological perspective to evaluating the influence of factors such as nutritional status in enhancing the toxicity of heavy metals is likely to make an important contribution to this area.

I would like to thank Dr. Joseph Cotruvo, Director, Drinking Water and Standard, U.S. EPA, for providing copies of recently completed EPA funded reports on the effects of arsenic in drinking water on human health. The information presented on sodium has been previously presented and published elsewhere. The sodium research was supported by EPA grant R-805612-02 to Robert W. Tuthill and Edward J. Calebrese.

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