Original Contribution

Evidence From Chile That Arsenic in Drinking Water May Increase Mortality From Pulmonary Tuberculosis

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Arsenic in drinking water causes increased mortality from several cancers, ischemic heart disease, bronchiectasis, and other diseases. This paper presents the first evidence relating arsenic exposure to pulmonary tuberculosis, by estimating mortality rate ratios for Region II of Chile compared with Region V for the years 1958–2000. The authors compared mortality rate ratios with time patterns of arsenic exposure, which increased abruptly in 1958 in Region II and then declined starting in 1971. Tuberculosis mortality rate ratios in men started increasing in 1968, 10 years after high arsenic exposure commenced. The peak male 5-year mortality rate ratio occurred during 1982–1986 (rate ratio = 2.1, 95% confidence interval: 1.7, 2.6; *P* < 0.001) and subsequently declined. Mortality rates in women were also elevated but with fewer excess pulmonary tuberculosis deaths (359 among men and 95 among women). The clear rise and fall of tuberculosis mortality rate ratios in men following high arsenic exposure are consistent with a causal relation. The findings are biologically plausible in view of evidence that arsenic is an immunosuppressant and also a cause of chronic lung disease. Finding weaker associations in women is unsurprising, because this is true of most arsenic-caused health effects. Confirmatory evidence is needed from other arsenic-exposed populations.

arsenic; Chile; mortality; tuberculosis, pulmonary; water

Abbreviations: CI, confidence interval; ICD, *International Classification of Diseases*; RR, rate ratio.

Tuberculosis is a major public health problem worldwide. As noted by Das and Horton in 2010 (1), in the past year alone there have been 2 million deaths from tuberculosis and 9 million new infections. There is more tuberculosis today than at any other time in history. Increased susceptibility to tuberculosis has been identified with human immunodeficiency virus infection (2), diabetes mellitus (3), end-stage renal disease (4), and chronic lung diseases such as silicosis (5). Immune suppression is thought to be a mechanism involved in increasing tuberculosis rates with these conditions. Arsenic in drinking water has been found to cause immune suppression (6–8) and chronic lung diseases including bronchiectasis (9), but the relation between arsenic in water and pulmonary tuberculosis has not been investigated until now.

Arsenic in drinking water is a serious public health problem affecting many countries, with millions of people throughout the world exposed (10). Marked increases in mortality from many different causes have been established to follow prolonged consumption of arsenic-contaminated water, with the 3 main causes of death being lung cancer, bladder cancer, and acute myocardial infarction (11–16). Surprisingly, the lung is a target organ for ingested arsenic, with the main cause of long-term mortality from arsenic exposure being lung cancer. Evidence suggests that lung cancer risks relate to the absorbed dose of arsenic, regardless of whether arsenic is ingested in water or inhaled via occupational exposure (17). Nonmalignant effects in the lung have also been related to arsenic in drinking water, including reduction in lung function (18) and increased mortality from bronchiectasis (9). We have therefore been
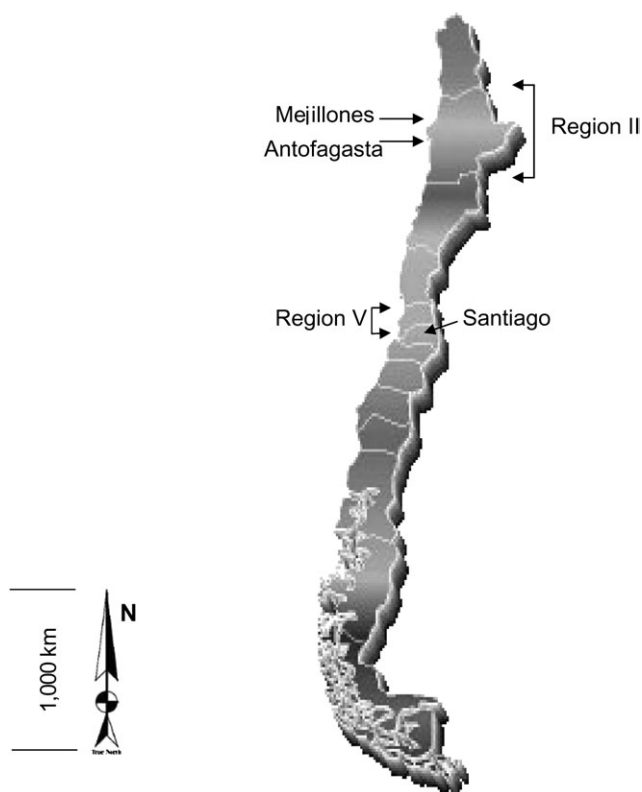
Figure 1.   Map of Chile.

studying mortality from all causes, particularly causes involving the respiratory system. We recently analyzed our study data from northern Chile to assess mortality from pulmonary tuberculosis.

MATERIALS AND METHODS

Exposure data

Because of some unique features, we believe that Region II in northern Chile (refer to Figure 1), with a population of 477,000 in 2000, is the best place in the world to assess long-term mortality from arsenic in drinking water. There are several reasons for this. One reason is that it is the driest inhabited place on earth, and all cities and towns have municipal water as their only source of drinking water. Another reason is that the concentration of arsenic in these municipal sources of water has been measured since 1950. Finally, Region II of Chile experienced some abrupt changes in arsenic water concentrations. In particular, the main city of Antofagasta (combined with nearby Mejillones, current population = 318,000) changed its water source in 1958 to a piped system coming from 2 arsenic-contaminated rivers, and water concentrations of arsenic immediately increased from about 90 μg/L to an average of about 870 μg/L (19). Then, in 1971, arsenic concentrations were abruptly reduced after the installation of an arsenic removal plant, initially to about 110 μg/L and continuing with improvements over the years, such that the water arsenic concentration is now less than 10 μg/L (Figure 2). We have obtained some of the historical data, including about 2,000 water arsenic measurements for Antofagasta in the period 1960–1980. Other towns and cities in the region also had arsenic-contaminated water so that the total population-weighted average water concentration was about 580 μg/L, but by the late 1980s, almost all the towns and cities with populations over 1,000 had arsenic concentrations of less than 100 μg/L (19). National surveys of arsenic in urine demonstrate little evidence of exposure outside Region II, and Valparaiso (the largest city in Region V) had average urinary arsenic concentrations of 15 μg/L in a 1984 survey, a concentration which is
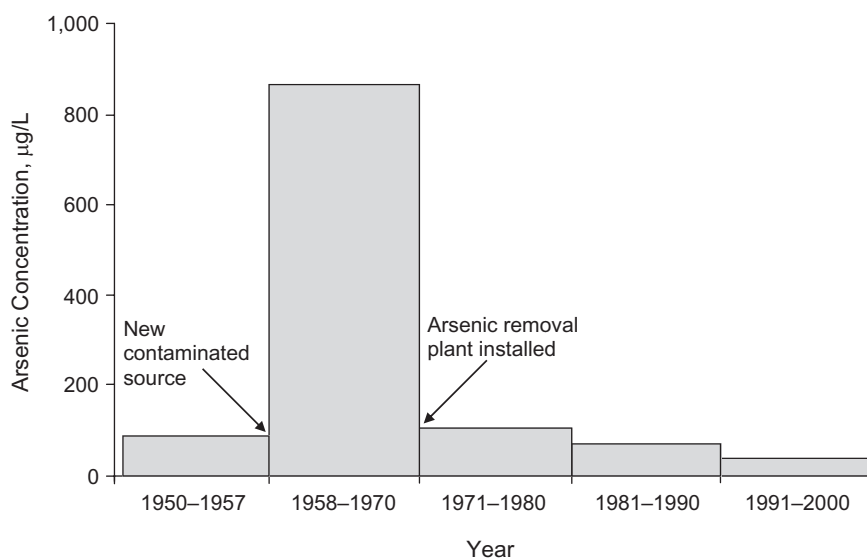

Figure 2.   Arsenic concentrations in water by year, Antofagasta and Mejillones, Chile, 1950–2000. New arsenic-contaminated water sources were used from 1958 onward, and an arsenic removal plant was installed in 1971.

Table 1. Sociodemographic Characteristics of Chilean Regions II (Population = 493,984) and V (Population = 1,539,852) According to the 2002 Census[a]

	Region II	Region V
Female, %	48.1	51.1
Over age 50 years, %	18.6	24.6
Catholic, %	71.7	75.4
Urban (vs. rural), %	97.7	91.6
Literacy rate, %	98.0	97.0
Education, %		
No schooling	5.2	5.6
University or professional	17.2	15.1
Cooking fuel, %		
Liquid or natural gas	96.4	97.5
Single family homes, %	84.8	82.4
Home appliances, %		
Refrigerator	81.9	85.8
Computer	27.5	20.2
Internet connection	12.0	9.4
Auto ownership, %	38.8	31.1

[a] Refer to census data at http://www.ine.cl/cd2002/index.php.

consistent with no meaningful exposure from drinking water (20).

Selection of the comparison population

Because mortality data were not available electronically for all of Chile, it was necessary to select an alternative referent population to span the whole study period, 1958–2000. It was desirable that the referent population be significantly larger than that of Region II, in order to maximize statistical precision. After careful consideration, we selected Region V, with a population about 4 times that of Region II. In 1980, the population of Region II was 314,807, while the population of Region V was 1,230,498. This ratio has been similar throughout the study period of 1958–2000. Arsenic-contaminated water has not been found in the comparison Region V, and its largest city, Valparaíso, has water arsenic concentrations close to 1 μg/L (21).

To ensure that Region V was an appropriate choice, preliminary investigations were conducted to compare per capita income, smoking rates, and death certification between Region II and Region V and with national Chilean data. The per capita income in Region V in 1990 was similar to that of the rest of the country (US $2,053 vs. US $2,011). Region II had a higher per capita income (US $3,853), but this was due to exports generated by the mining industry, rather than signifying higher personal income. Smoking surveys were carried out on random population samples in 1990 and 1992, with both years yielding similar data. In 1990, 26.6% of men and 19.3% of women in Chile said they smoked. The corresponding numbers from Regions II and V were similar: 27.4% and 28.5% for men and 16.6% and 20.2% for women (19). We also obtained information concerning death certification by Health Services Regions in the country, based on

a study conducted in 1983 (22). For the whole country, 85.6% of the death certificates in that year were certified by a physician. The corresponding percentages in Regions II and V were 89.8% and 94.5%. Thus, the vast majority of death certificates were completed by physicians, with both Regions II and V having higher percentages than the national average. As seen in Table 1, data from the Chilean 2002 Census also show that these 2 regions are similar in other key sociodemographic variables, including factors such as education, urban versus rural environment, and indicators of personal wealth.

Mortality data collection

As noted above, electronically stored mortality data were not available for Chile from 1958 to 1970. It was impractical and prohibitively expensive for the study team to code all of the death certificates for Chile for these years. For the years 1958–1970, 140,194 death certificates for Regions II and V were photographed, displayed on computer monitors, and coded by trained nosologists according to the *International Classification of Diseases* (ICD), Ninth Revision. Death certificates from both regions were intermingled, and nosologists were kept blind as to the region from which each death certificate originated. Computerized mortality data first became available in Chile in 1971. These data, already coded to the ICD, Ninth Revision, for all regions of Chile for the years 1971–1979 (excluding 1976), were obtained from the Chilean National Institute of Statistics (Instituto Nacional Estadisticas). For 1976, the information that is normally stored on computer disk at the Chilean National Institute of Statistics was never completed because of political unrest in the country. Mortality data for all regions of Chile for the years 1980–2000 were obtained from the Ministry of Health. ICD, Ninth Revision, codes had been used for 1980–1998, and ICD, Tenth Revision, codes had been used for 1999 and 2000. For this analysis, the ICD, Tenth Revision, codes A15–A16 for pulmonary tuberculosis were converted to the ICD, Ninth Revision, code 011.

Annual estimates of the population living in Regions II and V for the period 1958–2000, stratified by age and gender, were obtained from the National Institute of Statistics. The estimates are obtained by linear interpolation between census data collected approximately every 10 years.

Statistical analysis

To investigate the temporal relation of pulmonary tuberculosis mortality to changes in arsenic concentration, we first categorized calendar years into 3 time periods: 1958–1970 (the period of high exposure in Region II), 1971–1985 (intermediate exposure), and 1986–2000 (low exposure). We estimated mortality rate ratios using Poisson regression analysis, comparing Region II with Region V in each exposure time period for men and women separately, first stratified by age in 10-year strata and then for all ages combined and adjusted for age (Web Tables 1 and 2 posted on the *Journal*'s Web site (http://aje.oupjournals.org/)).

Poisson regression analysis was performed by using the PROC GENMOD procedure provided in SAS, version 9.2,

Table 2. Age-adjusted Rate Ratios for Pulmonary Tuberculosis Mortality for Region II (Exposed) Compared With Region V (Unexposed), Chile, for 1958–1970 (Peak Exposure Period), 1971–1985 (After an Arsenic Removal Plant Was Installed in the Major City of Antofagasta), and 1986–2000

Sex and Age	Mortality, 1958–1970					Mortality, 1971–1985					Mortality, 1986–2000				
	Region II Deaths, No.	Region V Deaths, No.	RR	95% CI	P Value	Region II Deaths, No.	Region V Deaths, No.	RR	95% CI	P Value	Region II Deaths, No.	Region V Deaths, No.	RR	95% CI	P Value
Male															
0–29 years	95	205	1.51	1.19, 1.93	<0.001	48	50	3.16	2.12, 4.69	<0.001	3	17	0.53	0.16, 1.82	0.32
30–59 years	420	1,699	0.85	0.77, 0.95	<0.01	284	691	1.49	1.30, 1.71	<0.001	86	210	1.36	1.05, 1.74	0.02
≥60 years	288	749	1.58	1.38, 1.81	<0.001	250	652	1.86	1.61, 2.16	<0.001	117	313	1.86	1.50, 2.30	<0.001
All ages	803	2,653	1.09	1.01, 1.18	0.03	582	1,393	1.71	1.56, 1.89	<0.001	206	540	1.58	1.34, 1.85	<0.001
Female															
0–29 years	75	263	1.04	0.80, 1.34	0.79	44	49	3.13	2.09, 4.71	<0.001	2	7	0.92	0.19, 4.43	0.92
30–59 years	137	542	1.05	0.87, 1.27	0.58	74	209	1.46	1.12, 1.90	<0.01	20	55	1.36	0.82, 2.27	0.24
≥60 years	94	363	1.35	1.08, 1.70	<0.01	61	254	1.33	1.01, 1.76	0.05	40	138	1.59	1.12, 2.26	<0.01
All ages	306	1,168	1.13	0.99, 1.28	0.06	179	512	1.60	1.35, 1.90	<0.001	62	200	1.48	1.11, 1.97	<0.01

Abbreviations: CI, confidence interval; RR, rate ratio.

software (SAS Institute, Inc., Cary, North Carolina). Analyses were conducted with the link function as the log and the offset as the log of the total population in each region, sex, and age stratum.

To further identify trends in the pulmonary tuberculosis mortality rate ratio over time, we plotted 5-year mortality rate ratio estimates by calendar year. For each year in the study period, we estimated the rate ratio for that year, combined with the 2 years before and the 2 years after it.

RESULTS

Table 2 presents the age-stratified numbers of the pulmonary tuberculosis deaths and rate ratios comparing Region II with Region V, for men and women separately in 3 time periods (year-by-year mortality data are given in supplemental tables). In 1958–1970, mortality rate ratios were close to 1 (men: rate ratio (RR) = 1.09; women: RR = 1.13). However, in the period 1971–1985, they were considerably increased (men: RR = 1.71, $P < 0.001$; women: RR = 1.60, $P < 0.001$). Rate ratios remained elevated in the period 1986–2000 but had reduced to 1.58 for men and 1.48 for women. The number of tuberculosis deaths among men greatly exceeds that among women. For example, in 1971–1985, there were 582 deaths among men in Region II due to pulmonary tuberculosis compared with 179 deaths among women ($P_{interaction} < 0.01$). We therefore focused our attention on the time trends among males in view of the much greater precision in rate ratio estimation. Figure 3 presents the time trend of mortality rate ratios for men in Region II compared with those in Region V, with each point representing an estimate for the 5-year period around which it is centered. A clear latency pattern emerged. Initially, pulmonary tuberculosis mortality rates were virtually identical for men in Region II compared with men in Region V (RRs ~ 1.0). An increasing trend can be seen starting around 1968, 10 years after the high exposures commenced. The highest 5-year rate ratio was for the period 1982–1986 (RR = 2.1, 95% confidence interval (CI): 1.7, 2.6; $P < 0.001$). Subsequently, the rate ratios fell so that, in the last 5-year period, 1996–2000, the rate ratio was close to 1 (RR = 1.3, 95% CI: 0.9, 1.8). Using the expected rate ratios based on Region V, we estimate that there were 359 excess pulmonary tuberculosis deaths in Region II in the period 1968–1995 among men and 95 among women.

DISCUSSION

We believe that this is the first evidence that arsenic in water may be related to pulmonary tuberculosis. The strength of the evidence includes the large population exposed, resulting in good precision in mortality rate ratio estimates, and the clear latency pattern that emerged among men, who are more susceptible to arsenic health effects than women are. Adding plausibility to the findings are the clear latency patterns that we have previously found in this population for causes of death known to be related to arsenic, including lung cancer and bladder cancer (16), kidney
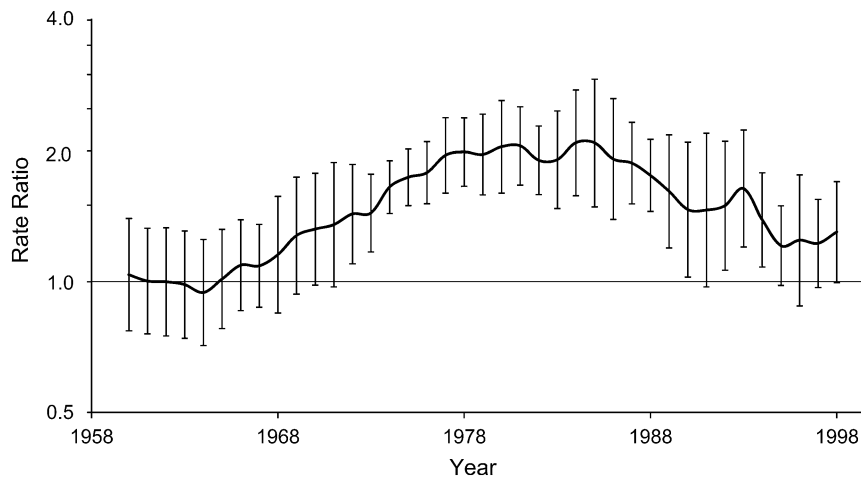
Figure 3. Age-adjusted rate ratios and 95% confidence intervals for pulmonary tuberculosis mortality for men of all ages, Region II (exposed) compared with Region V (unexposed), Chile, 1958–2000. Each point represents an estimate for 5 years and is plotted at the midpoint of the 5-year period, starting with the estimate for 1958–1962, which is plotted at the year 1960.

cancer (23), and mortality from myocardial infarction (15), as well as bronchiectasis (9). All health effects from chronic exposure to arsenic in drinking water, including skin lesions (24), have latencies from first exposure of 10 years or more.

Although initially it may seem counterintuitive that arsenic in water would affect the lungs, it has become increasingly apparent that the lung is one of the main target sites for the effects of ingesting arsenic in water. In fact, lung cancer is the major cause of long-term mortality from ingested arsenic (9, 16). Urinary arsenic concentrations give a good biomarker of the absorbed dose of arsenic, since about 70% is excreted in the urine (25). When related to urinary arsenic concentrations, lung cancer risks are about the same whether arsenic is ingested or inhaled (17). This is a surprising finding that indicates that arsenic ingested in drinking water not only reaches the lungs but has major toxic effects there, including causing lung cancer.

The biologic plausibility for finding arsenic in drinking water affecting pulmonary tuberculosis rates can also be based on the fact that arsenic is a known immunosuppressant, based in part on animal experimental studies. Evidence in mice includes the arsenic-compromised immune response to influenza A infection (26) and evidence that it alters expression of immune response genes in the mouse lung (27). In addition, an increasing body of evidence shows arsenic to be an immunosuppressant in humans (6, 7). Interesting recent evidence suggests that this effect is greater in males than in females. In a prospective study of in utero arsenic exposure and child immunity in Bangladesh, evidence of reduced thymic development was seen especially in male infants, along with evidence of increased acute respiratory infections (8).

The incidence of many arsenic health effects is higher in males than females. Evidence from studies in different countries shows that the characteristic skin lesions resulting from arsenic in drinking water are more common among men than women (28, 29). Mortality attributable to arsenic in drinking water includes lung cancer, bladder cancer, and myocardial infarction, but the incidence is much greater in men than in women. For example, in Region II of Chile, we estimated that there were 3,277 excess deaths among men due to these 3 causes of death compared with 947 excess deaths among women (15). It has been suggested that the enhanced male response is due to higher proportions of the inorganic arsenic metabolite monomethylated arsenic in men compared with women, which includes a trivalent form of monomethylated arsenic that is the most toxic form of inorganic arsenic in vitro, having greater toxicity than arsenite (24, 30).

The strengths of this study include the large size of the exposed population: There were over 125,000 residents in Antofagasta and Mejillones combined in 1970 exposed to arsenic water concentrations of 870 μg/L. The second largest city in Region II, Calama, also had high arsenic water concentrations, as did nearly all towns and villages. This study is by far the largest study in the world of a population with known high concentrations of arsenic in drinking water. The largest cohort study conducted in Taiwan involved only 698 subjects exposed to arsenic concentrations of greater than 300 μg/L (31). Recently published cohort studies in Bangladesh involved 10,431 subjects exposed to concentrations of greater than 300 μg/L in the largest study (32) and 2,889 subjects exposed to concentrations of greater than 150 μg/L in the second (33). In addition, each of these cohort studies had major problems with exposure ascertainment in the distant past. In contrast, our study region is the driest inhabited place on earth (34), and all residents had only 1 water source, the city water supply. The contrast in exposure between Antofagasta in the period 1958–1970 (water arsenic concentration, 870 μg/L) and the rest of Chile, including Region V, is very large and clear-cut. Other highly exposed populations, including those in Taiwan and Bangladesh, have received their water from town wells or individual private wells with wide variations in arsenic

concentrations, even between closely located wells. Wells used decades ago may now be closed, and water arsenic concentrations in early life are usually unknown. None of these complicated exposure scenarios is present in Region II of Chile; for example, children who drink water at school drink from the same town water supply that they drink from at home.

One apparent weakness of this study is that it is ecologic in nature, comparing 2 regions of Chile. However, the study does not have the usual problems associated with what is sometimes termed the "ecologic fallacy" (35), since everyone drinks water, and in the exposed region all water sources were contaminated with arsenic. The only other ecologic bias would be from in-out migration. People migrating into Region II would dilute overall exposure and, therefore, would dilute the evidence of effects. The bias would thus be to underestimate real effects and not to produce spurious increased risks. Clearly, with the increased mortality reported here, this bias is not an issue. A weakness of the study is that there are no data for risk factors for tuberculosis including human immunodeficiency virus infection, substance abuse, silicosis, and diabetes. However, there is no reason that these risk factors should follow the latency time pattern in relation to arsenic exposure found here. Another weakness of this study is that it involves mortality data with no information on incidence rates. This means that we cannot tell if arsenic is increasing the incidence of disease, or increasing mortality among incident cases, or both. In addition, the main effects found were before 1990, and most Region II medical records for that time period are not available, so we could not confirm the cause of death given on the death certificates. Confirmatory studies are needed in other arsenic-exposed populations, preferably with diagnosis of incident cases.

In conclusion, we have presented evidence from Chile suggesting that increased mortality from pulmonary tuberculosis could be yet another serious outcome from exposure to arsenic in drinking water. If verified, the findings will have important public health implications, since some of the largest arsenic-exposed populations are in developing countries with widespread tuberculosis. If arsenic in water increases mortality from tuberculosis, then particular attention will be needed to ensure that patients with tuberculosis are not drinking arsenic-contaminated water.

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