Chronic Arsenic Exposure and Risk of Infant Mortality in Two Areas of Chile

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Chronic arsenic exposure has been associated with a range of neurologic, vascular, dermatologic, and carcinogenic effects. However, limited research has been directed at the association of arsenic exposure and human reproductive health outcomes. The principal aim of this study was to investigate the trends in infant mortality between two geographic locations in Chile: Antofagasta, which has a well-documented history of arsenic exposure from naturally contaminated water, and Valparaíso, a comparable low-exposure city. The arsenic concentration in Antofagasta's public drinking water supply rose substantially in 1958 with the introduction of a new water source, and remained elevated until 1970. We used a retrospective study design to examine time and location patterns in infant mortality between 1950 and 1996, using univariate statistics, graphical techniques, and Poisson regression analysis. Results of the study document the general declines in late fetal and infant mortality over the study period in both locations. The data also indicate an elevation of the late fetal, neonatal, and postneonatal mortality rates for Antofagasta, relative to Valparaíso, for specific time periods, which generally coincide with the period of highest arsenic concentration in the drinking water of Antofagasta. Poisson regression analysis yielded an elevated and significant association between arsenic exposure and late fetal mortality [rate ratio (RR) = 1.7; 95% confidence interval (CI), 1.5–1.9], neonatal mortality (RR = 1.53; CI, 1.4–1.7), and postneonatal mortality (RR = 1.26; CI, 1.2–1.3) after adjustment for location and calendar time. The findings from this investigation may support a role for arsenic exposure in increasing the risk of late fetal and infant mortality. *Key words*: arsenic, Chile, drinking water, infant mortality, neonatal death, reproductive effect, stillbirth. *Environ Health Perspect* 108:667–673 (2000). [Online 6 June 2000]

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Arsenic is a naturally occurring element that is present in the environment in both organic and inorganic forms. Human exposures to the more toxic inorganic arsenic compounds result from exposures in occupational settings, such as metal smelting and pesticide production, as well as from medicinal treatments and environmental sources (1,2). The use of drinking water with elevated arsenic concentrations, primarily from natural contamination, has been the main source of environmental exposures in populations worldwide, including but not limited to communities in Taiwan (3), India (4), Bangladesh (5), Thailand (6), Mexico (7), Chile (8), Argentina (9), China (10), and Hungary (11). In the United States, it is estimated that 350,000 people obtain their drinking water from sources containing > 50 μg/L arsenic, the current maximum contaminant level (MCL) set by the U.S. Environmental Protection Agency (EPA) (12). Although higher exposures are more common in western states, recent concerns have also focused on other geographic regions where private well use is common. In areas where arsenic has been more extensively measured, levels are near the EPA MCL (12) or the World Health Organization recommended guidance values of 10 μg/L (e.g.,

Minnesota, New Hampshire, and Michigan) (13–15).

Chronic arsenic exposure at high doses has neurologic, dermatologic, vascular, and carcinogenic effects (1,2,16,17). Exposure to arsenic from drinking water increases the risks of skin, lung, and bladder cancers (18–20), and also seems to be associated with diabetes (21,22).

The possible impact of arsenic on reproductive effects has been given less attention, but the collective evidence from human and laboratory studies suggests the potential for adverse effects on several reproductive end points. Studies have reported adverse reproductive impacts among the offspring of employees and nearby residents of a Swedish copper smelter where arsenic exposures were documented (23–26). Female workers gave birth to lower weight infants than women who resided outside the smelter area, and the difference was greater if the mothers worked in highly exposed jobs (25). An incremental trend in the rates of spontaneous abortions was observed with increasing occupational and residential exposure (24,25). Congenital malformations appeared to be more frequent if the mother was employed in highly exposed jobs during pregnancy (26). In Bulgaria, the incidence of toxemia of

pregnancy and the mortality from congenital malformations were significantly higher than the national rates in an area near a smelter with environmental contamination from various metals (27). A study in Texas found an increase in the rates of stillbirths in relation to residential exposures from an arsenic pesticide factory (28). Although arsenic exposures were documented in all of these studies on reproductive effects, confounding from other metals or from other potential risk factors could not be excluded.

Studies of populations exposed to arsenic from drinking water have found increased rates of spontaneous abortions and stillbirths in Hungary (11) and Argentina (29). In the United States, three studies reported adverse reproductive effects, including increases in mortality from congenital cardiovascular anomalies (30,31) and spontaneous abortions (32). Exposed groups from these studies had arsenic levels that were quite low, making the results difficult to interpret.

Given the methodologic limitations of the current epidemiologic evidence, the literature on arsenic and adverse reproductive outcomes is suggestive, but not conclusive. However, the teratogenicity of arsenic in animals is well documented and generally consistent, showing that arsenic induces neural tube defects as well as malformations of other systems (33–36). The effects are dependent on dose, route, and timing of administration (35). Placental transfer of inorganic arsenic occurs in both animals and humans (37–42). A recent study in an area of Argentina with

high arsenic in drinking water (250 µg/L) found a close relationship between placental and cord blood arsenic levels, indicating considerable placental transfer of arsenic to the developing fetus during pregnancy (43).

Several areas of northern Chile have had a history of arsenic exposure. The surface water that supplies most of the towns and villages in the Atacama Desert region comes from rivers originating in the Andes mountains. Antofagasta, the largest city in this area, with a current population of approximately 250,000 people, has had a unique pattern of arsenic exposure that has been well described and which warrants further epidemiologic investigation. In 1958, because of insufficient water supply to serve the growing population and the decrease in water availability, water from the Toconce River was introduced as the new main water source. The river was later found to have arsenic concentrations of approximately 800 µg/L. The first reported cases of chronic arsenic health effects in Antofagasta appeared in 1962 (44), and a number of publications followed (8,20,45,46). After 12 years of high arsenic exposure, an arsenic-removal plant was installed in 1970 at the public water supply company, which led to a subsequent decrease in arsenic concentrations.

The purpose of this study was to compare the rates of stillbirth and infant mortality over time between Antofagasta, an area with historically high water arsenic levels, and Valparaíso, a comparison community with low arsenic concentrations in drinking water. We studied 47 years spanning from 1950 to 1996. This study period allows us to examine changes that may be related to the sharp increase in arsenic levels found in the drinking water of Antofagasta starting in 1958 and to the subsequent decrease starting in 1970. We also examined the general time trends in infant mortality of these two major Chilean cities over almost half a century.

Materials and Methods

Study design and population. This study used a retrospective ecologic design, incorporating secondary vital statistics data and environmental measurement data of arsenic levels in the public water supplies of Antofagasta and Valparaíso. Our primary interest was to compare infant mortality rates over time between Antofagasta, an area with historic high water arsenic levels, and Valparaíso, a comparison community with no historical evidence of high arsenic water contamination. Both cities are major Chilean ocean ports, similar in size and other sociodemographic characteristics (Table 1). Their locations are shown in Figure 1.

Vital statistics data. We obtained vital statistics data from the Instituto Nacional de Estadísticas (INE) in Santiago, Chile, which centralizes both local and national vital statistics and census information. Natality and mortality data were obtained for the period 1950 to 1996 from INE annual reports. The INE infant mortality data are classified separately as late fetal deaths (over 28 weeks of gestation, also commonly referred to as stillbirths) and infant deaths, dichotomized into categories of infants younger than 28 days of age (neonatal) and those 28 days to 1 year of age (postneonatal).

The birth and mortality data were reported by geographic locations. Since 1976, Chile has been stratified into regions numbered 1–12 from north to south. The regions have been further divided into provinces, and then into comunas (equivalent to counties in the United States). Before 1976, Chile was divided into 25 provinces, and throughout the years, changes in both the number and jurisdiction of geographic boundaries occurred. An in-depth reclassification of geographic areas developed common units of analysis to achieve compatibility across time for all regions of Chile, using the comuna as the

smallest unit of analysis (52). The majority of the population in the comunas of Antofagasta and Valparaíso live in cities bearing the same names (99 and 97%, respectively), thus making the comuna and city almost the same.

Births and deaths are reported by both place of occurrence and place of maternal residence. Because our interest is in the relationship between infant mortality and arsenic exposure from drinking water (either through maternal or infant ingestion), we used the location of maternal residence for coding the birth and death data.

Environmental exposure data. We obtained the average levels of arsenic from public water supplies for the period 1950–1996 from summarized data collected from local water company records and the

Figure 1. Map of Chile, including study locations of Antofagasta and Valparaíso. Adapted from *Maps of the Americas* (51).

Table 1. Demographic characteristics of Valparaíso and Antofagasta.[a]

	Valparaíso				Antofagasta			
Year	1950	1970	1982	1992	1950	1970	1982	1992
Total population of county or province[b]	424,799	254,812	272,520	283,000	165,005	127,967	186,341	228,000
Number of persons per household (average)	4.9	–	4.0	3.9	4.8	–	4.4	4.3
Population served by public water supply (%)	80.9	81.0	94.5	97.3	60.9	88.4	93.0	97.9
Population with electricity (%)	81.7	–	–	98.0	78.2	–	–	98.6
Educational status (%)								
Basic (grades 1–7)	82.4	67.0	55.0	47.2	73.2	64.7	53.9	45.3
Middle (grades 8–12)	16.4	22.2	32.9	40.0	24.2	21.8	30.5	38.3
High (postsecondary)	1.2	3.0	5.9	10.5	2.6	4.7	9.8	13.7
Poverty level								
Indigent (%)	–	–	–	4.7	–	–	–	4.2
Poor, not indigent (%)	–	–	–	17.5	–	–	–	12.4

–, data not available in the census reports reviewed by authors.
[a]Data from Census reports (47–50). [b]1970, 1982, and 1992 data for county; 1950 data for province.

regional health service (53) (Table 2). Before 1958, arsenic levels in the water of Antofagasta averaged 90 μg/L. After the introduction of the Toconce River as the main water source, the mean arsenic levels during the period 1958–1970 rose to approximately 860 μg/L. In 1970, the city installed an arsenic-removal plant for this water supply. Results of subsequent measurements indicated a decline in the arsenic levels over the next 26 years, with 1996 levels close to 50 μg/L.

In contrast, Valparaíso has no recorded evidence of elevated arsenic concentrations in the drinking water. Recent water surveys for Valparaíso, conducted by the Chilean National Environmental Commission (CONAMA) (54) and by our group, show low arsenic levels (< 5 μg/L). Data collected from water companies from 1990 to 1994 and summarized in the CONAMA study (54) also show that arsenic water levels in Valparaíso were below the analytical detection limit (20 μg/L). Although we do not have data before 1990, there is no reason to believe that Valparaíso had past exposures to arsenic from drinking water. The natural high arsenic contamination of water from geologic sources is specific to areas in northern Chile. Consequently, no major populations have the history of high exposures to arsenic from drinking water experienced by Region II, which includes Antofagasta (20). For the purpose of this study, we assumed that Valparaíso had low drinking water arsenic concentrations over the time period of study.

Statistical analysis. We used univariate statistics and graphical techniques to calculate and examine the time trends in infant mortality for Antofagasta and Valparaíso over the study period. We calculated annual infant mortality rates by dividing the number of deaths by the number of live births per location and multiplying by 1,000. For late fetal mortality, we divided the number of fatalities in each year by the number of live births plus late fetal deaths to obtain the death rate per total births. After calculating yearly mortality rates for each group, we noted considerable variation from year to year, given the small number of annual deaths at each study location. Therefore, we grouped the rates into 4-year periods (except for the last period, for which we only had 3

Table 2. Average drinking water arsenic levels in Antofagasta.[a]

Years	Concentration (μg/L)
1950–1957	90
1958–1970	860
1971–1979	110
1980–1987	70
1988–1996	40

[a]Data represent an average of existing arsenic water measurements, as presented by Pedreros (53).

years of data) to improve the stability of the mortality rates while maintaining a distinct time period of high arsenic exposure in Antofagasta.

For 3 years (1968–1970), the INE infant mortality data were reported as late fetal deaths and live-born infants who died before the end of their first year, without subdividing the latter into neonatal and postneonatal groups. For these 3 years, we imputed the number of neonatal and postneonatal deaths by linear interpolation. We calculated the ratio of neonatal deaths to the total number of infant deaths for each of the three previous years (1965–1967) and the three subsequent years (1971–1973). We used the slope of the fitted line through these six data points to estimate the proportion of neonatal deaths for the missing years, and multiplied it by the total number of deaths of infants younger than 1 year of age to obtain the neonatal deaths. We used the same method to estimate the number of postneonatal deaths. Rate differences were calculated between Antofagasta and Valparaíso for the three mortality outcomes for each 4-year period. We used rate differences to estimate the number of excess late fetal, neonatal, and postneonatal deaths that could be associated, at least in part, with the increase in arsenic exposure from drinking water in Antofagasta over the peak exposure years.

Poisson regression analysis. We used Poisson regression analysis to fit the mortality rates (late fetal, neonatal, and postneonatal) as a function of the estimated exposure to arsenic by log-linear regression models while adjusting for location and calendar time. Predictor variables in the model included location (Antofagasta or Valparaíso), calendar time (by 4-year intervals beginning in 1950), and arsenic exposure, entered into the model either as a continuous or dichotomous exposure variable. The inclusion of city in the models enabled us to control for differences other than arsenic that can explain variations in infant mortality, such as socioeconomic or health-care-related factors. For arsenic as a continuous variable, we used available historical arsenic levels in drinking water supplies to estimate averages for each 4-year period in each location. For the low exposures in Valparaíso, we assumed arsenic water levels of 5 μg/L. The dichotomous variable (present/absent) was created to serve as an exposure indicator only for Antofagasta during the years of high arsenic exposure (1958–1970). Because arsenic levels decreased after the installation of the arsenic-removal plant in March 1970, we only considered three high-arsenic year groups: 1958–1961, 1962–1965, and 1966–1969. For all other time periods and locations, this indicator variable was coded as a zero (absent). City, calendar time,

and one of the arsenic exposure variables were included in the Poisson regression models and goodness-of-fit was evaluated using graphical approaches plotting observed and expected rates over calendar time.

We calculated adjusted rate ratios (RRs) and the associated 95% confidence intervals (CIs) from the parameters estimated by the model. The calendar time period 1974–1977 served as the referent period for the model, chosen because it was after the end of the high arsenic period and quite close to the mid point of the entire study time. The analysis was performed using the PROC GENMOD procedure provided in the SAS software (55). The model was fit with the Poisson distribution with the link function as the log and the offset as the log of the appropriate denominator (i.e., total births). The results obtained using the arsenic exposure variable as either a continuous or as a categorical variable were not materially different; therefore, the results are shown for arsenic as a categorical variable.

Results

Demographic data for Valparaíso and Antofagasta representing several decades were obtained from INE census reports (47–50) and are presented in Table 1. These data indicate that Antofagasta and Valparaíso are comparable on a number of characteristics, although these indicators have changed over time.

Infant and late fetal mortality rates declined markedly in Chile during the study period of 1950–1996, as illustrated in Figure 2. This decrease is characteristic of most Latin American countries; it follows the general trend observed in industrialized nations and is largely due to improvements in living conditions and health care (56). The rate of decline up to the 1980s was the most pronounced for postneonatal mortality, with more gradual declines evident for neonatal and late fetal mortality.

Figures 3–5 show secular trends in late fetal, neonatal, and postneonatal mortality rates, respectively, by 4-year intervals, for Antofagasta and Valparaíso. Between 1950 and 1996, Antofagasta experienced an 86% decline in the late fetal mortality rate, an 81% decline in the neonatal mortality rate, and a 92% decline in the postneonatal mortality rate. Similarly, the declines in infant mortality rates for Valparaíso were 64, 77, and 92%, respectively. It is evident that Antofagasta experienced a more substantial decline in the late fetal mortality rate over this calendar period, whereas the relative decreases in neonatal and postneonatal mortality rates were similar in both locations. Despite the overall decline, rates for all outcomes increased in Antofagasta during the

calendar period 1958–1961 and declined thereafter. The increases and declines vary by outcome, but overall they coincide with the period of higher arsenic levels in the drinking water supply of Antofagasta. Table 3 shows the comparison of rates between the two areas. During the period of maximum difference in rates between the two communities (1958–1961), Antofagasta had an excess rate of approximately 20 late fetal deaths, 24 neonatal deaths, and 24 postneonatal deaths per 1,000 births (Table 3). The total estimated excess of 68 deaths per thousand births is equivalent to approximately 770 of the 1,900 combined late fetal and infant deaths which occurred during that time period. Subsequent to 1974, mortality rates exhibit a more gradual decline and are very similar between the two communities.

Results from the Poisson regression analysis of the rates of late fetal, neonatal, and postneonatal mortality are given in Table 4. We observed significantly elevated RRs for high arsenic exposure in association with each of the three mortality outcomes, after adjustment for location and calendar time. The association between arsenic exposure and late fetal mortality exhibited the strongest association (RR = 1.72; CI, 1.54–1.93), with neonatal mortality (RR = 1.53; CI, 1.40–1.66), and postneonatal mortality (RR = 1.26; CI, 1.18–1.34) also yielding elevated RRs, respectively. The variable for location demonstrated a significant association with each outcome, although the magnitude was less than that between arsenic exposure and each outcome. The rate ratios for the 4-year calendar groups exhibited the predictable secular declines over time.

Discussion

The results of this study indicate that exposure to inorganic arsenic from public water supplies may be associated with an increased risk of infant mortality. Specifically, the data suggest that arsenic exposure may represent a greater risk for late fetal mortality with a lower, but still elevated, risk for neonatal and postneonatal mortality. This association was evident after controlling for geographic location and calendar time in Poisson regression models.

The mortality rates in both Antofagasta and Valparaíso reflect the well-established decline in late fetal, neonatal, and postneonatal mortality that occurred in Chile over the study period (57). Improvement in the standard of living, development of programs for maternal and infant care (prenatal, nutritional supplementation, and health education, among others), and the decrease in birth rate are considered the primary factors accounting for the substantial improvement in infant mortality rates during this period (56,58,59). The steeper decline in postneonatal mortality supports these changing patterns of infant mortality because diarrheal infections and other childhood diseases that are much less fatal under improved health and living conditions are common throughout the first year of life.
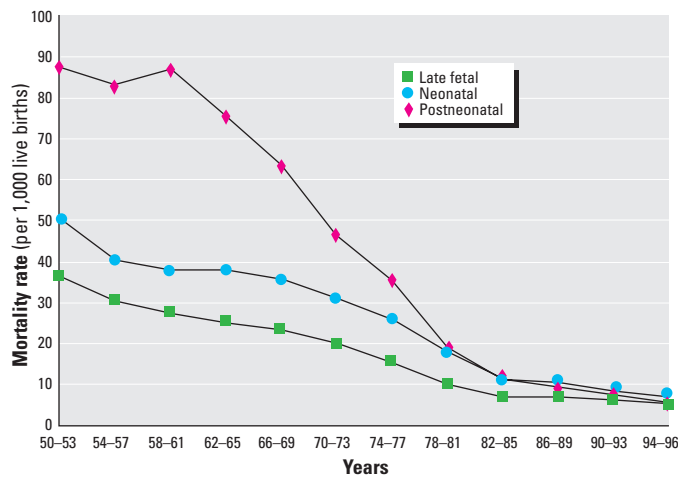

Figure 2. Late fetal, neonatal, and postnatal mortality rates for Chile, by 4-year periods from 1950 to 1996.
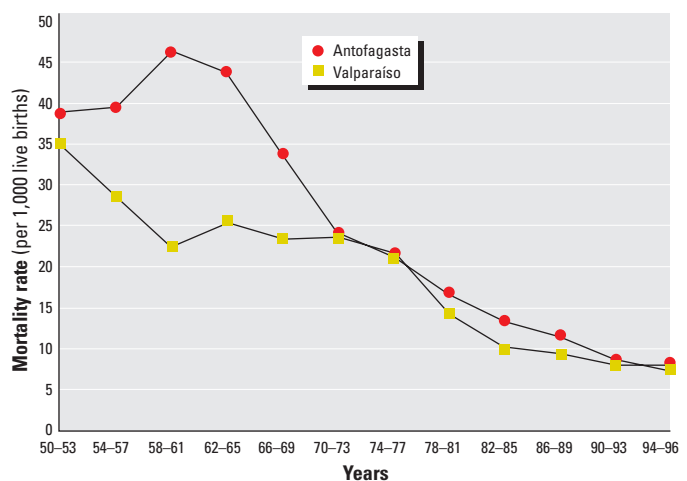

Figure 4. Neonatal mortality rates for Antofagasta and Valparaíso, by 4-year periods from 1950 to 1996.
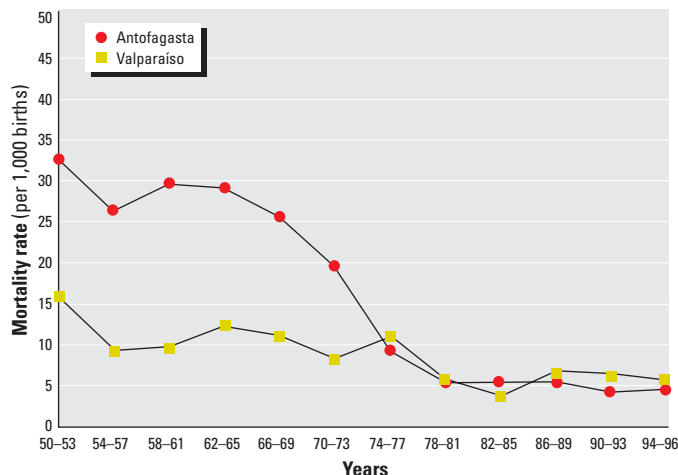

Figure 3. Late fetal mortality rates for Antofagasta and Valparaíso, by 4-year periods from 1950 to 1996.
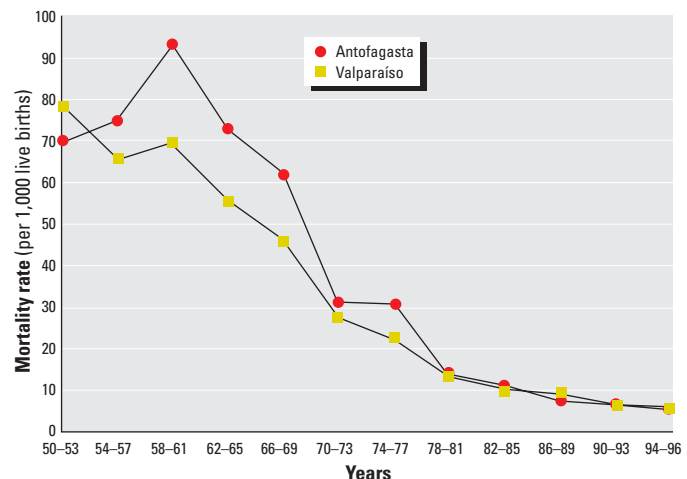

Figure 5. Postneonatal mortality rates for Antofagasta and Valparaíso, by 4-year periods from 1950 to 1996.

Table 3. Mortality rates and rate differences for Antofagasta and Valparaíso, by 4-year periods.[a]

Years	Late fetal				Neonatal				Postneonatal			
	ANTOF	VALP	RD	CI	ANTOF	VALP	RD	CI	ANTOF	VALP	RD	CI
1950–1953	32.2	15.9	16.3	15.4–17.3	38.4	34.7	3.7	3.0–4.4	69.8	78.4	-8.6	(7.8–9.4)
1954–1957	25.9	9.3	16.7	15.8–17.4	39.0	28.3	10.7	9.9–11.5	74.8	65.5	9.2	8.5–10.1
1958–1961	29.3	9.6	19.7	18.9–20.5	45.7	22.1	23.6	22.7–24.5	93.0	69.3	23.7	22.8–24.6
1962–1965	28.6	12.3	16.4	15.6–17.0	43.2	25.2	18.0	17.2–18.8	73.1	55.4	17.6	16.8–18.6
1966–1969	25.2	11.0	14.3	13.5–14.9	33.5	23.2	10.3	9.6–11.0	62.1	45.8	16.3	15.4–17.2
1970–1973	19.4	8.3	11.1	10.5–11.7	23.8	23.1	0.7	0.2–1.3	31.0	26.9	4.0	3.5–4.7
1974–1977	9.1	10.9	-1.7	(1.3–2.3)	20.9	21.3	-0.5	(0.1–0.9)	30.5	22.2	8.4	7.6–9.0
1978–1981	5.3	5.9	-0.5	(0.3–0.9)	16.5	14.1	2.3	1.9–2.9	13.0	13.5	-0.5	(0.03–1.0)
1982–1985	5.4	3.8	1.6	1.3–1.9	13.2	9.9	3.3	2.8–3.8	11.2	10.1	1.1	0.7–1.5
1986–1989	5.4	6.5	-1.0	(0.7–1.5)	11.4	9.3	2.2	1.7–2.5	7.1	9.3	-2.2	(1.8–2.6)
1990–1993	4.3	6.3	-2.1	(1.6–2.4)	8.5	8.0	0.5	0.1–0.9	7.0	6.7	0.3	0.04–0.6
1994–1996	4.5	5.8	-1.2	(0.9–1.7)	7.3	8.0	-0.7	(0.3–1.2)	5.4	6.1	-0.8	(0.3–1.1)

Abbreviations: ANTOF, Antofagasta; VALP, Valparaíso; RD, rate difference.
[a]Mortality rates were calculated per 1,000 live births for neonatal and postneonatal period, and per 1,000 total births (live + late fetal) for the late fetal period.

Although both Antofagasta and Valparaíso experienced substantial improvements in their overall infant mortality rates over the study period, the pattern of infant mortality for these two communities was quite different before the 1970s. Antofagasta exhibited marked increases in late fetal, neonatal, and postneonatal mortality in 1958–1961. As compared to Valparaíso, these rates remained elevated until 1974–1977 for late fetal mortality, and until 1970–1973 for neonatal and postneonatal mortality. The pattern of increase and subsequent decline in Antofagasta's mortality rates show a close temporal relationship with the rather sudden and sharp rise in the levels of arsenic in the city's public water supply from 1958 until March 1970, when an arsenic-removal facility was installed, and suggest a possible role for inorganic arsenic in the observed increase in infant mortality.

As in the rest of the country, the decline in mortality rates in Antofagasta during the overall study period was likely a result of other nonarsenic-related factors such as improvement in health care and standard of living, which affected all of the regions in Chile. Moreover, starting in the 1960s, Region II, which includes the city of Antofagasta, experienced a surge of economic expansion, with a rate of growth and development greatly surpassing that of the rest of the country: the increase in adjusted annual per-capita income was greater by far in Region II than any other region (60). This expansion brought improvements in regional health care as well, which may explain, at least in part, the fact that in the period before 1958 Antofagasta had higher late fetal and infant mortality rates than Valparaíso, whereas after 1970 the rates declined to comparable levels between the two towns. It appears that the increase in arsenic in the water supply served to delay the improvement in fetal and infant health until the arsenic-removal plant was installed (Figures 3–5).

The results of this study should be considered within the context of limitations in the study design and in the type of data obtained. In general, ecologic studies are susceptible to biases that pertain to the lack of individual data on exposure, outcomes, and confounders. These biases, known as the ecologic fallacy, have been discussed in detail elsewhere (61). In this study, although exposure was measured at the group level, public water was consumed by most residents in each of the communities, the water supply came from one main source at each location, and we adjusted for community differences in the model. However, we lacked data on individual-level confounders, and therefore we cannot definitely exclude the possibility of an ecologic bias. Nevertheless, the distinct temporal pattern of infant mortality rates in Antofagasta as compared to Valparaíso argues against this bias. That is, residual confounding from factors not available would have to closely relate to the timing of the high arsenic exposure documented in Antofagasta. The change in the arsenic level

of the water supply was an indisputable event, and no other environmental pollutant has been described to account for the many documented health effects experienced by the population of Antofagasta during the study time period (8,20,44,46,62–65). Thus, it would not be surprising if these reproductive events were also due to the consumption of water with high arsenic.

The underascertainment of both birth and death registrations is typically a potential concern of studies of this design. With regard to birth registration, there is evidence of underascertainment, which has substantially declined over time. In Chile, children whose births are not registered by March of the year after they were born are categorized separately. A study of birth registrations from 1955–1988 showed variations ranging from 11.4 to 4.2% in late birth registrations (66). We also observed variations between regions; Antofagasta and Valparaíso were consistently among those with the lowest late registration rates. The increase in births that occur in hospitals (42.3% in 1953 vs.

Table 4. Poisson regression analysis for secular trends in fetal, neonatal, and postneonatal mortality by arsenic exposure, location, and calendar time.

Variable	Fetal mortality		Neonatal mortality		Postneonatal mortality	
	RR	CI	RR	CI	RR	CI
Arsenic exposure						
No	1.0	(Referent)	1.0	(Referent)	1.0	(Referent)
Yes	1.7	1.5–1.9	1.5	1.4–1.7	1.3	1.2–1.3
Location						
Valparaíso	1.0	(Referent)	1.0	(Referent)	1.0	(Referent)
Antofagasta	1.5	1.4–1.6	1.1	1.1–1.2	1.1	1.0–1.1
Calendar time						
1950–1953	2.1	1.8–2.3	1.7	1.6–1.9	3.0	2.8–3.3
1954–1957	1.4	1.2–1.6	1.5	1.4–1.6	2.7	2.5–2.9
1958–1961	1.2	1.1–1.4	1.2	1.1–1.3	2.8	2.6–3.0
1962–1965	1.4	1.2–1.6	1.3	1.1–1.4	2.2	2.1–2.4
1966–1969	1.2	1.1–1.4	1.1	1.0–1.2	1.8	1.7–2.0
1970–1973	1.2	1.1–1.4	1.1	1.0–1.2	1.1	1.0–1.2
1974–1977	1.0	(Referent)	1.0	(Referent)	1.0	(Referent)
1978–1981	0.6	0.5–0.7	0.7	0.6–0.8	0.5	0.5–0.6
1982–1985	0.4	0.4–0.5	0.5	0.5–0.6	0.4	0.4–0.5
1986–1989	0.6	0.5–0.7	0.5	0.4–0.5	0.3	0.3–0.4
1990–1993	0.5	0.4–0.6	0.4	0.3–0.4	0.3	0.2–0.3
1994–1996	0.5	0.4–0.6	0.4	0.3–0.4	0.2	0.2–0.3

99.7% in 1994) and births assisted by medical professionals (57.5% in 1953 vs. 100% in 1994) also impacts the completeness of birth registration. Regional statistics show that Antofagasta and Valparaíso were two of the four provinces with the highest percentage of physician-assisted births in 1953, compared to the rest of Chile (*67*).

Death registration is also characterized by omissions, especially for newborns that died in the first hours or days after birth. A study conducted in Santiago in 1968–1969 showed that over one-half of the hospital-born babies who died were not registered (*68*). Another study in Santiago found that 13% of the deaths of children younger than 5 years of age (*69*) were not registered, and most of this underregistration occurred for deaths in the neonatal period. In Chile, the certification of infant deaths by a physician increased from 55% in 1952 (*68*) to 96% in 1994 (*58*). The omissions in death reporting and the late birth registrations affect mortality rates, which will be biased up or down depending on whether birth or death omissions were higher. However, given the much greater number of births than deaths, underreporting of deaths will have a much greater effect on the rates. In a study of 1976–1978 mortality by region, medical certification was used as an indirect measure of relative accuracy in the reporting of death (*69,70*). Antofagasta and Valparaíso were among the few provinces with < 5% of deaths lacking medical certificates (*69,70*). There is no evidence that underreporting was significantly different between the two study areas, but we did not find any published report with specific comparisons of fetal and infant mortality omissions by geographical locations across time.

In addition to the ecologic nature of the study and the potential effects of underascertainment of births or deaths, our analysis did not include other contaminants. For example, differences in exposures to pesticides or other metals could have an effect on infant mortality. Although we do not have specific information on pesticides, their use has been historically very limited in the Antofagasta region because it is a desert area with only local small-scale agriculture. On the contrary, the Valparaíso region is one of the most productive agricultural areas of the country. If pesticide exposure increased infant mortality, it would tend to increase the rates in Valparaíso so that the true RRs due to arsenic could be higher than those observed. On the other hand, the Antofagasta region has a history of mining and smelting that could have the opposite effect. However, most exposed activities are not close to the city of Antofagasta. Most importantly, it is unlikely that the clear sharp increase in arsenic water

levels, followed by the decrease 12 years later with the installation of the arsenic-removal plant, would be accompanied by another contaminant with a similar temporal pattern.

Summary and Recommendations

Although there is suggestive evidence for arsenic-related human developmental toxicity, the existing literature falls short of establishing a clear causal association between environmental arsenic exposure and reproductive health effects. The findings presented in this paper, albeit not definitive, support a role for arsenic in the increased late fetal and infant mortality observed in Antofagasta. Further studies are needed to investigate the broad range of reproductive and developmental effects, ranging from low birth weight to infant death, that may be causally related to arsenic in environmentally exposed populations around the world. The study designs of these investigations should consider using defined populations, with individual-level data and well-delineated methods of exposure assessment for arsenic and collection of data for potential confounding variables.

Results from the present study, the prospective cohort study under way in Chile by our group, and additional studies of this nature are important in the context of the ongoing review of the arsenic drinking water standard.

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