 International Journal of Epidemiology 1998;27:561–569

Lung and kidney cancer mortality associated with arsenic in drinking water in Córdoba, Argentina

Claudia Hopenhayn-Rich,[a] Mary Lou Biggs[b] and Allan H Smith[b]

Background Studies in Taiwan have found dose-response relations between arsenic ingestion from drinking water and cancers of the skin, bladder, lung, kidney and liver. To investigate these associations in another population, we conducted a study in Córdoba, Argentina, which has a well-documented history of arsenic exposure from drinking water.

Methods Mortality from lung, kidney, liver and skin cancers during the period 1986–1991 in Córdoba's 26 counties was investigated, expanding the authors' previous analysis of bladder cancer in the province. Counties were grouped *a priori* into low, medium and high arsenic exposure categories based on available data. Standardized mortality ratios (SMR) were calculated using all of Argentina as the reference population.

Results We found increasing trends for kidney and lung cancer mortality with arsenic exposure, with the following SMR, for men and women respectively: kidney cancer, 0.87, 1.33, 1.57 and 1.00, 1.36, 1.81; lung cancer, 0.92, 1.54, 1.77 and 1.24, 1.34, 2.16 (in all cases, $P < 0.001$ in trend test), similar to the previously reported bladder cancer results (0.80, 1.28, 2.14 for men, 1.22, 1.39, 1.81 for women). There was a small positive trend for liver cancer but mortality was increased in all three exposure groups. Skin cancer mortality was elevated for women only in the high exposure group, while men showed a puzzling increase in mortality in the low exposure group.

Conclusions The results add to the evidence that arsenic ingestion increases the risk of lung and kidney cancers. In this study, the association between arsenic and mortality from liver and skin cancers was not clear.

Keywords Argentina, arsenic, lung neoplasm, kidney neoplasm, water pollutants, environmental epidemiology

Accepted 4 December 1997

Chronic exposure to inorganic arsenic (In-As) is known to cause a wide range of adverse health effects, including characteristic skin alterations such as keratosis, hyperpigmentation and skin cancer from In-As ingestion, and lung cancer from In-As inhalation.[1] In recent years, attention has focused on evidence suggesting that ingestion of In-As also causes cancer of the bladder, lung, kidney and liver. The potential of In-As to increase the risks of these more fatal internal cancers could have serious public health implications, since In-As is found in drinking water in many parts of the world, both from naturally occurring and anthropogenic sources.

Most of the epidemiological evidence linking In-As ingestion and internal cancers comes from a group of studies of a population in southwestern Taiwan exposed to In-As from deep water wells.[2–6] Significant dose-response increases in mortality from bladder, lung, kidney and liver cancer were associated with mean In-As concentrations ranging from 170 to 800 µg/l. Based on data from these studies it was estimated that the risk of dying from lifetime daily consumption of water containing 50 µg/l of In-As (the current standard of the US Environmental Protection Agency) could be of the order of one in a hundred,[7,8] placing In-As as an environmental carcinogen comparable to radon and environmental tobacco smoke.

Additional evidence supports the association between ingestion of In-As and internal cancers. A cohort study of patients treated with Fowler's solution (a tonic containing potassium arsenite) found a threefold increase in bladder cancer,[9] and an investigation of arsenic-poisoned patients in Japan observed an

[a] University of Kentucky, Department of Preventive Medicine and Environmental Health, 1141 Red Mile Rd, Lexington, KY 40504, USA.

[b] School of Public Health, University of California, 140 Warren Hall, Berkeley, CA 94720, USA.

Reprint requests to : Dr Allan H Smith.

elevated occurrence of urinary tract cancers.[10] A recent study of a US population exposed to comparatively much lower levels of arsenic in drinking water found a positive trend for bladder cancer but only for smokers, and chance could not be dismissed as a possible explanation.[11] An elevated risk of lung and possibly liver cancer was reported for Moselle vintners who drank arsenic-contaminated wine,[12] and elevated lung cancer mortality was observed in two Japanese cohorts drinking arsenic-contaminated water.[13] However, these studies were either small or likely to suffer from bias and confounding. An analytical review of the evidence concluded that although it seemed probable that In-As did cause bladder cancer, as well as kidney, lung and liver cancers, confirmatory studies were needed.[14]

Large populations exposed to elevated levels of arsenic in drinking water have been reported in countries around the world, including Argentina,[15–17] Mexico,[18,19] Chile,[20,21] India[22] and China.[23] In Argentina, several provinces have been affected by natural arsenic water contamination.[24–27] The best characterized endemic area is in the eastern region of the province of Córdoba, located in the centre of Argentina. High arsenic levels in drinking water have been measured throughout this area, often above >100 μg/l and reaching levels over >2000 μg/l.[28,29] As early as the beginning of the century, physicians noted an increased incidence of clinical skin alterations in patients from certain areas of Córdoba and the high arsenic content of drinking water from wells in these regions was found to be the cause.[30]

Most reports from Argentina have focused on pathological skin alterations, but a few investigations suggested increased bladder and lung cancer mortality in Córdoba in the arsenic region,; one based on comparison of crude mortality rates of an arsenic-endemic area to the rest of the province,[31] and two follow-up case series of patients with arsenical skin disease.[16,32]

Based on the existing evidence and the available data resources, we conducted an ecologic cancer study by counties and exposure groups in Córdoba. We first focused on bladder cancer, since it was the cancer with the steepest slope and highest relative risks in Taiwan[7,8] and with more supportive evidence from other studies. We found a dose-related relation between arsenic exposure and bladder cancer mortality, consistent with the results from the Taiwanese studies.[33] In this paper, we expand the analysis to include kidney, lung, liver and skin cancer, the other main target sites previously found to be associated with arsenic in drinking water.

Methods

Study area

The province of Córdoba occupies an area of about 165 000 km^2 in the centre of Argentina, and has a population of approximately 2 750 000.[34] It is divided into 26 departamentos, similar to, and henceforth referred to as counties (Figure 1). According to the last census conducted in 1991, the population of the counties in Córdoba ranged from 4800 in Minas to 1 179 372 in Córdoba Capital (this refers to the provincial capital, which in itself constitutes a county). The majority of the counties had between 25 000 and 200 000 inhabitants. The province is a rich agricultural and cattle ranching area, with sizable industrial development centred mainly around the two largest cities of Córdoba Capital and Río Cuarto.

Mortality and population data

Córdoba mortality statistics for all causes of death for the years 1986–1991 were obtained from the Córdoba Department of Vital Statistics. These data are based on information recorded on death certificates, which includes underlying cause of death using the Ninth Revision of International Classification of Diseases (ICD), and county of usual residence of the deceased. Mortality data for all of Argentina for the year 1989 were provided by the National Ministry of Health in Buenos Aires. Population figures for Argentina and for each Córdoba county were extracted from the Argentina national census of 1991.[34] Based on available population and mortality statistics, we first conducted an ecologic study of arsenic and bladder cancer mortality in Córdoba by county, and found a dose-response relation.[33] For this paper, we used the same analytical approach and expanded the analysis to include kidney, lung, liver and non-melanoma skin cancer.

Exposure data

Previous studies have described the areas in Córdoba where clinical signs of arsenicism had been an endemic problem,[35–37] and have presented data on arsenic water measurements.[28–30] The combination of these two types of data sources indicated that some counties in the eastern region of the province had suffered from higher exposures to arsenic. The elevated groundwater arsenic concentrations are caused by the natural geological soil composition of the area.[38,39] Exposure has been generally limited to well water, which served as a main source of drinking water in the region for many years. In recent decades, aqueducts from rivers low in arsenic have been built to replace contaminated groundwater usage, as the health effects of arsenic became well known. Although the dates on which these new water supplies started serving different towns vary, most of them were not in full operation until the 1970s and 1980s. Even today, some populations, especially in smaller towns or localities, continue to use groundwater in combination with rain water collected in 'aljibes', specially constructed large outdoor storage containers. Since the average latency for most cancers is 20 or more years from first exposure, the mortality experience of the study period 1986–1991 should reflect exposure dating up to the 1970s.

In order to assess exposure, we used all available data on water measurements from previous studies. These included official reports of water analyses performed in the 1930s,[28] two scientific sampling studies[29,40] and a water survey conducted around a locality in southeastern Córdoba.[41] The representativeness of these measurements cannot be assessed, and the exposure data are not adequate to accurately characterize all counties by a mean exposure level.[42] However, the existing arsenic water measurements and the evidence from many reports of arsenical skin disease, provided sufficient data to group the counties into three exposure categories defined *a priori*: high, medium and low (Figure 1). Since Capital and Río Cuarto represent the major urban and industrial areas of the province, these two counties were not included in the three exposure categories. The analysis by exposure groups was thus restricted to rural counties to limit the effect of potential confounders.

The classification of counties into the three exposure groups is explained in detail elsewhere.[33] Briefly, the high exposure

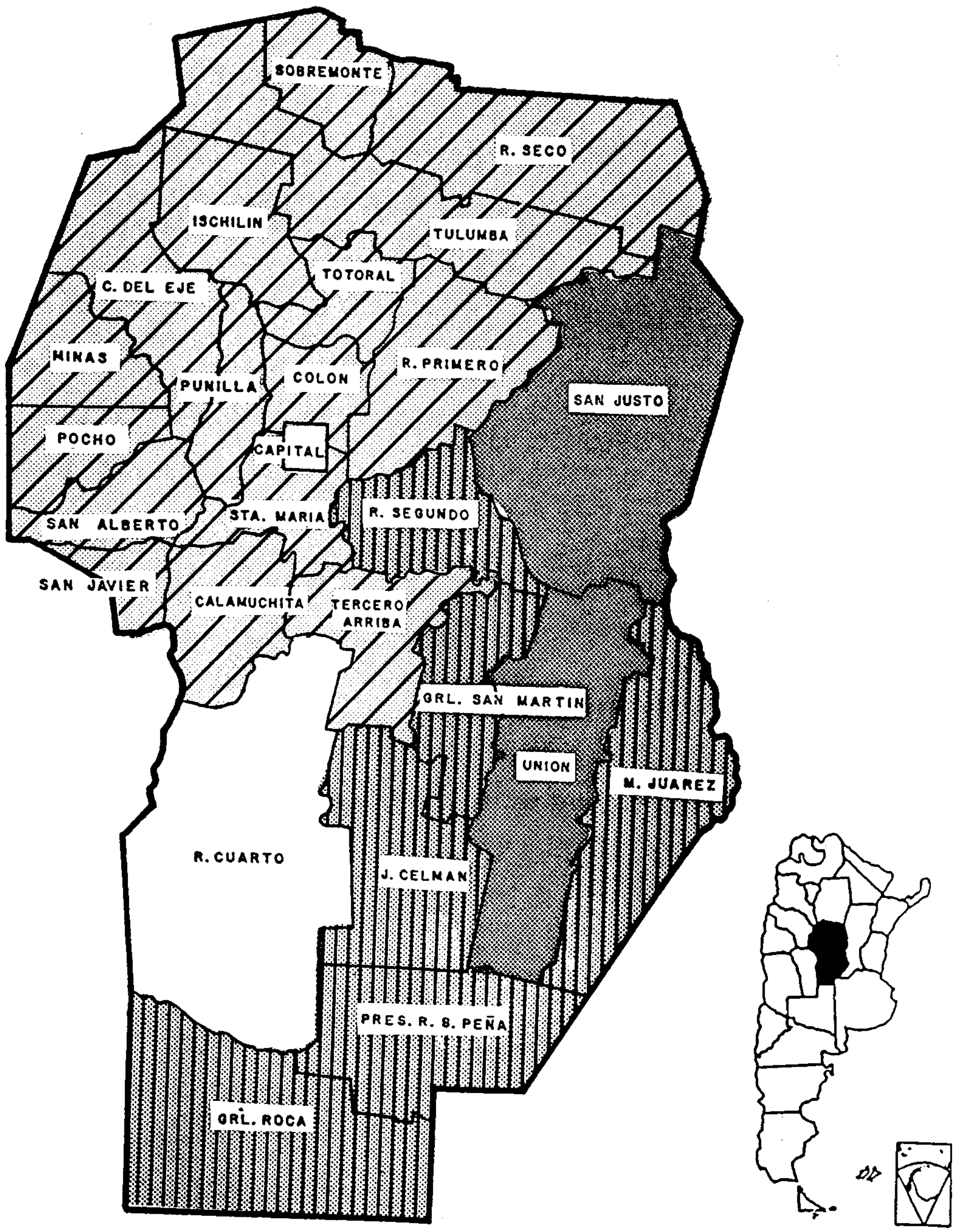

Figure 1 Map of Córdoba, Argentina, subdivided into counties and exposure categories; low-exposure group = diagonal lines; medium-exposure group = vertical lines; high-exposure group = gray; excluded from exposure classification = white

group includes San Justo and Unión, the two counties with the greatest relative numbers of clinical reports of arsenicism[31,36] (Tello EE, Universidad Nacional de Córdoba, personal communication, 1993) and high arsenic levels measured in water.[28,29] We compiled arsenic measurements from San Justo and Unión from a major water survey source,[28] from which we calculated a crude estimate of exposure. These data were matched to the population listings from the national census bureau.[34] Of the 46 towns in the census listings, 33 had one or more arsenic water measurements at or above the reported detection limit of 40 μg/l. Using all measurements ⩾40 μg, we estimated a crude average of 178 μg/l for the high exposure group (Unión and San Justo), which would apply only to that portion of the population exposed to arsenic-contaminated drinking water. Since water usage data were not available we could not calculate a weighted average for arsenic levels by exposure group.

The medium exposure group consists of six counties: Marcos Juárez, General San Martín, Juárez Celman, Presidente Roque Sáenz Peña, Río Segundo and General Roca. Together with Unión and San Justo, these form the general geographical region of eastern Córdoba generally described as the arsenical zone.[31,35,43] The counties in the medium exposure category also had information indicating both elevated arsenic levels in water[28,29,40,41,44] and occurrence of arsenical skin disease[44] (Tello EE, Universidad Nacional de Córdoba, personal communication, 1993, 1994), though to a lesser degree than the two counties in the high exposure group. Data extracted from a major national water survey listed the towns having at least one measurement over >120 µg/l.[38] For Córdoba, there were 43 towns: 15 located in one of the two high exposure counties; 22 in the six medium exposure counties; 4 in Río Cuarto, which was excluded from the grouped analyses as described above, and the remaining 2 in two other counties.

Finally, the remaining 16 rural counties of Córdoba constituted the low exposure group. Although some isolated elevated measures of arsenic have been reported, they are quite sparse compared with the commonly referred to arsenical region in southeastern Córdoba, which includes the counties classified as medium and high exposure groups.

Statistical analysis

We calculated standardized mortality ratios (SMR) for cancers of the kidney, lung, liver and skin for each county, separately for males and females. We used the SMR as the measure of effect because the gender-specific populations of six counties were under <10 000, and most of the cancers studied had small numbers of deaths. In such situations, the SMR is preferred to directly standardized mortality rates, since it is less sensitive to instabilities inherent in small number calculations.[45] Examination of age-specific SMR did not reveal evident heterogeneity, and the age distribution of the three exposure groups were very similar. We calculated expected deaths for each cancer based on cancer mortality rates in all of Argentina for 1989, by 5-year age groups, from 20–24 years to 80+ and applied these gender- and age-specific rates to the 1991 population of each county in Córdoba. We multiplied by six to obtain the expected deaths for the study period (1986–1991), and summed across all age groups to get the total expected numbers. We calculated 95% confidence intervals (CI) based on the method of Breslow and Day.[45]

Smoking is the main risk factor for lung and bladder cancer in the general population.[46] Since there was no available information on smoking patterns by county to assess its potential confounding effect, we used mortality from chronic obstructive pulmonary diseases (COPD) as a surrogate measure for smoking, since about 80% of COPD mortality is attributable to cigarette smoking.[47] The ICD codes used to assess COPD mortality were 490–496 (bronchitis, chronic bronchitis, emphysema, bronchiectasis, extrinsic allergic alveolitis, and chronic airways obstruction), excluding 493 (asthma).

In addition to the cancers investigated based on their previous association with arsenic ingestion, we included stomach cancer in our analysis. We used it as a control cancer to evaluate the distribution by county of a cancer site not known to be related to arsenic exposure in order to seek evidence of any diagnostic and detection biases in the study area.

To assess dose-response relations, we used the Poisson trend statistic.[45] Because of the *a priori* assumption of increased cancer risks associated with arsenic exposure, one-tailed *P*-values were used for kidney, lung, liver and skin cancer.

Results

The distribution of the population by gender and by county, with the corresponding SMR, are shown in Tables 1 and 2. Counties are listed by exposure category, in addition to the two counties of Córdoba Capital and Río Cuarto which were excluded from the exposure group analysis.

There is considerable variation in SMR across individual counties within each exposure group, mainly due to the small size of most county gender-specific populations and the corresponding small numbers of cancer deaths. Nevertheless, there is a general tendency for SMR to be more elevated in the medium and high exposure groups, especially for kidney and lung cancers, with much more fluctuation in the low exposure category. In particular, this is clear for Unión and San Justo, the two counties in the high exposure group.

The results of the analysis by exposure groups are presented by gender in Tables 3 and 4. The findings for bladder cancer from our previous report[33] are also presented for the purposes of comparison and completeness, amended as published subsequently.[48] Dose-response relations in SMR from low to high exposure, with significant increasing trend, are observed for lung cancer (0.92, 1.54 and 1.77 for men, 1.24, 1.34 and 2.16 for women; [$P < 0.001$ for both]) and kidney cancer (0.87, 1.33 and 1.57 for men, 1.00, 1.36 and 1.81 for women, [$P < 0.001$ for both]), similar to what we found previously for bladder cancer.

A slight trend is also seen for liver cancer, with elevated SMR in all exposure groups: 1.54, 1.80 and 1.84 for men, $P = 0.06$, and 1.69, 1.87 and 1.92 for women, $P = 0.14$. For skin cancer, the results do not show any clear pattern: among men, the highest SMR was for the low exposure group (2.04 compared to 1.49 in both medium and high groups), and for women, a substantial elevation was seen for the high exposure group only (2.78 versus less than 1.0 in the two other groups).

The findings show no exposure-related trend for stomach cancer, with all SMR point estimates close to 1.0. Low SMR were found for COPD in all exposure groups for men (0.87, 0.72 and 0.72) and in the medium and high exposure categories in women (1.18, 0.84 and 0.70).

Discussion

The results of this study in Córdoba, Argentina show clear dose-response relations between arsenic in drinking water based on *a priori* exposure classification and cancers of the kidney and lung, as was previously reported for bladder cancer.[33] In spite of limitations characteristic of ecologic studies, such as lack of individual exposure data, the potential effect of migration, and the lack of information regarding confounders, the trends are clear and generally consistent in direction with those found in Taiwan. The effect of certain unknown factors, such as use of bottled water and migration, would be likely to dilute the effect and lead to an underestimation of the association.

Although there was no systematic sampling of the study area's water supplies to accurately assess exposure, there was sufficient evidence from clinical observations and from existing water measurements to confirm arsenic exposure. The SMR by county (Tables 1 and 2) show the instability of the estimates due to the small sample sizes of some counties, however, they indicate a general consistency in the findings for kidney and lung

Table 1 Standardized mortality ratios (SMR) for kidney, lung, liver and skin cancers by county, for males, Córdoba Province, 1986–1991

		Kidney		Lung		Liver		Skin	
County	**Population[a]**	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
Capital	564 612	1.18	0.98–1.41	0.98	0.93–1.04	1.08	0.92–1.26	0.87	0.51–1.39
Río Cuarto	106 554	1.30	0.89–1.84	1.11	0.99–1.24	1.63	1.25–2.09	1.61	0.69–3.17
Low exposure									
Calamuchita	19 504	0.43	0.05–1.55	0.95	0.71–1.24	0.76	0.28–1.65	2.94	0.59–8.59
Colón	61 720	0.59	0.24–1.22	0.85	0.71–1.02	2.18	1.56–2.96	1.25	0.25–3.65
Cruz de Eje	24 131	1.16	0.42–2.52	0.87	0.65–1.14	2.04	1.19–3.27	1.96	0.22–7.08
Ischilín	13 876	0.63	0.07–2.27	0.76	0.50–1.10	0.60	0.12–1.75	3.33	0.37–12.0
Minas	2533	0.00	–	0.27	0.03–0.97	0.00	–	0.00	–
Pocho	2641	0.00	–	0.64	0.21–1.49	1.75	0.20–6.32	0.00	–
Punilla	58 205	0.89	0.47–1.52	0.75	0.63–0.89	1.75	1.26–2.37	1.60	0.52–3.73
Río Primero	19 048	0.98	0.26–2.51	1.12	0.84–1.46	1.08	0.43–2.23	2.22	0.25–8.02
Río Seco	5528	0.00	–	0.98	0.52–1.68	0.00	–	0.00	–
San Alberto	12 672	1.98	0.64–4.62	0.63	0.38–0.98	1.23	0.40–2.87	0.00	–
San Javier	20 737	0.46	0.05–1.66	0.58	0.39–0.83	1.99	1.09–3.34	0.98	0.01–5.45
Santa María	34 466	1.19	0.51–2.34	1.03	0.82–1.28	0.77	0.33–1.52	3.17	0.85–8.12
Sobremonte	2240	8.33	2.24–21.3	0.98	0.36–2.13	2.78	0.31–10.0	0.00	–
Tercero Arriba	51 201	0.56	0.22–1.15	1.39	1.21–1.59	1.74	1.20–2.43	2.99	1.20–6.16
Totoral	7057	1.45	0.16–5.24	0.92	0.53–1.49	1.80	0.48–4.61	6.67	0.75–24.1
Tulumba	5988	2.56	0.69–6.55	0.26	0.08–0.61	0.76	0.09–2.74	0.00	–
Medium exposure									
General Roca	16934	1.56	0.57–3.40	1.68	1.33–2.10	2.15	1.14–3.68	3.57	0.72–10.4
Gral. San Martín	51 305	1.63	1.00–2.52	1.49	1.30–1.70	1.77	1.23–2.47	1.71	0.46–4.38
Juárez Celman	26 058	0.82	0.26–1.91	1.31	1.06–1.60	1.54	0.86–2.54	1.59	0.18–5.74
Marcos Juárez	48 119	1.32	0.78–2.09	1.62	1.43–1.83	1.92	1.38–2.60	0.71	0.08–2.56
Pte. R.S. Peña	17 321	1.13	0.36–2.64	1.54	1.22–1.91	1.85	0.98–3.16	2.22	0.25–8.02
Río Segundo	41 809	1.27	0.66–2.22	1.58	1.36–1.83	1.65	1.07–2.44	1.04	0.12–3.75
High exposure									
San Justo	87 181	1.57	1.09–2.19	1.79	1.63–1.96	1.84	1.41–2.35	1.37	0.50–2.98
Unión	48 028	1.56	0.94–2.44	1.72	1.51–1.95	1.83	1.27–2.55	1.71	0.46–4.38

[a] Population figures from 1991 National Census.[34]

cancer in the three exposure categories. This is most evident for lung cancer among men, which involved the largest numbers of deaths as shown on Table 3.

It is clear that the exposure was not uniform within counties, and that not all the population was exposed. We previously reported that a rough estimation based on existing data indicated that about 20% of the population in the high exposure group may have been exposed to levels ⩾40 μg/l, ⩾20 years ago. Under this assumption, the SMR calculated would be an underestimation of the true relative risk for those exposed.

Given that the SMR for COPD were under unity for men in all exposure groups and women in the medium and high exposure groups, substantial confounding by smoking, the main population-wide risk factor for lung and bladder cancer, is unlikely. The lower rate of COPD mortality in the study region probably reflects the fact that the 24 counties are mainly rural areas where smoking prevalence may be lower. In addition, other factors such as industrial and urban pollution, which may also contribute to COPD[47] are reduced. Accordingly, COPD rates for Córdoba Capital, a large, industrial city of about 1.2 million people, were higher than in any of the exposure-grouped counties, with an SMR of 1.20 (95% CI : 1.09–1.31) and 1.31 (95% CI : 1.11–1.53) for males and females, respectively (results not shown).

Our exclusion of Capital and Río Cuarto counties, containing the two largest cities of the province, restricted the comparison of SMR to a rural, more homogeneous population. This step reduced the potential for confounding by environmental and occupational carcinogens found in large urban areas.

Although smoking is the main risk factor for lung and bladder cancer, other potential confounders should be considered. *Mate*, a type of tea infusion very common in Uruguay and Argentina, has been investigated in two studies in relation to bladder cancer. One study in Uruguay found a dose-response relation, with an odds ratio of 7.2 among heavy drinkers (more than >1.5 l/day) compared to light drinkers (<0.5 l/day), controlling for smoking, age and other variables.[49]

Another investigation conducted in La Plata, Argentina, found that while cases did drink more mate than controls, after adjusting for smoking there was no elevation in the relative risk.[50] Given the widespread habit of mate drinking in some areas of South America, it clearly warrants further investigation.

Table 2 Standardized mortality ratios (SMR) for kidney, lung, liver and skin cancers by county, for females, Córdoba province, 1986–1991

		Kidney		Lung		Liver		Skin	
County	**Population**[a]	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
Capital	614 760	0.93	0.70–1.20	1.21	1.08–1.35	1.15	0.99–1.33	0.76	0.43–1.25
Río Cuarto	111 322	1.08	0.59–1.81	1.31	1.02–1.66	1.36	1.00–1.81	1.16	0.37–2.71
Low exposure									
Calamuchita	19 300	1.90	0.51–4.86	1.57	0.86–2.63	2.55	1.43–4.21	0.00	–
Colón	63 682	0.99	0.36–2.15	1.41	0.99–1.95	2.31	1.63–3.17	0.98	0.11–3.54
Cruz de Eje	24 519	0.83	0.09–3.00	1.06	0.53–1.90	2.49	1.45–3.99	1.04	0.01–5.79
Ischilín	14 463	0.64	0.01–3.56	1.07	0.43–2.20	2.86	1.48–5.00	3.70	0.42–13.4
Minas	2267	0.00	–	0.00	–	0.00	–	0.00	–
Pocho	2416	0.00	–	0.00	–	2.78	0.31–10.0	0.00	–
Punilla	63 010	1.74	0.95–2.92	0.91	0.61–1.30	0.83	0.49–1.31	1.04	0.21–3.04
Río Primero	18 338	1.56	0.31–4.56	2.42	1.46–3.78	1.42	0.57–2.93	1.67	0.02–9.29
Río Seco	5067	0.00	–	2.15	0.58–5.50	1.67	0.19–6.03	0.00	–
San Alberto	12 432	1.67	0.19–6.03	1.46	0.58–3.01	1.92	0.70–4.18	0.00	–
San Javier	21 832	0.00	–	0.96	0.44–1.82	1.12	0.45–2.31	0.00	–
Santa María	35 004	0.56	0.06–2.02	1.30	0.78–2.03	1.15	0.57–2.06	1.75	0.20–6.32
Sobremonte	1956	0.00	–	2.38	0.27–8.59	1.67	0.02–9.29	0.00	–
Tercero Arriba	52 515	0.63	0.17–1.61	1.21	0.82–1.72	1.87	1.27–2.65	0.00	–
Totoral	6770	0.00	–	1.09	0.22–3.18	1.67	0.34–4.88	0.00	–
Tulumba	5303	0.00	–	0.76	0.09–2.74	1.72	0.35–5.03	0.00	–
Medium exposure									
General Roca	15 932	0.57	0.01–3.17	1.84	0.98–3.15	2.85	1.52–4.87	0.00	–
Gral. San Martín	53 856	2.10	1.15–3.52	1.32	0.92–1.83	1.70	1.15–2.43	0.90	0.10–3.25
Juárez Celman	25 432	1.45	0.39–3.71	1.33	0.76–2.16	2.42	1.46–3.77	0.00	–
Marcos Juárez	49 476	0.85	0.31–1.85	1.23	0.86–1.71	1.84	1.27–2.57	0.83	0.09–3.00
Pte. R.S. Peña	17 174	2.45	0.79–5.72	1.49	0.79–2.55	1.61	0.73–3.06	0.00	–
Río Segundo	42 584	0.83	0.22–2.12	1.27	0.82–1.87	1.59	0.97–2.46	1.79	0.36–5.23
High exposure									
San Justo	89 516	1.47	0.86–2.35	2.09	1.70–2.55	1.64	1.22–2.16	2.74	1.37–4.90
Unión	48 289	1.76	0.88–3.15	2.29	1.74–2.96	2.45	1.75–3.34	2.86	1.04–6.23

[a] Population figures from 1991 National Census.[34]

However, in our study it is unlikely to confound the arsenic-bladder cancer association since there is no reason to suspect that mate drinking would vary by arsenic exposure group. Similarly, although radon is an established environmental lung carcinogen,[51] and there is a lack of information regarding radon distribution in the study area, there is no evidence for a correlation of arsenic and radon concentrations. In addition, the association between arsenic and lung cancer is consistent with the results from other studies. Therefore, confounding by residential radon exposure is unlikely.

The liver cancer findings show a slight increasing trend for both men and women in relation to exposure, but even in the low exposure group the SMR are significantly elevated. The reason for this increase is not known, but it is in agreement with results of a cancer mortality study reporting that the province of Córdoba had high rates of liver cancer compared to all of Argentina, with rate ratios of 1.6 for males and 1.5 for females.[52] It was proposed that the high rates seen in some provinces may be a reflection of inaccurate diagnosis and inclusion of metastatic liver tumours as the primary target site.[52,53] The fact that the SMR for liver cancer were not significantly elevated in Córdoba Capital (Table 2), a large city with probably better access to medical care, lends support to the likelihood of more frequent misclassification of secondary tumours as primary liver cancers in more remote locations.

In Taiwan, the dose-response trend between In-As and liver cancer, which had a lower slope than with bladder, lung or kidney cancer, may be due to the interaction of arsenic with other risk factors. The high background rates of liver cancer among Chinese have been related to hepatitis B infection,[54,55] and exposures to aflatoxin.[55] In the arsenic endemic area of Taiwan, the high prevalence of hepatitis B infection of about 20% is about the same as that of the general population in the rest of the country.[56] Evidence suggests that liver cancer is of multifactorial origin with likely interactions between viral infections and chemical agents,[57] and it has been suggested that arsenic may thus increase the risk of liver cancer among hepatitis B carriers in the arsenic endemic area.[3] It is thus possible that this added susceptibility accounts for the increased liver cancer risks found in Taiwan, whereas the same is not found in Argentina, where hepatitis B infection is not widespread and where the background liver cancer rates are much

Table 3 Standardized mortality ratios (SMR) by arsenic exposure groups for males in Córdoba, 1986–1991

Cancer site (ICD)	Exposure group	Observed	Expected	SMR	95% CI
Bladder (188)	Low	113	140.65	0.80	0.66–0.96
	Medium	116	90.90	1.28	1.05–1.53
	High	131	61.24	2.14	1.78–2.53
Kidney (189)	Low	66	76.21	0.87	0.66–1.10
	Medium	66	49.74	1.33	1.02–1.68
	High	53	33.81	1.57	1.17–2.05
Lung (162)	Low	826	901.13	0.92	0.85–0.98
	Medium	914	593.70	1.54	1.44–1.64
	High	708	400.73	1.77	1.63–1.90
Liver (155)	Low	186	120.48	1.54	1.32–1.78
	Medium	142	79.08	1.80	1.51–2.11
	High	98	53.28	1.84	1.49–2.24
Skin (173)	Low	31	15.18	2.04	1.38–2.89
	Medium	15	10.08	1.49	0.83–2.45
	High	10	6.72	1.49	0.71–2.73
Stomach (151)	Low	327	313.02	1.04	0.93–1.16
	Medium	247	204.00	1.21	1.06–1.37
	High	143	137.46	1.04	0.87–1.22
COPD[a] (490–496)	Low	288	329.94	0.87	0.77–0.97
(excluding 493)	Medium	53	212.16	0.72	0.61–0.84
	High	103	142.62	0.72	0.58–0.87

[a] Chronic obstructive pulmonary disease.

Table 4 Standardized mortality ratios (SMR) by arsenic exposure groups for females in Córdoba, 1986–1991

Disease (ICD)	Exposure group	Observed	Expected	SMR	95% CI
Bladder (188)	Low	39	31.92	1.22	0.86–1.67
	Medium	29	20.88	1.39	0.93–1.99
	High	27	14.88	1.81	1.19–2.64
Kidney (189)	Low	38	37.86	1.00	0.71–1.37
	Medium	34	25.02	1.36	0.94–1.89
	High	27	14.88	1.81	1.19–2.64
Lung (162)	Low	194	156.96	1.24	1.06–1.42
	Medium	138	103.14	1.34	1.12–1.58
	High	156	72.36	2.16	1.83–2.52
Liver (155)	Low	173	102.24	1.69	1.44–1.96
	Medium	125	66.72	1.87	1.55–2.23
	High	90	46.86	1.92	1.54–2.36
Skin (173)	Low	11	12.96	0.85	0.42–1.51
	Medium	7	8.58	0.82	0.32–1.68
	High	17	6.12	2.78	1.61–4.44
Stomach (151)	Low	196	158.46	1.24	1.06–1.42
	Medium	98	103.68	0.95	0.76–1.15
	High	83	72.48	1.15	0.91–1.41
COPD[a] (490–496)	Low	99	84.18	1.18	0.95–1.43
(excluding 493)	Medium	46	55.02	0.84	0.61–1.11
	High	27	38.40	0.70	0.46–1.02

[a] Chronic obstructive pulmonary disease.

lower than in Taiwan (for males, they are 5.6/100 000[52] and 28.0/100 000,[4] respectively).

The skin cancer results are hard to interpret and were presented here mainly for the purpose of completeness, given the known association between arsenic ingestion and skin carcinoma. However, non-melanoma skin cancers have a relatively low fatality rate, and hence the results from Argentina likely indicate that mortality data does not reliably represent underlying skin cancer incidence.

We did not observe any pattern of increased stomach cancer rates by exposure groups, in agreement with the lack of evidence from other studies of an association between arsenic and stomach cancer. Thus, diagnostic or detection bias in the affected areas is not a likely explanation for the consistent trends found for cancers of the bladder, kidney and lung.

In conclusion, we found a dose-related association between arsenic ingestion from drinking water and increased risk of kidney and lung cancer. The results are consistent with those of the Taiwanese studies, adding support to the relationship between arsenic ingestion and internal cancers. Similar findings were also found in a recent study conducted in Chile.[58] The association between arsenic exposure and liver cancer was not clear in this population. Given the well-established arsenic-skin cancer causal relationship, the lack of a well-defined association in this study is likely due to the generally low fatality rates of skin cancer and to diagnostic inaccuracies.

Although individual-based studies with accurate exposure assessment are needed to clearly ascertain the magnitude of the risks and the shape of the dose-response relationships, and are currently underway, there is growing evidence indicating that the risks of the more fatal, internal cancers should be taken into consideration in arsenic risk assessments and in the establishment of safe arsenic drinking water standards.

Acknowledgements

Support for this work was provided by grants P30-ES01896 and P42-ES04705 from the National Institute of Environmental Health Sciences, and its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS, NIH. Additional support was received from the Center for Occupational and Environmental Health and the Health Effects Component of the University of California Toxic Substances Program. We are grateful to Dr Analía Fuchs for her local assistance in data collection, and to Drs R Bergoglio, E Tello, E Matos and H Nicolli for their helpful information. We thank the Ministerio de Salud, Departamento de Estadísticas, Buenos Aires, Argentina and the Departamento de Estadísticas Vitales, Ministerio de Salud, Córdoba, Argentina, for providing the data for this study.

References

1 International Agency for Research on Cancer. IARC monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Metals and Metallic Compounds. Lyon, France: World Health Organization, 1980.

2 Tseng WP, Chu HM, How SW, Fong JM, Lin CS, Yeh S. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J Natl Cancer Inst* 1968;**40:**453–63.

3 Chen CJ, Chuang YC, Lin TM, Wu HY. Malignant neoplasms among residents of a Blackfoot Disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. *Cancer Res* 1985;**45:**5895–99.

4 Chen CJ, Kuo TL, Wu MM. Arsenic and cancers (letter). *Lancet* 1988; **i:**414–15.

5 Wu M-M, Kuo T-L, Hwang Y-H, Chen C-J. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am J Epidemiol* 1989;**130:**1123–32.

6 Chen C, Wang C. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. *Cancer Res* 1990;**50:**5470–75.

7 Smith AH, Hopenhayn-Rich C, Bates MN *et al.* Cancer risks from arsenic in drinking water. *Environ Health Perspect* 1992;**97:**259–67.

8 Chen C-J, Chen CW, Wu M-M, Kuo T-L. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. *Br J Cancer* 1992;**66:**888–92.

9 Cuzick J, Sasieni P, Evans S. Ingested arsenic, keratoses, and bladder cancer. *Am J Epidemiol* 1992;**136:**417–21.

10 Tsuda T, Babazono A, Yamamoto EM *et al.* Ingested arsenic and internal cancer: a historical cohort study followed for 33 years. *Am J Epidemiol* 1995;**141:**198–209.

11 Bates MN, Smith AH, Cantor KP. Case-control study of bladder cancer and arsenic in drinking water. *Am J Epidemiol* 1995;**141:**523–30.

12 Luchtrath H. The consequences of chronic arsenic poisoning among Moselle wine growers. *J Cancer Res Clin Oncol* 1983;**105:**173–82.

13 Tsuda T, Nagira T, Yamamoto MKN, Hotta N, Harada M, Aoyama H. Malignant neoplasms among residents who drank well water contaminated by arsenic from a king's yellow factory. *Sangyo Ika Daigaku Zasshi* 1989;**11:**289–301.

14 Bates MN, Smith AH, Hopenhayn-Rich C. Arsenic ingestion and internal cancers: A review. *Am J Epidemiol* 1992;**135:**462–76.

15 Biagini RE. Hidroarsenicismo crónico en la República Argentina. *Med Cut ILA* 1975;**6:**423–32.

16 Tello EE. Arsenicismos hídricos: que es el hidroarsenicismo crónico regional endémico Argentino (HACREA)? *Archivos Argentinos de Dermatología* 1986;**36:**197–214.

17 Astolfi E. Estudio de arsénico en agua de consumo. *Prensa Médica Argentina* 1971;**58:**1342–43.

18 Cantellano-Alvarado L, Viniegra G, García RE, Acevedo JA. El arsenicismo en la Comarca Lagunera. Estudio epidemiológico de arsenicismo en las colonias Miguel Alemán y Eduardo Guerra, de Torreón, Coah. *Salud Publ Mex* 1964;**Epoca V.VI:**375–85.

19 Cebrián ME, Albores A, Aguilar M, Blakely E. Chronic arsenic poisoning in the North of Mexico. *Hum Toxicol* 1983;**2:**121–33.

20 Borgoño JM, Vicent P, Venturino H, Infante A. Arsenic in the drinking water of the city of Antofagasta: epidemiological and clinical study before and after the installation of a treatment plant. *Environ Health Perspect* 1977;**19:**103–05.

21 Zaldívar R. Arsenic contamination of drinking water and food-stuffs causing endemic chronic poisoning. *Beitr Path Bd* 1974;**151:**384–400.

22 Chakraborti AK, Saha KC. Arsenical dermatosis from tubewell water in West Bengal. *Indian J Med Res* 1987;**85:**326–34.

23 Liang M, Zhen-dong L, Ge-you Z *et al.* Clinical analysis and pathogenic changes of skin in endemic chronic arsenicism. Book of Posters from the SEGH Second International Conference on Arsenic Exposure and Health Effects, San Diego, CA, June 12–14, 1995. Denver, Colorado: Environmental Sciences, University of Colorado, 1995.

24 Biagini RE, Salvador M. Arsenicismo crónico en la Provincia de Salta. *Arch Argent Dermat* 1983;**33:**193–97.

25 De los Ríos EH, Alperovich BA, López CA *et al.* Estudio integral del H.A.C.R.E. en la Provincia de Tucumán. *Rev. Argentina De Dermatología* 1984;**65:**243–57.

[26] Grinspan D, Biagini R. Hidroarsenicismo crónico regional endémico (HACRE); Las manifestaciones de la intoxicación arsenical por el agua de consumo. *Medicina Cutánea Ibero-Americana* 1985;**13:**85–109.

[27] Enríquez AE. Bosquejo de un mapa de arsenicismo crónico en la provincia del Chaco. Comunicaciones al VII Congr. Arg. Dermat, Corrientes 22–24 Sept, 1976, pp.659–64.

[28] Obras Sanitarias de la Nación. *OSN, El problema del agua potable en el interior del país. Tomo II: Análisis Químicos*. Buenos Aires: Ministerio De Obras Públicas, Argentina, 1942.

[29] Nicolli HB, O'Connor TE, Suriano JM *et al.* Geoquímica del arsénico y de otros oligoelementos en aguas subterráneas de la llanura Sudoriental de la provincia de Córdoba, Miscelánea No. 71. Córdoba, Argentina. Academia Nacional De Ciencias, 1985.

[30] Ayerza A. Arsenicismo regional endémico. *Bol Acad Nac Med* 1917; 1–24.

[31] Bergoglio RM. Mortalidad por cáncer en zonas de aguas arsenicales de la Provincia de Córdoba, República Argentina. *Prensa Médica Argentina* 1964;**51:**994–98.

[32] Biagini RE, Rivero M, Salvador M, Cordoba S. Hidroarsenicismo crónico y cáncer de pulmón. *Archivos Argentinos de Dermatología* 1978;**28:**151–58.

[33] Hopenhayn-Rich C, Biggs ML, Fuchs A *et al.* Bladder cancer mortality associated with arsenic in drinking water in Córdoba, Argentina. *Epidemiology* 1996;**7:**117–24.

[34] Instituto Nacional De Estadística y Censos (INDEC). *Censo Nacional de Población y Vivienda 1991. Serie B, No 4. Resultados Definitivos: Características Seleccionadas, Córdoba*. Buenos Aires: República Argentina, Ministerio de Economía y Obras y Servicios Públicos, Secretaría de Programación Económica, 1993.

[35] Tello EE, Arguello RA, Pitt LA. Los epiteliomas en el hidroarsenicismo crónico regional endémico (HACRE). *Actas Finales Del V° Congresso Ibero Latino Americano De Dermatología* 1963, pp.507–14.

[36] Tello EE. Estado actual del problema de los epiteliomas hidroarsenicales. *Rev Fac Cienc Med Córdoba* 1972;**30:**29–38.

[37] Biagini RE, Magnani AV. Hidroarsenicismo queratosis palmoplantar. *La Semana Médica* 1972;**140:**308–11.

[38] Trelles RA, Largghi A, Paex JP. El problema sanitario de las aguas destinadas a la bebida humana, con contenido elevado de arsénico, vanadio y flúor. Buenos Aires: *Instituto de Ingeniería Sanitaria Pública, Universidad de Buenos Aires* 1970;**12:**17–30.

[39] Nicolli HB, Suriano JM, Gómez Peral MA, Ferpozzi LH, Baleani OA. Groundwater contamination with arsenic and other trace elements in an area of the Pampa, Province of Córdoba, Argentina. *Environ Geol Water Sci* 1989;**14:**3–16.

[40] Bitesnik H. *Descripción Hidrogeológica de la Región de Marcos Juárez*. Instituto Nacional de Geología y Minería, 1968, p.115.

[41] Guatelli MA, Gallego Gándara de Fernicola NA, Neira Rodríguez MM, Franchetti EP. Contenido de arsénico en el agua de consumo de la localidad de Mattaldi, Prov. de Córdoba, República Argentina. *La Semana Médica* 1973;**143:**443–46.

[42] Gavarotto MC, Mazzola de Martínez MD, Petcheneshsky T, Poiliser de Sued C. Contenido de arsénico en aguas en la República Argentina. Ideas Básicas para un programa nacional. 6° congreso Argentino de Saneamiento 21 al 25 de Septiembre de 1983, Salta, Argentina, 1983.

[43] Tello EE. Les epitheliomas d'origine arsenicale. *Laval Medical* 1963;**34:** 762–67.

[44] Lerda D. Sister-chromatid exchange (SCE) among individuals chronically exposed to arsenic in drinking water. *Mutat Res* 1994; **312:**111–20.

[45] Breslow NE, Day NE. *Statistical Methods in Cancer Research Vol. II. The Design and Analysis of Cohort Studies*. IARC Scientific Publications No. 82. Lyon, France: International Agency for Research on Cancer, 1987, pp.69,91–93.

[46] US Department of Health and Human Services. *The Health Benefits of Smoking Cessation*. DHHS Publication No. (CDC) 90–8416. Rockville, MD. US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990.

[47] Snider GL. Chronic obstructive pulmonary disease: risk factors, pathophysiology and pathogenesis. *Annu Rev Med* 1989;**40:**411–29.

[48] Hopenhayn-Rich *et al.* Erratum, *Epidemiology* 1997;**8:**334.

[49] De Stefani E, Correa P, Fierro L, Fontham E, Chen V, Zavala D. Black tobacco, mate, and bladder cancer. *Cancer* 1991;**67:**536–40.

[50] Iscovich J, Castelleto R, Esteve J *et al.* Tobacco smoking, occupational exposure and bladder cancer in Argentina. *Int J Cancer* 1987;**40:**734–40.

[51] National Research Council (NRC). *Health Risks of Radon and Other Internally Deposited Alpha-Emitters*. Washington, DC: BEIR IV, National Academy Press, 1988.

[52] Matos EL, Parkin DM, Loria DI, Vilensky M. Geographical patterns of cancer mortality in Argentina. *Int J Epidemiol* 1990;**19:**860–70.

[53] Matos EL, Loria DI, Vilenski M. Cancer mortality and poverty in Argentina: a geographical correlation study. *Cancer Epidemiol Biomarkers Prev* 1994;**3:**213–18.

[54] Beasley RP, Hwang L-Y, Lin C-C, Chien C-S. Hepatocellular carcinoma and hepatitis B virus. *Lancet* 1981;**i:**1129–33.

[55] Yeh F-S, Yu MC, Mo C-C, Luo S, Tong MJ, Henderson BE. Hepatitis B virus, aflatoxins, and hepatocellular carcinoma in southern Guangxi, China. *Cancer Res* 1989;**49:**2506–09.

[56] Lu J-N, Chen C-J. Prevalence of hepatitis B surface antigen carrier status among residents in the endemic area of chronic arsenicism in Taiwan. *Anticancer Res* 1991;**11:**229–34.

[57] Wogan GN. Aflatoxins as risk factors for hepatocellular carcinoma in humans. *Cancer Res* 1992;**52(Suppl.):**2114–18.

[58] Smith AH, Goycolea M, Haque R, Biggs ML. Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. *Am J Epidemiol* 1998;**147:**660–69.