2. Studies of Cancer in Humans

Major epidemiological studies of cancer in relation to arsenic in drinking-water include ecological studies and fewer case–control and cohort studies. For most other known human carcinogens, the major source of causal evidence arises from case–control and cohort studies, with little, if any, evidence from ecological studies. In contrast, for arsenic in drinking-water, ecological studies provide important information on causal inference, because of large exposure contrasts and limited population migration. As a consequence of widespread exposure to local or regional water sources, ecological measures provide a strong indication of individual exposure. Moreover, in the case of arsenic, the ecological estimates of relative risk are often so high that potential confounding with known causal factors cannot explain the results. Hence, in the review that follows, ecological studies are presented in detail.

2.1 Cancer of the urinary bladder and kidney

The findings of epidemiological studies on arsenic in drinking-water and the risk for cancers of the urinary bladder and kidney are summarized in Table 22.

Historically, several case reports have related cancers of the urinary tract with medicinal arsenic treatments or arsenic-related diseases such as Bowen disease. In 1953, a series of 27 cases with multiple skin cancers attributed to arsenical medicines was reported (Sommers & McManus, 1953). Of these cases, 10 were diagnosed as also having internal cancers at various sites, three of which were urinary tract tumours. Graham and Helwig (1959) first investigated an association between Bowen disease and primary internal cancers. Twenty-eight (80%) of 35 cases had primary internal cancers, two of which were malignant tumours of the bladder and one a tumour of the kidney. Cuzick *et al*. (1982) examined a cohort of subjects in the United Kingdom who had taken Fowler's solution (potassium arsenite) between 1945 and 1969. After further follow-up of the cohort through 1990 (Cuzick *et al*., 1992), a threefold increase in mortality from bladder cancer (standardized mortality ratio [SMR], 3.07; 95% confidence interval [CI], 1.01–7.3) was reported, strengthening the evidence on bladder cancer reported previously (Cuzick *et al*., 1982).

Bergoglio (1964) published the first report of bladder cancer associated with arsenic in drinking-water in the Province of Cordóba in Argentina. He identified 2355 deaths between 1949 and 1959 in nine towns of a highly exposed region and found that cancer was the cause of death of 24%; 11% of these cancer deaths involved cancers of the urinary tract. Biagini (1972) followed 116 patients with arsenic-related skin lesions in the same region and found that 12.5% of the cancer deaths were patients with urinary tract cancers.

Table 22. Summary of epidemiological studies of arsenic in drinking-water and risk for bladder and kidney cancers

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Ecological studies							
Taiwan							
Chen *et al.* (1985)	84 villages from four neighbouring townships on the SW coast	Mortality 1968–82	Comparison of mortality in an area endemic for Blackfoot disease with general population	*Bladder* Men Women *Kidney* Men Women	Obs/exp. 167/15.2 165/8.2 42/5.4 62/5.5	SMR (95% CI) 11.1 (9.3–12.7) 20.1 (17.0–23.2) 7.7 (5.4–10.1) 11.2 (8.4–14.0)	Reference: national rates
Chen *et al.* (1988a)	Area endemic for Blackfoot disease	Mortality 1973–86	Village of residence; median arsenic levels of well-water samples			SMR	Age-standardized mortality rates per 100 000; 899 811 person–years Reference: world population in 1976
				Bladder Men			
			General population			3.1	
			< 300 µg/L			15.7	
			300–590 µg/L			37.8	
			≥ 600 µg/L			89.1	
				Women			
			General population			1.4	
			< 300 µg/L			16.7	
			300–590 µg/L			35.1	
			≥ 600 µg/mL			91.5	
				Kidney Men			
			General population			1.1	
			< 300 µg/L			5.4	
			300–590 µg/L			13.1	
			≥ 600 µg/L			21.6	
				Women			
			General population			0.9	
			< 300 µg/L			3.6	
			300–590 µg/L			12.5	
			≥ 600 µg/L			33.3	

Table 22 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Wu *et al.* (1989)	42 villages in an area endemic for Blackfoot disease	Mortality 1973–86	Arsenic levels: 3 groups based on median level of well-water/village		Age-adjusted mortality rates per 100 000	Reference: world population in 1976
			Group 1 (< 300 µg/L)	*Bladder*		
			Men (248 728)	Men	22.64 ($p < 0.001$)	
			Women (248 728)	Women	25.60 ($p < 0.001$)	
				Kidney		
				Men	8.42 ($p < 0.05$)	
			Group 2 (300–590 µg/L)	Women	3.42 ($p < 0.001$)	
			Men (138 562)	*Bladder*		
			Women (127 502)	Men	61.02 ($p < 0.001$)	
				Women	57.02 ($p < 0.001$)	
				Kidney		
				Men	18.90 ($p < 0.05$)	
			Group 3 (≥ 600 µg/L)	Women	19.42 ($p < 0.001$)	
			Men (79 883)	*Bladder*		
			Women (74 083)	Men	92.71 ($p < 0.001$)	
				Women	111.30 ($p < 0.001$)	
				Kidney		
				Men	25.26 ($p < 0.05$)	
				Women	57.98 ($p < 0.001$)	

Table 22 (contd)

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Chen & Wang (1990)	314 geographical units (precincts and townships), including 4 townships in the endemic area of Blackfoot disease	Mortality 1972–83	Average arsenic levels in water samples of all geographical units. 73.9% of study precincts or townships had < 5% of wells with > 50 µg/L; 14.7% had 5–14%; 11.5% had ≥ 15%.	**All 314 precincts and townships** *Bladder* Men Women *Kidney* Men Women **170 south-western townships** *Bladder* Men Women *Kidney* Men Women		 3.9 (0.5) 4.2 (0.5) 1.1 (0.2) 1.7 (0.2) 3.7 (0.7) 4.5 (0.7) 1.2 (0.2) 1.7 (0.3)	Reference: world population in 1976. Analysis weighted by population in each group. Regression coefficients indicating an increase in age-adjusted mortality/100 000 person–years for every 0.1 µg/L increase in arsenic level (SE)
Chiang *et al.* (1993)		Incidence 1981–85	Exposure not evaluated Endemic area	*Bladder* Total Men Women	140 81 59	Incidence per 100 000 23.5 26.1 21.1	Adjusted for age
			Neighbouring endemic area	Total Men Women	13 7 6	4.5 4.7 4.3	
			All Taiwan	Total Men Women	2135 1608 527	2.3 3.3 1.2	

Table 22 (contd)

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Guo *et al.* (1997)	National survey of 83 656 wells in 243 townships	Incidence of transitional-cell carcinoma 1980–87	Arsenic levels in town of residence (ppm) < 0.05 0.05–0.08 0.09–0.16 0.17–0.32 0.33–0.64 > 0.64	*Bladder* Men Women *Kidney* Men Women	 1185 363 158 81	 0.57 (0.07) 0.33 (0.04) 0.03 (0.02) 0.142 (0.013)	Estimates of rate difference (per 100 000 person–years) for one unit increase in the predictor and associated standard error for exposure > 0.64 ppm (SE). Results shown for transitional-cell carcinoma
Tsai *et al.* (1999)	4 townships	Mortality 1971–94	Area endemic for Blackfoot disease	**Deaths** *Bladder* Men Women *Kidney* Men Women	 312 295 94 128	 8.9 (7.96–9.96) 10.5 (9.4–11.7) 14.1 (12.5–15.8) 17.7 (5.7–19.8) 6.7 (5.5–8.3) 6.8 (5.5–8.3) 8.9 (7.4–10.6) 10.5 (8.8–12.5)	 Local reference (Chiayi-Tainan county) National reference (Taiwan) Local National Local National Local National

Table 22 (contd)

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
South America							
Hopenhayn-Rich *et al.* (1996a, 1998)	26 counties in the Province of Córdoba, Argentina	Mortality 1986–91	Exposure levels	**Deaths**		SMR (95% CI)	
				Bladder			
			Low (690 421)	Men	113	0.8 (0.7–0.96)	
				Women	39	1.2 (0.9–1.7)	
			Medium (406 000)	Men	116	1.3 (1.05–1.5)	
				Women	29	1.4 (0.93–1.99)	
			High (mean arsenic level, 178 µg/L) (273 014)	Men	131	2.1 (1.8–2.5)	
				Women	27	1.8 (1.2–2.6)	
				Kidney			
			Low (690 421)	Men	66	0.9 (0.7–1.1)	
				Women	38	1.0 (0.7–1.4)	
			Medium (406 000)	Men	66	1.3 (1.02–1.7)	
				Women	34	1.4 (0.94–1.9)	
			High (273 014)	Men	53	1.6 (1.2–2.1)	
				Women	27	1.8 (1.2–2.6)	
Rivara *et al.* (1997)	Chile	Mortality 1950–92	Arsenic-contaminated Region II of northern Chile versus non-contaminated region VIII	Bladder		SMR (95% CI) 10.2 (8.6–12.2)	SMR for period 1976–92
				Kidney		3.8 (3.1–4.7)	
Smith *et al.* (1998)	Chile	Mortality 1989–93	Region II of northern Chile with population-weighted average arsenic concentration up to 569 µg/L compared with rest of Chile; exposure generally < 10 µg/L			SMR (95% CI)	Population of about 400 000
				Bladder			
				Men		6.0 (4.8–7.4)	
				Women		8.2 (6.3–10.5)	
				Kidney			
				Men		1.6 (1.1–2.1)	
				Women		2.7 (1.9–3.8)	
Australia							
Hinwood *et al.* (1999)	Victoria	Incidence 1982–91	Median arsenic concentration in drinking-water ranged 1–1077 µg/L			SIR (95% CI)	State rates used as reference
				Bladder	303	0.9 (0.8–1.1)	
				Kidney	134	1.2 (0.98–1.4)	

Table 22 (contd)

Reference	Location	End-point	Exposure	No. of cases		Study outcome		Comments
Case–control studies								
Taiwan								
Chen *et al.* (1986)	4 neighbouring townships in endemic area of Blackfoot disease	Mortality 1980–82	Median arsenic content of artesian well-water, 0.78 ppm Years of artesian water consumption	Community controls	Bladder cancer cases	OR	OR from multiple logistic regression analyses	Adjusted for age and sex
			0	136	17	1.0	1.0	
			1–20	131	19	1.2	1.3	
			21–40	50	10	1.6	1.7	
			≥ 40	51	23	3.9	4.1	
USA								
Bates *et al.* (1995)	10 areas of the USA	Incident cases (aged 21–84 years) diagnosed in a 1-year period in the 1970s. Age-, sex- and area-matched controls			Bladder cancer cases	OR (90% CI)		Adjusted for sex, age, smoking, years of exposure to chlorinated surface water, history of bladder infection, educational level, urbanization of the place of longest lifetime residence, ever employed in a high-risk occupation
			Cumulative dose (mg)	Controls		All subjects		
			< 19	47	14	1.0		
			19–32	36	21	1.6 (0.8–3.2)		
			33–52	39	17	0.95 (0.4–2.0)		
			≥ 53	38	19	1.4 (0.7–2.9)		
			mg/L × years					
			< 33	42	18	1.0		
			33–52	42	16	0.7 (0.3–1.5)		
			53–73	40	16	0.5 (0.3–1.2)		
			≥ 74	36	21	1.0 (0.5–2.1)		

Table 22 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Bates *et al.* (1995) (contd)			Cumulative dose (mg)		Never smoked	
			< 19		1.0	
			19–32		1.1 (0.4–3.1)	
			33–52		0.7 (0.2–2.3)	
			≥ 53		0.5 (0.1–1.9)	
			mg/L × years			
			< 33		1.0	
			33–52		0.2 (0.1–0.8)	
			53–73		0.3 (0.1–0.9)	
			≥ 74		0.9 (0.3–3.2)	
			Cumulative dose (mg)		Ever smoked	
			< 19		1.0	
			19–32		3.3 (1.0–10.8)	
			33–52		1.9 (0.6–6.2)	
			≥ 53		3.3 (1.1–10.3)	
			mg/L × years			
			< 33		1.0	
			33–52		1.95 (0.7–5.6)	
			53–73		1.2 (0.4–3.7)	
			≥ 74		1.4 (0.5–4.3)	

Table 22 (contd)

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Europe							
Kurttio *et al.* (1999)	Areas in Finland in which < 10% of population belong to the municipal drinking-water system	Incidence 1981–95	Concentration of arsenic in water	*Short latency*	**Bladder**		Case–cohort design
						Relative risk (95% CI)	Adjusted for age, sex and smoking
			< 0.1 µg/L	23		1.0	
			0.1–0.5 µg/L	19		1.5 (0.8–3.1)	Short latency: exposure in the 3rd to 9th calendar year prior to the cancer diagnosis
			≥ 0.5 µg/L	19		2.4 (1.1–5.4)	
			Total	61		1.4 (0.95–1.96)	
				Long latency			Long latency: exposure in the 10th calendar year and earlier prior to the cancer diagnosis
			< 0.1 µg/L	26		1.0	
			0.1–0.5 µg/L	18		0.8 (0.4–1.6)	
			≥ 0.5 µg/L	17		1.5 (0.7–3.4)	
			Total	61		0.96 (0.6–1.6)	
			Concentration of arsenic in water	*Short latency*	**Kidney**		
			< 0.1 µg/L	23		1.0	
			0.1–0.5 µg/L	12		0.8 (0.4–1.7)	
			≥ 0.5 µg/L	14		1.5 (0.7–3.3)	
			Total	49		1.2 (0.8–1.7)	
				Long latency			
			< 0.1 µg/L	25		1.0	
			0.1–0.5 µg/L	9		0.3 (0.1–0.8)	
			≥ 0.5 µg/L	15		1.07 (0.5–2.5)	
			Total	49		0.7 (0.4–1.4)	

Table 22 (contd)

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Cohort studies							
Taiwan							
Chen *et al.* (1988b)	4 neighbouring townships in area endemic for Blackfoot disease	Mortality 1968–93	Comparison of mortality with general and endemic population	Cancer deaths		SMR	95% CI calculated by the Working Group
				Bladder	15	38.8 [21.7–64.0]	General population as reference
				Kidney	3	19.5 [4.0–57.0]	
						SMR	
				Bladder	15	2.6 [1.4–4.2]	Area endemic for Blackfoot disease as reference
				Kidney	3	1.6 [0.3–4.7]	
Chiou *et al.* (1995)	4 neighbouring townships in area endemic for Blackfoot disease (BFD)		Cumulative index derived for each subject: Σ (Ci × Di). Cumulative exposure (mg/L × year)	BFD patients	263	*Bladder cancer* RR* (95% CI)	*Relative risk after adjustment for age, sex and smoking **Relative risk after adjustment for age, sex, smoking and BFD status Ci, median concentration of arsenic in wells of village; Di, duration of drinking water in that village
				Healthy controls	2293		
			0	Bladder cancer cases	29	1.0	
			0.1–19.9			2.1 (0.6–7.2)	
			≥ 20			5.1 (1.5–17.3)	
						RR** (95% CI)	
			0			1.0	
			0.1–19.9			1.6 (0.4–5.6)	
			≥ 20			3.6 (1.1–12.2)	

Table 22 (contd)

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Chiou *et al.* (2001)	North-eastern Taiwan	Incidence 1991–94	Area endemic for arseniasis			RR (95% CI)	Adjusted for age, sex, smoking and duration of drinking well-water
		Person–years of observation	Arsenic concentration in well-water (µg/L)			*Urinary tract*	
		7978	< 10.0	3		1.0	
		6694	10.1–50.0	3		1.5 (0.3–8.0)	
		3013	50.1–100.0	2		2.2 (0.4–13.7)	
		5220	> 100.0	7		4.8 (1.2–19.4)	*p* for trend < 0.01
						Transitional-cell carcinoma	
		7978	< 10.0	1		1.0	
		6694	10.1–50.0	1		1.9 (0.1–32.5	
		3013	50.1–100.0	2		8.2 (0.7–99.1)	
		5220	> 100.0	6		15.3 (1.7–139.2)	*p* for trend < 0.05
Japan							
Tsuda *et al.* (1995)	Niigata prefecture	1959–92		No. of persons exposed	Urinary Obs/exp.	SMR (95% CI)	
			Arsenic concentration in well-water (ppm) from arsenic-polluted area	at concentration level (1955–59)			
			< 0.05	254	0/0.3	0 (0–12.5)	
			0.05–0.99	76	0/0.08	0 (0–47.1)	
			≥ 1	113	3/0.10	31.2 (8.6–91.8)	
			Total	443	3/0.48	6.3 (1.7–18.4)	

Table 22 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
USA						
Lewis *et al.* (1999)	Millard County, UT	Mortality	Index of exposure to arsenic calculated for each cohort member and derived from number of years of residence and median arsenic concentration in the given community		SMR (95% CI)	Confidence intervals not given for exposure categories 4058 members in cohort (2092 men and 1966 women)
					Bladder/other urinary cancers	
			Low exposure	Men	0.36	
			(< 1000 ppb–years)	Women	1.18	
			Medium exposure	Men	–	
			(1000–4999 ppb–years)	Women	–	
			High exposure	Men	0.95	
			(≥ 5000 ppb–years)	Women	1.10	
			Total	Men	0.4 (0.1–1.2)	
				Women	0.8 (0.1–2.9)	
					Kidney cancer	
			Low exposure	Men	2.51	
			(< 1000 ppb–years)	Women	2.36	
			Medium exposure	Men	1.13	
			(1000–4999 ppb–years)	Women	1.32	
			High exposure	Men	1.43	
			(≥ 5000 ppb–years)	Women	1.13	
			Total	Men	1.8 (0.8–3.3)	
				Women	1.6 (0.4–4.1)	

SMR, standardized mortality ratio; CI, confidence interval; SIR, standardized incidence ratio; OR, odds ratio; RR, relative risk; BFD, Blackfoot disease

More systematic studies were conducted in various parts of the world, the most extensive being in Taiwan, China.

2.1.1 *Studies in Taiwan, China*

There are two areas in Taiwan, China, where exposure to arsenic is endemic. One is located in the south-western coastal area where Blackfoot disease, a unique peripheral vascular disease induced by long-term ingestion of arsenic from artesian well-water, is endemic. Eighty-four villages constitute the four Blackfoot disease-endemic townships of Peimen, Hsuehchia, Putai and Ichu, and artesian wells and patients with Blackfoot disease were also found in the two neighbouring townships of Yensui and Hsiaying (Wu *et al.*, 1989). Residents in the south-western endemic areas in Taiwan drank artesian well-water with high concentrations of arsenic from the early 1910s to the late 1970s. The concentrations of arsenic in artesian well-water, tested by Natelson's method in 1964–66 in 42 villages of the six townships, ranged from 10 to 1752 μg/L, and were mostly above 100 μg/L (Kuo, 1968; Tseng *et al.*, 1968). As well-water was the only source of drinking-water in the endemic area, all residents of a given village consumed the water from a small number of shared wells in their daily home and working environments. Most residents were engaged in fishing, salt production and farming, and the migration rate was low. More than 90% of residents had lived in the study area all their lives. As the study population lived in a small area, they shared similar dietary patterns, lifestyle, socioeconomic status and health care facilities. The piped water supply system using surface water was first implemented in the south-western endemic area, but its coverage was not complete until the late 1970s (Wu *et al.*, 1989).

Another area with exposure to arsenic is located in the Lanyang Basin in north-eastern Taiwan (Chiou *et al*., 2001), and is comprised of four townships: Chiaohsi (four villages), Chuangwei (seven villages), Wuchieh (three villages) and Tungshan (four villages). Residents in this area of endemic arseniasis used river water for drinking and cooking before the Second World War, and started to use water from tubewells in their houses in the late 1940s. The concentrations of arsenic in the water of 3901 wells in the endemic area was tested from 1991 to 1994 by hydride generation combined with flame atomic absorption spectrometry, and ranged from undetectable (< 0.15 μg/L) to 3.59 ng/L, but were mostly between 10 and 100 μg/L, with a median of 27.3 μg/L. A piped water supply system using surface water was first implemented in the endemic area in late 1997, and its coverage was almost complete in 2001. Residents in the endemic area were engaged in farming, and most of them had lived in the area all their lives.

(*a*) *Ecological studies*

Chen *et al*. (1985) reported an elevation in mortality from cancers of the urinary bladder and kidney during the period 1968–82 in endemic areas of Blackfoot disease (four neighbouring townships comprising 84 villages) compared with the general population of Taiwan. The arsenic content of well-water ranged from 0.35 to 1.14 ppm

[mg/L] with a median of 0.78 ppm, while shallow well-water contained arsenic at concentrations ranging from 0 to 0.3 ppm with a median of 0.04 ppm (Chen *et al.*, 1962). The SMRs for bladder cancer and kidney cancer increased with the prevalence of Blackfoot disease. Similarly, the SMRs for cancers of the bladder and kidney were highest in villages where only artesian wells were in use and lowest in those villages using shallow wells. The high SMRs for bladder and kidney cancer were not readily explained by the higher rate of cigarette smoking in the Blackfoot disease-endemic area compared with all of Taiwan (40% versus 32%).

Chen *et al*. (1988a) briefly described a dose–response relationship between median arsenic levels in artesian well-water in the 84 villages studied by Chen *et al*. (1985) and rates of mortality from bladder cancer. The study period (1973–86) covered 899 811 person–years of observation, and exposure was stratified into three categories (< 300, 300–590 and ≥ 600 μg/L arsenic) based on concentrations from a survey of over 83 000 wells, including 313 townships in all of Taiwan, conducted from 1962 to 1964.

Wu *et al*. (1989) examined age-adjusted mortality rates for various cancers in an area of south-western Taiwan that comprised 42 villages in six townships (27 villages studied by Chen *et al*. (1988a) and another 15 villages). The arsenic content of the 155 wells sampled, measured in 1964–66, ranged from 10 to 1750 μg/L. The villages were classified according to median arsenic levels in water into three exposure groups (< 300, 300–590 and ≥ 600 μg/L). Death certificates were used to ascertain cause of death during the period 1973–86. A dose–response relationship was found with concentration of arsenic in water for cancers of the bladder and kidney for both men and women.

Chen and Wang (1990) further investigated cancer mortality rates throughout Taiwan in 1972–83. Of 361 administrative areas, 314 were included in the study following measurements of arsenic contents in well-water in 1974–76. Exposure measurements were derived from a national water survey of over 83 000 wells throughout Taiwan. About 19% of the wells contained levels of arsenic above 50 μg/L, and most of them were in north-western and south-eastern Taiwan. Indices of urbanization and industrialization were included in the analysis to adjust for the possible confounding effect of differing socioeconomic characteristics between the 314 precincts and townships. Mortality data were used to evaluate 21 malignant neoplasms, using population-weighted regression. Results were presented for increases in mortality per 100 000 that were calculated to occur for every 0.1-mg/L increase in arsenic concentration in water.

Chiang *et al*. (1993) showed that the age-adjusted incidence of bladder cancer in the period 1981–85 in the Blackfoot disease-endemic area of Taiwan was higher than that in a neighbouring area of Taiwan and in the country as a whole.

Guo *et al.* (1997) used tumour registry data and the exposure data from the 1974–76 nationwide water-quality survey used by Chen and Wang (1990), which included concentrations of arsenic in drinking-water from 243 townships with about 11.4 million residents. The annual incidence of cancers of the bladder and kidney for townships in 1980–87 and subcategories of those cancer diagnoses were regressed against a model that included six variables for the proportion of wells in each of six categories of arsenic

concentration in each township. Sex-specific models were adjusted for age and included an urbanization index and the annual number of cigarettes sold *per capita*. Regression models were weighted by the total population of each township. A total of 1962 bladder, 726 kidney, 170 ureter and 57 urethral cancers were included. The investigators found associations of high arsenic concentrations (more than 0.64 ppm) in both sexes with transitional-cell carcinomas of the bladder, kidney and ureter, and all urethral cancers combined, but they did not present relative risk estimates.

Tsai *et al*. (1999) compared mortality in people aged over 40 years in the Blackfoot disease-endemic area of Taiwan with both local and national references for the period 1971–94. Greater mortality was found for men and women with cancers of the bladder and kidney.

(*b*) *Case–control study*

In a retrospective case–control study using death certificates from 1980–82, Chen *et al*. (1986) examined the relationship between exposure to high concentrations of arsenic in artesian well-water and mortality from internal malignancies, including tumours of the bladder ($n = 69$) in four townships from the Blackfoot disease-endemic area. Controls ($n = 368$) were selected by random sampling from the same geographical areas as the cases and were frequency-matched on age and sex. The response rate was 93% for proxies of cases and 92% for matched controls. Adjustment for age, sex and other variables (smoking, tea drinking, vegetarianism and frequency of consumption of vegetables and fermented beans) was performed by logistic regression analysis. The results indicated increasing trends in odds ratios with increasing duration of intake of artesian well-water containing arsenic. The highest risks were seen for over 40 years of exposure, with an odds ratio of 4.1 for bladder cancer in a multivariate analysis. Smoking, alcohol consumption and other potential risk factors evaluated in the study did not confound the association between arsenic and cancer.

(*c*) *Cohort studies*

Chen *et al.* (1988b) studied the association between arsenic in artesian well-water in relation to Blackfoot disease and cancer from a multiple risk factor perspective. The study area included the four townships in south-western Taiwan where high rates of Blackfoot disease had been described. Levels of arsenic were reported to be high in water, soil and food, and estimates of ingestion of arsenic by local residents were up to 1 mg per day. The study examined mortality in a cohort of people who had or had since developed Blackfoot disease in 1968, totalling 789 patients and 7578 person–years of observation through 1984. Follow-up started in 1968, since this was the year that registration of deaths in Taiwan was computerized and completeness and quality of death certificate registration was improved. Mortality of persons who had died ($n = 457$) and were not lost to follow-up ($n = 84$) was compared with that of the general population of Taiwan using age- and sex-specific mortality rates from 1968 through 1983. The SMRs for cancers of the bladder and kidney (men and women combined) were 38.8 [95% CI, 21.7–64.0] and 19.5

[95% CI, 4.0–57.0], respectively. The latter result, however, is based on only three deaths. SMRs were also calculated using all residents in the Blackfoot disease-endemic area, which includes people exposed to arsenic. These much lower SMRs were 2.6 [95% CI, 1.4–4.2] for bladder cancer and 1.6 [95% CI, 0.3–4.7] for kidney cancer, indicating that patients with Blackfoot disease had somewhat higher rates for these cancers than the residents in the arsenic-exposed region combined.

Chiou *et al*. (1995) investigated the relationship between incidence of internal cancers and arsenic in relation to Blackfoot disease in 2256 subjects from 1986 to 1993. Patients with Blackfoot disease ($n = 263$) and a referent group of 2293 residents of the same region were followed for 7 years. In contrast to many other studies that evaluate mortality, incident cancer was the outcome of interest. Follow-up occurred many years after exposure to elevated concentrations of arsenic in drinking-water had ended. Information on exposure to other risk factors was gathered by individual interviews. Several measures of exposure were evaluated, including average concentration of arsenic in artesian wells and cumulative exposure to arsenic from drinking artesian well-water. Relative risks were calculated using Cox's proportional hazard regression analysis. After controlling for the effects of age, sex and smoking in the regression analysis, a dose–response relationship was observed between exposure to arsenic from drinking well-water and the incidence of bladder cancer. Patients with Blackfoot disease were found to be at increased risk even after adjustment for cumulative exposure to arsenic.

Chiou *et al.* (2001) studied the incidence of urinary tract cancers among 8102 residents in the arsenic-endemic area in north-eastern Taiwan from 1991 to 1994. Levels of arsenic in the drinking-water ranged from less than 0.15 μg/L (undetectable) to 3590 μg/L. Exposure for each member of the cohort was assessed by measuring concentrations of arsenic in the well associated with the individual's household at one point in time only, although most households had used their current wells for at least 10 years (Chen & Chiou, 2001). Using the general population as referent, the standardized incidence ratio (SIR) for bladder cancer was 1.96 (95% CI, 0.9–3.6), while that for kidney cancer was 2.8 (95% CI, 1.3–5.4). These results were based on 10 subjects with bladder cancer and nine with kidney cancer. A dose–response relationship was observed between urinary tract cancers, particularly transitional-cell carcinoma, after adjusting for age, sex and smoking.

2.1.2 *Studies in Japan*

A retrospective cohort study was conducted in a small Japanese population, which, between 1955 and 1959, used well-water contaminated with arsenic from a factory producing King's yellow (As_2O_3; Tsuda *et al*., 1995). The levels of arsenic measured in 34 of 54 wells tested in the area around the factory ranged from undetectable to 3000 μg/L, with 11 wells having levels exceeding 1000 μg/L. A total of 454 residents were enlisted in the cohort. Death certificates, autopsy records and medical records were obtained for the period 1 October 1959 to 30 September 1987. Smoking and occupational histories were ascertained from residents or close relatives. Expected numbers of deaths

were based on sex-, age- and cause-specific mortality in Niigata Prefecture from 1960 to 1989. Exposure was grouped into high (≥ 500 µg/L), medium (50–500 µg/L) and low (< 50 µg/L), based on the arsenic content of the well-water. The SMR for urinary-tract cancer in the high-exposure group was 31.2 (95% CI, 8.6–91.8) based on three observed deaths versus 0.1 expected. Two of these were deaths from bladder cancer and one from cancer of the renal pelvis. [Excluding the cancer of the renal pelvis, the SMR for bladder cancer alone would be at least 20.]

2.1.3 *Studies in South America*

(*a*) *Argentina*

As early as the beginning of the twentieth century, physicians noted an increase in the incidence of clinical skin alterations due to arsenic in well-water in certain areas of the Province of Córdoba, Argentina (Hopenhayn-Rich *et al*., 1996a). In a study of 2355 deaths in 1949–59 in a highly exposed region, Bergoglio (1964) found that 24% of deaths in the exposed region were due to cancer compared with 15% in the Province of Córdoba. In a 14-year follow-up of 116 patients diagnosed with arsenic-related skin lesions, 30.5% died of cancer, and 12.5% of these deaths were due to cancers of the urinary tract (Biagini, 1972). This was later contrasted with bladder cancer mortality in all of Argentina in 1980, with 2.9% of all cancer deaths attributable to bladder cancer (Hopenhayn-Rich *et al*., 1996a).

These early reports led to an ecological study on bladder cancer mortality for the period 1986–91 comparing counties categorized as previously having had high, medium and low concentrations of arsenic in water in Córdoba, Argentina (Hopenhayn-Rich *et al*., 1996a). The majority of reported cases of arsenic-related skin lesions were residents of two counties that were classified as having high exposure since there were extensive reports of elevated concentrations of arsenic in the water there. The average concentration of arsenic in water tested in these counties was 178 µg/L. The medium-exposure group comprised six counties based on some reports of elevated arsenic levels in the water and the occurrence of a few cases of skin lesions. The remaining 16 rural counties were classified as having low exposure. Clear trends in mortality from bladder cancer were observed. Increasing trends were also observed for mortality from kidney cancer as exposure to arsenic increased (Hopenhayn-Rich *et al.*, 1998). No differences were found between the exposure groups for chronic obstructive pulmonary disease, suggesting that the trends for bladder and kidney cancer were not attributable to confounding by smoking.

(*b*) *Chile*

Chile is a long and narrow country divided into geopolitical units called regions (like provinces in other countries), which are numbered sequentially from north to south, starting with Region I. Region II is thus located in the northern part of Chile, in an arid zone where the Atacama Desert is situated. At the time of the 1992 Census, the population in Region II was about 420 000. About 90% of the population live in the cities and towns

in this Region, and more than half of the population lives in the city of Antofagasta (Smith *et al*., 1998). In view of the extremely low level of rainfall and the inability to obtain water from wells, each city and town obtains drinking-water from rivers which originate in the Andes mountains, located on the eastern border of the Region. Many of these rivers are naturally contaminated with inorganic arsenic, some at very high concentrations. This has resulted in widespread exposure of the population of Region II to varying levels of arsenic in the drinking-water. In 1955–70, the majority of the population of Region II was exposed to very high levels of arsenic in drinking-water (see Table 17). Prior to 1955, the drinking-water supply in the main city of Antofagasta had an arsenic concentration of about 90 μg/L. A growing population, and the consequent increased need for water, led to supplementation of the drinking-water supply at Antofagasta with water from the Toconce and Holajar Rivers, which, unknown at the time, had arsenic concentrations of 800 μg/L and 1300 μg/L, respectively. The concentration of arsenic in the drinking-water at Antofagasta, together with that of neighbouring Mejillones, which shared the same supply, increased to an average of 870 μg/L. As shown in Table 17, the other towns in the region, with the exception of Taltal, also had high concentrations of arsenic in the drinking-water for variable periods. The population-weighted average concentration of arsenic in drinking-water for the entire region was about 580 μg/L over a period of approximately 15 years (1955–70). With the introduction in 1970 of a water-treatment plant, the concentration of arsenic in the water at Antofagasta initially dropped to 260 μg/L, and further reductions occurred as a result of improvements to the treatment plant. At present, levels of arsenic in water in Antofagasta are about 40 μg/L. Other cities and towns also implemented water-treatment strategies or used alternative sources that reduced arsenic levels. By the late 1980s, all of the towns with populations over 1000 had concentrations of arsenic in drinking-water of less than 100 μg/L, with the exception of San Pedro de Atacama (population about 3700, some of whom still drink the contaminated water). In contrast, most water sources in the rest of Chile have had low concentrations of arsenic (less than 10 μg/L) (Ferreccio *et al.*, 2000).

Evidence of chronic arsenic toxicity in Region II was noted in the 1960s with the emergence of classic dermatological manifestations (Borgoño & Greiber, 1971; Zaldívar, 1974; Zaldívar *et al*., 1978). In 1969, in a study of 180 residents in Antofagasta, abnormal skin pigmentation was found in 144 of the participants, 43.7% of whom also had hyperkeratoses (Borgoño *et al*., 1977). Evidence of effects on the respiratory and cardiovascular system, together with skin lesions, was also reported by Zaldívar *et al*. (1978), who conducted a series of studies concerning the effects of arsenic in Antofagasta during the high-exposure period.

Two ecological mortality studies were conducted on kidney and bladder cancer in Region II. Rivara *et al*. (1997) conducted a study comparing mortality for both sexes combined in Region II with that in Region VIII for the period 1950–92. SMRs for bladder cancer and kidney cancer were 10.2 (95% CI, 8.6–12.2) and 3.8 (95% CI, 3.1–4.7), respectively.

Smith *et al*. (1998) also investigated cancer mortality in Region II for the years 1989–93, using mortality rates in the rest of Chile (excluding Region II) in 1992, a census year, for reference. SMRs were calculated for men and women over the age of 30 years, using 10-year age groupings. The results indicated marked increases in mortality from bladder cancer and kidney cancer in Region II. Data on smoking obtained from a national survey of stratified random samples carried out in 1990, comparing the two largest cities of Antofagasta and Calama with the rest of Chile, were included. No overall increases in mortality from chronic obstructive pulmonary disease were observed in Region II: the SMR for men was 1.0 (0.8–1.1) and mortality among women was lower than expected (SMR, 0.6; 0.4–0.7). In addition, not only did the national survey not find higher rates of smoking in Region II, but in Antofagasta, 76.4% of respondents reported being non-smokers at that time compared with 75.1% of respondents in the rest of Chile. The proportion of people who smoked more than one pack per day was lower in Antofagasta (0.8%) and Calama (1.1%) than in the rest of Chile (1.5%). The SMRs for other causes of death excluding cancers of the bladder, kidney, lung, liver and skin were 1.0 (95% CI, 0.99–1.05) for men and 1.0 (95% CI, 0.97–1.03) for women.

2.1.4 *Studies in the USA*

Some ecological studies have been reported in the USA but they are not informative in view of the relatively small contrasts in exposure between counties.

(*a*) *Case–control study*

Bates *et al.* (1995) linked 71 cases of bladder cancer and 160 controls from a subsample of residents of Utah from the large national bladder cancer study conducted in 1978 (Cantor *et al.*, 1987) to levels of arsenic in water supplies. Exposures ranged from 0.5 to 160 µg/L, but most concentrations were very low, with only 1.1% of samples having concentrations greater than 50 µg/L. The findings did not provide evidence for an overall increase in the incidence of bladder cancer with the two indices of exposure used. However, among smokers only, there was an increase in risk for the highest category of cumulative dose of arsenic.

(*b*) *Cohort study*

Levels of arsenic in drinking-water and mortality were investigated in a cohort of members of the Church of Jesus Christ of Latter-day Saints in Millard County, UT (Lewis *et al*., 1999). The cohort was assembled from an earlier study that consisted of 2073 participants (Southwick *et al*., 1983). Most of these individuals had a history of at least 20 years of exposure in their respective places of residence. The cohort was expanded to include all persons who lived for any length of time in the study area, resulting in a total combined cohort of 4058 members. More than 70% of the cohort had reached the age of 60 years at the end of the follow-up period or by the time of their deaths. Approximately 7% of the cohort was lost to follow-up. Arsenic concentrations in the drinking-water supplies were

based on measurements maintained by the state of Utah dating back to 1964. The median drinking-water concentrations ranged from 14 to 166 ppb [μg/L], with wide variability in each town. An index of exposure to arsenic was calculated from the number of years of residence and the median concentration of arsenic in drinking-water in a given community, and was categorized as low (< 1000 ppb–years), medium (1000–4999 ppb–years) and high (> 5000 ppb–years). Data on confounding factors were not available; however, Church members are prohibited from using tobacco and consuming alcohol or caffeine. SMRs for kidney cancer were increased in the low- and high-exposure groups among men and in the low- and medium-exposure groups among women. The overall SMRs for cancers of the bladder and other urinary organs were below unity for both sexes, but these results were based on only three and two bladder cancers in men and women, respectively. [The Working Group noted that there were several problems in the interpretation of this study. The exposure assessment was ecological in nature because of relatively low exposures. There was widespread variability in water concentrations, which adds to the uncertainty of the study. Furthermore, the findings are influenced by lower rates of smoking for the cohort compared with all of Utah. This is manifest in the SMRs for non-malignant respiratory disease (SMR for men, 0.7; 95% CI, 0.5–0.9; SMR for women, 0.9; 95% CI, 0.7–1.2) and for mortality from chronic bronchitis, emphysema and asthma (SMR for men, 0.6; 95% CI, 0.4–0.9; SMR for women, 0.5; 95% CI, 0.1–1.2). For these reasons, the study is uninformative with regard to the relationship between exposure to arsenic and mortality from bladder and kidney cancer.]

2.1.5 *Studies in Europe*

In a type of case–control study known as case–cohort, Kurttio *et al*. (1999) investigated the association between low exposure to arsenic in well-water in Finland and the risk for cancers of the bladder and kidney. Cases of bladder and kidney cancer were identified from 1981 to 1995 within a registry-based cohort of the population who had lived at an address outside the municipal drinking-water system during 1967–80. The final study population consisted of 61 cases of bladder cancer and 49 cases of kidney cancer and an age- and sex-matched random sample of 275 subjects from the population register. The daily dose of arsenic in drinking-water was calculated from the concentration of arsenic in well-water and its reported consumption in the 1970s. Cumulative dose was defined as the integral of duration and intensity of exposure to arsenic from well-water. For the shorter latency period of 3–9 years prior to diagnosis of bladder cancer, cumulative dose was estimated from the beginning of use of well-water until 2 years before the diagnosis of cancer. For the longer latency period, the cumulative dose was calculated until 10 years before diagnosis. The concentrations of arsenic in the wells of the reference cohort ranged from less than 0.05 to 64 μg/L (median, 0.14 μg/L). After adjusting for age, sex and smoking, an increasing trend of arsenic in drinking-water and incidence of bladder cancer was observed with shorter latency but not with longer latency, whereas no evidence of an association between kidney cancer and arsenic in well-water was observed.

2.1.6 *Studies in Australia*

Two geographical areas in Victoria, Australia, were selected for study because of reports of concentrations of arsenic in the soil above 100 μg/g and/or concentrations in water above 10 μg/L (Hinwood *et al*., 1999). Median concentrations of arsenic in water were reported for various towns and showed a wide range up to a median of 1077 μg/L for Ballarat, which had a population of 43 947 in 1986. However, the extent to which contaminated water was used for drinking was not known. The authors noted that "high percentages of the population may be relying on alternative drinking-water sources such as bottled water and tank rain water". Cancer incidence was assessed for the period 1982–91 using the Victorian Cancer Registry. SIRs were estimated for the exposed population in 22 areas of Victoria, using cancer incidence rates for all of the State of Victoria as reference. SIRs for both bladder and kidney cancers were close to unity. [The Working Group noted that no information was presented on the actual use of water contaminated with arsenic for drinking by the population.]

2.2 Liver and lung cancer

2.2.1 *Liver cancer*

A previous IARC monograph on arsenic noted reports of liver angiosarcoma due to medicinal exposure to Fowler's solution (IARC, 1980). A summary of the findings of epidemiological studies on arsenic in drinking-water and risk for liver cancer, mainly hepatocarcinoma, are shown in Table 23.

(*a*) *Taiwan, China*

(i) *Ecological studies*

Chen *et al.* (1985) studied the mortality from liver cancer during the period 1968–82 among residents in 84 villages exposed to arsenic of four townships in south-western coastal Taiwan. Increased mortality was observed among both men and women. There was an exposure–response relationship between SMR and prevalence of Blackfoot disease. An exposure–response gradient for mortality from liver cancer was noted in evaluating the risk in areas with shallow wells (presumably with low exposure to arsenic), both shallow and artesian wells (intermediate exposure) and artesian wells only (highest exposure). In villages with artesian wells, the SMR was approximately 2.0 [CI not reported] for liver cancer.

Chen *et al.* (1988a) and Wu *et al.* (1989) reported the age-adjusted mortality rates for liver cancer for men and women in 42 villages in south-western Taiwan and calculated age-adjusted cancer mortality during the period 1973–86 within three groups of villages stratified by exposure concentration (< 300 μg/L, 300–590 μg/L and ≥ 600 μg/L arsenic) tested in 1964–66. Age-adjusted mortality rates (per 100 000 person–years) from liver cancer for residents of all ages in Taiwan (referent) increased with increasing concen-

Table 23. Summary of epidemiological studies on arsenic in drinking-water and risk for liver cancer

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Ecological studies							
Taiwan							
Chen *et al.* (1985)	84 villages on the SW coast	Mortality 1968–82, all ages	Endemic area for chronic arsenic toxicity (Blackfoot disease)	Men Women	305 146	Age- and sex-adjusted SMR (95% CI) 1.7 (1.5–1.9) 2.3 (1.9–2.7)	Mid-year population: 141 733 in 1968, 120 607 in 1982; national rate in 1968–82 used as the standard for estimation of SMR
Chen *et al.* (1988a)	42 villages on the SW coast	Mortality 1973–86, all ages	Average arsenic (1962–64) General population < 300 µg/L 300–590 µg/L ≥ 600 µg/mL General population < 300 µg/L 300–590 µg/L ≥ 600 µg/mL	 Men Women 		Age-adjusted SMR 28.0 32.6 42.7 68.8 8.9 14.2 18.8 31.8	899 811 person–years, rate per 100 000, age-standardized to 1976 world population
Wu *et al.* (1989)	42 villages on the SW coast	Mortality 1973–86, age ≥ 20	Average arsenic (1962–64) < 300 µg/L 300–590 µg/L ≥ 600 µg/mL < 300 µg/L 300–590 µg/L ≥ 600 µg/mL	 Men Women 	 54 42 27 25 16 10	 47.8 67.7 86.7 *p* for trend < 0.05 21.4 24.2 31.8 *p* for trend < 0.05	Men, 257 935 person–years; women, 234 519 person–years; rate per 100 000, age-standardized to 1976 world population

Table 23 (contd)

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Chen & Wang (1990)	Taiwan	Mortality 1972–83, all ages	National survey of 83 656 wells (1974–76); average arsenic for each of 314 precincts or townships			*β (SE) from regression* Men 6.8 (1.3) Women 2.0 (0.5) *Percentiles of age-adjusted mortality rate/100 000 person–years* Men 25th 21.8 50th 27.0 75th 34.1 Women 25th 7.0 50th 8.7 75th 11.6	Regression coefficient (β) estimates increase in age-adjusted mortality per 100 000 per 100 µg/L arsenic increase in water
Tsai *et al.* (1999)	SW Taiwan, 4 townships	Mortality 1971–94, all ages	Arsenic-exposed area	Men Women	631 224	SMR (95% CI) 1.8 (1.7–1.98) 1.9 (1.6–2.1)	Men, 1 508 623 person–years; women, 1 404 759 person–years; national rates in 1971–94 used as the standard for estimation of SMR
South America							
Rivara *et al.* (1997)	Region II and VIII, northern Chile	Mortality 1976–92	Arsenic-contaminated Region II			Relative risk 1.2 (0.99–1.6)	Population: 411 000 in Region II, 1 700 000 in Region VIII. Antofagasta (Region II) versus Region VIII.
Hopenhayn-Rich *et al.* (1998)	Córdoba Province, Argentina, 26 counties	Mortality 1986–91, age ≥ 20	County group *Men* Low exposure (341 547) Medium exposure (201 546) High exposure (135 209) *Women* Low exposure (348 874) Medium exposure (204 454) High exposure (137 805)	 186 142 98 173 125 90		SMR 1.5 (1.3–1.8) 1.8 (1.5–2.1) 1.8 (1.5–2.2) 1.7 (1.4–1.96) 1.9 (1.6–2.2) 1.9 (1.5–2.4)	National rate in 1989 used as the standard for estimation of SMR

Table 23 (contd)

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Smith *et al.* (1998)	Region II, Northern Chile	Mortality 1989–93, age ≥ 30	5-year intervals, 420 µg/L average	Men Women	48 37	SMR 1.1 (0.8–1.5) 1.1 (0.8–1.5)	National rates in 1991 used as the standard estimation of SMR; arsenic concentration is population-weighted average for major cities or towns in Region II, 1950–74
Australia							
Hinwood *et al.* (1999)	Victoria	Incidence 1982–91	Median concentration of arsenic in drinking-water ranged 1–1077 µg/L	749		SIR (95% CI) 0.5 (0.3–0.8)	State rates in 1982–91 used as the standard for estimation of SIR
Cohort studies							
Chen *et al.* (1988b)	SW Taiwan	Mortality	Area endemic for Blackfoot disease	17		SMR: 4.66 ($p < 0.001$) compared with national standard; 2.48 ($p < 0.01$) compared with regional standard	789 patients with Blackfoot disease followed from 1968 to 1984. National and regional rates in 1968–83 used as the standard for estimation of SMR
Tsuda *et al.* (1995)	Niigata Prefecture, Japan	Mortality, 1959–92, all ages	Level of arsenic < 0.05 mg/L 0.05–0.99 mg/L ≥ 1.0 mg/L Total	 0 0 2 2		SMR 0.0 (0–4.4) 0.0 (0–15.1) 7.2 (1.3–26.1) 1.5 (0.3–5.5)	113 persons who drank from industrially contaminated wells in 1955–59, then followed for 33 years; rates in Niigata Prefecture in 1960–89 used as the standard for estimation of SMR
Lewis *et al.* (1999)	Millard County, UT, USA	Mortality	Arsenic in well-water ranged 3.5–620 µg/L	Men Women	3 7	SMR 0.9 (0.2–2.5) 1.4 (0.6–2.9)	State rates in 1950–92 used as the standard for estimation of SMR.
Nakadaira *et al.* (2002)	Niigata Prefecture, Japan	Mortality	Industrially contaminated well-water in the town of Nakajo	1		O/E = 0.7	86 patients with chronic arsenic poisoning. National rates in 1959–92 used as the standard for estimation of SMR

Table 23 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Case–control study						
Chen *et al.* (1986)	SW Taiwan, 4 townships	Mortality	Duration of consumption of artesian well-water containing high levels of arsenic	65 cases 368 controls	Age- and gender-adjusted ORs by years of consuming high-arsenic artesian well-water: Never 1.00 1–20 years 0.85 21–40 years 1.24 > 40 years 2.67	ORs calculated using subjects who never consumed artesian well-water as referent Mantel-Haenszel χ^2 value: 9.01 ($p < 0.01$)

SMR, standardized mortality ratio; CI, confidence interval; SIR, standardized incidence ratio; O/E, observed/expected; OR, odds ratio

trations of arsenic in water for both men and women in the first study (Chen *et al.,* 1988a), as well as for residents aged 20 years or older in the second study (Wu *et al.*, 1989).

Chen and Wang (1990) analysed nationwide cancer mortality in Taiwan using measurements of arsenic concentrations in water from 83 656 wells located in 314 precincts and townships from 1974 to 1976. Using a multiple regression approach, the authors compared age-adjusted mortality for all ages during the period 1972–83 with arsenic concentrations in these locations. A significant association with concentration of arsenic was found for liver cancer in both men and women. Using multiple linear regression models, a regression coefficient indicating the change in age-adjusted mortality per 100 000 person–years for every 0.1 μg/L increase in arsenic in well-water was calculated, after adjusting for indices of industrialization and urbanization.

Tsai *et al.* (1999) studied mortality from liver cancer in four townships exposed to arsenic in south-western Taiwan during the period 1971–94. SMRs were calculated using two comparison groups: mortality in the whole of Taiwan and mortality in the two counties in which the four townships are located. Although differences in nutrition, socioeconomic status or other factors between populations in south-western Taiwan and the remainder of the country may influence their respective cancer rates, Tsai *et al.* (1999) provided evidence that such differences are relatively unimportant. SMRs in both men and women, using both regional and national references, were all close to 1.8.

(ii) *Case–control study*

Chen *et al.* (1986) carried out a case–control study on liver cancer and consumption of artesian well-water with high concentrations of arsenic in four townships of south-western Taiwan. A total of 65 cases of liver cancer, identified from death certificates, and 368 healthy controls were studied. Information on consumption of arsenic-contaminated artesian well-water, cigarette smoking, habitual alcohol and tea drinking, and consumption of vegetables and fermented beans was obtained through interview using a standardized questionnaire. Unconditional logistic regression was used to estimate multivariate-adjusted odds ratios for developing liver cancer and various risk factors. There was an exposure–response relationship between the duration of consumption of artesian well-water with high arsenic content and risk for liver cancer.

(*b*) *Japan*

Cohort study

Tsuda *et al.* (1995) found excess mortality from liver cancer among a cohort of 113 persons exposed to levels of arsenic above 1.0 mg/L from industrially contaminated drinking-water in villages of Niigata Prefecture, Japan. The expected number of deaths was based on sex-, age- and cause-specific mortality in Niigata Prefecture in 1960–89. Based on a subgroup of 86 study patients, Nakadaira *et al*. (2002) did not find excess mortality from liver cancer (SMR, 0.7 [95% CI, 0.02–3.9]; one case observed and 1.42 expected). [The small number of liver cancer deaths limited further analysis by severity of chronic arsenic poisoning.] [See complete comment by the Working Group in Section 2.1.2.]

(*c*) *Australia*

Hinwood *et al.* (1999) investigated the association between arsenic in drinking-water and liver cancer incidence in Victoria, Australia, in 1982–91. This study included 22 areas where the median arsenic concentration in drinking-water ranged from 14 to 166 µg/L. Using the incidence rate in Victoria, an SIR of 0.5 (95% CI, 0.3–0.8) was observed for liver cancer. [The small number of liver cancer deaths limited further analysis by severity of chronic arsenic poisoning.]

(*d*) *South America*

Ecological studies

Rivara *et al.* (1997) compared the mortality from liver cancer in Antofagasta in Region II with that in Region VIII of Chile in 1976–92. The relative risk for liver cancer was 1.2 (95% CI, 0.99–1.6) in arsenic-exposed Region II compared with the control area, Region VIII. [The data source and statistical analysis were not clearly described.]

Smith *et al.* (1998) examined liver cancer mortality during the period 1989–93 among persons 30 years of age and over in Region II of northern Chile. Concentrations of arsenic in drinking-water were well documented and had been high in all major population centres of Region II, especially before 1975. The population-weighted average in the years 1950–74 was 420 µg/L, with a maximum of 870 µg/L in Antofagasta, the largest city, between 1955 and 1969. SMRs for Region II were calculated using the national rate as the standard, and for liver cancer, were 1.1 for both men and women.

Hopenhayn-Rich *et al.* (1998) examined SMRs for liver cancer during the period 1986–91 among residents aged 20 years or older in the 26 counties of Córdoba Province, Argentina. They grouped counties into three strata according to the concentration of arsenic in drinking-water. The low- and intermediate-exposure groups were defined qualitatively. In the highest exposure group comprising two counties, the concentration of arsenic in drinking-water ranged from 40 to 433 µg/L in the towns of one county and from 50 to 353 µg/L in those of the other. Separate average concentrations in each county were 181 and 174 µg/L. SMRs were calculated using sex- and age-specific rates for Argentina as the referent. Increased mortality from liver cancer was observed for men and women, but SMRs were not related to exposure to arsenic.

(*e*) *USA*

Cohort study

Lewis *et al.* (1999) reported the association between arsenic in drinking-water and mortality from liver cancer in a cohort of residents of Millard County, UT, where the median concentration of arsenic in drinking-water ranged from 14 to 166 µg/L. [The limitations of this study are cited in Section 2.1.4.]

2.2.2 *Lung cancer*

A summary of the findings of epidemiological studies on arsenic in drinking-water and risk for lung cancer are shown in Table 24.

(*a*) *Taiwan, China*

(i) *Ecological studies*

In the study of Chen *et al.* (1985) (described in Section 2.1), increased mortality from lung cancer was observed among men and women in 1968–82 in an area endemic for Blackfoot disease. There was an exposure–response relationship between the SMR and the prevalence of Blackfoot disease. The exposure–response gradient for mortality from lung cancer was noted in evaluating the risk in areas with shallow wells (presumably with low exposure to arsenic), both shallow and artesian wells (intermediate exposure) and artesian wells only (highest exposure). In villages with artesian wells, SMRs were approximately 5.0 [CIs not reported] for lung cancer.

In the studies of Chen *et al.* (1988a) and Wu *et al.* (1989) (described in Section 2.1), age-adjusted mortality rates (per 100 000 person–years) from lung cancer increased with increasing concentrations of arsenic in water for both men and women, for residents of all ages in Taiwan (referent) (Chen *et al.*, 1988a), as well as for residents aged 20 years or older (Wu *et al.*, 1989).

In the analysis of Chen and Wang (1990) (described in Section 2.1.1), regression coefficients (SE) for lung cancer showed a significant association with concentration of arsenic for lung cancer in both men and women.

In the study of Tsai *et al.* (1999) (described in Section 2.1.1) using national and regional rates as standard, SMRs for lung cancer were also increased for both sexes.

(ii) *Cohort study*

Chiou *et al.* (1995) (described in Section 2.1.1) followed 2556 subjects in an area endemic for Blackfoot disease of south-western Taiwan for periods ranging up to approximately 7 years from 1986 to 1993, including 263 patients with Blackfoot disease and 2293 healthy individuals. Results, adjusted for cigarette smoking habits, showed an increased risk for lung cancer in relation to increasing average concentrations of arsenic and to increasing cumulative exposure to arsenic.

(iii) *Case–control study*

Chen *et al.* (1986) (described in Section 2.1.1) studied a total of 76 cases of lung cancer and 368 healthy controls and observed a dose–response relationship between the duration of consumption of artesian well-water containing high levels of arsenic and risk for lung cancer, showing the highest age- and gender-adjusted odds ratio for those who consumed artesian well-water for more than 40 years compared with those who never consumed artesian well-water.

Table 24. Summary of epidemiological studies on arsenic in drinking-water and risk for lung cancer

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Ecological studies							
Taiwan							
Chen *et al.* (1985)	84 villages on the SW coast	Mortality 1968–82, all ages	Area endemic for chronic arsenic toxicity (Blackfoot disease)	Men Women	332 233	Age- and sex-adjusted SMR (95% CI) 3.2 (2.9–3.5) 4.1 (3.6–4.7)	Mid-year population: 141 733 in 1968, 120 607 in 1982; national rate in 1968–82 used as the standard for SMR estimation
Chen *et al.* (1988a)	42 villages on the SW coast	Mortality 1973–1986, all ages	Average arsenic (1964–66) General population < 300 µg/L 300–600 µg/L ≥ 600 µg/L General population < 300 µg/L 300–600 µg/L ≥ 600 µg/L	Men Women 		Age-adjusted SMR 19.4 35.1 64.7 87.9 9.5 26.5 40.9 83.8	899 811 person–years, rate per 100 000, age-standardized to 1976 world population
Wu *et al.* (1989)	42 villages on the SW coast	Mortality 1973–86, age ≥ 20	Average arsenic (1964–66) < 300 µg/L 300–600 µg/L ≥ 600 µg/L < 300 µg/L 300–600 µg/L ≥ 600 µg/L	 Men Women 	 53 62 32 43 40 38	 49.16 100.67 104.08 (p for trend < 0.001) 36.71 60.82 122.16 (p for trend < 0.001)	Men: 257 935 person–years; females, Women: 234 519 person–years; rate per 100 000 age-standardized to 1976 world population

Table 24 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Chen & Wang (1990)	Taiwan	Mortality 1972–83, all ages	National survey of 83 656 wells (1974–76); average arsenic for each of 314 precincts or townships		*β (SE) from regression*	Regression coefficient (β) estimates increase in age-adjusted mortality per 100 000 per 100 µg/L arsenic increase in water
				Men	5.3 (0.9)	
				Women	5.3 (0.7)	
					Percentiles of age-adjusted mortality rate/100 000 person–years	
				Men	25th 11.8	
					50th 16.2	
					75th 20.7	
				Women	25th 5.2	
					50th 7.4	
					75th 10.4	
Tsai *et al.* (1999)	SW Taiwan, 4 townships	Mortality 1971–94, all ages	Arsenic-exposed area	Men 699 Women 471	SMR (95% CI)	Men: 1 508 623 person–years; Women: 1 404 759 person–years
				Men	2.6 (2.5–2.8)	National rates in 1971–94 used as the standard for estimation of SMR
				Women	3.5 (3.2–3.8)	
				Men	3.1 (2.9–3.3)	Regional rates in 1971–94
				Women	4.1 (3.8–4.5)	
South America						
Rivara *et al.* (1997)	Region II and VIII, northern Chile	Mortality 1976–92	Arsenic-contaminated Region II		Relative risk (95% CI) Region II versus region VIII 8.8 (8.1–9.5)	Population: 411 000 in Region II, 1 700 000 in Region VIII. Antofagasta (Region II) versus Region VIII.

Table 24 (contd)

Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Hopenhayn-Rich *et al.* (1998)	Córdoba Province, Argentina, 26 counties	Mortality 1986–91, age ≥ 20	County group: Low exposure Medium exposure High exposure Low exposure Medium exposure High exposure	 Men Women 	 826 914 708 194 138 156	 0.92 (0.85–0.98) 1.5 (1.4–1.6) 1.8 (1.6–1.9) 1.2 (1.1–1.4) 1.3 (1.1–1.6) 2.2 (1.8–2.5)	Population: low exposure, 341 547, medium exposure, 201 006; high exposure, 135 209; national rate in 1989 used as the standard for SMR estimation
Smith *et al.* (1998)	Region II, northern Chile	Mortality 1989–93, age ≥ 30	5-year intervals, 420 µg/L average	 Men Women	 544 154	SMR 3.8 (3.5–4.1) 3.1 (2.7–3.7)	National rates in 1991 used as the standard for estimation of SMR; arsenic concentration is population-weighted average for major cities or towns in Region II, 1950–74
Australia							
Hinwood *et al.* (1999)	Victoria	Incidence 1982–91	Median arsenic concentration in drinking-water ranging 1–1077 µg/L	20		SIR (95% CI) 1.0 (0.9–1.1)	State rates in 1982–91 used as the standard for estimation of SIR
Cohort studies							
Chen *et al.* (1988b)	SW Taiwan	Mortality 1968–83	Area endemic for Blackfoot disease	28		SMR: 10.49 ($p < 0.001$) compared with national standard; 2.84 ($p < 0.01$) compared with regional standard	789 patients with Blackfoot disease followed from 1968 to 1984. National and regional rates in 1968–83 used as the standard for estimation of SMR
Tsuda *et al.* (1995)	Niigata Prefecture, Japan	Mortality, 1959–92, all ages	Arsenic level: < 0.05 mg/L 0.05–0.99 mg/L ≥ 1.0 mg/L Total	 0 1 8 9		SMR 0.0 (0–2.4) 2.3 (0.1–13.4) 15.7 (7.4–31.0) 3.7 (1.8–7.0)	113 persons who drank from industrially contaminated wells in 1955–59, then followed for 33 years; rates in Niigata Prefecture in 1960–89 used as the standard for estimation of SMR

Table 24 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Chiou *et al.* (1995)	SW Taiwan; 4 neighbouring townships	Incidence 1986–93	Cumulative arsenic exposure (mg/L × year) < 0.1 0.1–19.9 ≥ 20 Average arsenic concentration (mg/L) < 0.05 0.05–0.70 ≥ 0.71	 3 7 7 5 7 7	Relative risk (95% CI) 1.0 3.1 (0.8–12.2) 4.7 (1.2–18.9) 1.0 2.1 (0.7–6.8) 2.7 (0.7–10.2)	Incidence among a cohort of 2556 subjects (263 Blackfoot disease patients and 2293 healthy individuals) followed for 7 years
Lewis *et al.* (1999)	Millard County, UT, USA	Mortality	Arsenic in well-water, 3.5–620 µg/L	Men 28 Women 6	SMR 0.6 (0.4–0.8) 0.4 (0.2–0.95)	State rates in 1950–92 used as the standard for SMR estimation.
Nakadaira *et al.* (2002)	Niigata Prefecture, Japan	Mortality	Industrially contaminated well-water in the town of Nakajo	Men 7 Women 1 Total 8	Poisson probability distribution in men: 9.6 0/E = 11.01	86 patients with chronic arsenic poisoning. National rates in 1959–92 used as the standard for SMR estimation.
Case–control studies						
Chen *et al.* (1986)	SW Taiwan, 4 townships	Mortality	Duration of consumption of artesian well-water containing high levels of arsenic	76 cases 368 controls	Age- and sex-adjusted OR by years of consuming high-arsenic artesian well-water Never 1.00 1–20 years 1.26 21–40 years 1.52 > 40 years 3.39	OR calculated using subjects who never consumed artesian well-water as referent Mantel-Haenszel $\chi 2$ value: 8.49 ($p < 0.01$)

Table 24 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Ferreccio *et al*. (2000)	Northern Chile	Incidence 1994–96	Individual ≥ 40-year average arsenic concentration from public water supply records during 1930–94	151 cases 419 matched hospital controls	Age- and sex-adjusted OR (95% CI)	OR calculated using subjects with average exposures of 0–10 µg/L as referent
			0–10 µg/L		1.0	
			10–29 µg/L		1.6 (0.5–5.3)	
			30–49 µg/L		3.9 (1.2–12.3)	
			50–199 µg/L		5.2 (2.3–11.7)	
			200–400 µg/L		8.9 (4.0–19.6)	

SMR, standardized mortality ratio; CI, confidence interval; SIR, standardized incidence ratio; OR, odds ratio

(*b*) *Japan*

Cohort study

Tsuda *et al.* (1995) (described in Section 2.1.2) found excess mortality from lung cancer among a cohort of 113 persons exposed to levels of arsenic above 1.0 mg/L from industrially contaminated drinking-water in villages of Niigata Prefecture, Japan. The expected number of deaths was based on sex-, age- and cause-specific mortality in Niigata Prefecture in 1960–89. Based on a subgroup of 86 study patients, Nakadaira *et al*. (2002) did not find excess mortality from lung cancer.

(*c*) *Australia*

Hinwood *et al.* (1999) investigated the association between levels of arsenic in drinking-water and lung cancer incidence in Victoria, Australia, during the period 1982–91. This study included 22 areas where median concentrations of arsenic in drinking-water ranged from 14 to 166 μg/L. Using the incidence rate in Victoria, an SIR of 1.0 was observed for lung cancer.

(*d*) *South America*

(i) *Ecological studies*

Rivara *et al.* (1997) compared the mortality from lung cancer in 1976–92 between Antofagasta in Region II with that in Region VIII of Chile. The relative risk for lung cancer was higher in Antofagasta compared with Region VIII. [The data source and statistical analysis were not clearly described.]

Smith *et al.* (1998) (described in Section 2.2.1) found elevated SMRs of about 3 for lung cancer for both sexes in Region II, using the national rate as standard.

In the study of Hopenhayn-Rich *et al.* (1998) (described in Section 2.2.1), significant increases in the incidence of lung cancer associated with increasing exposure to arsenic were observed for lung cancer.

(ii) *Case–control study*

Ferreccio *et al.* (2000) conducted a case–control study of incident lung cancer cases in northern Chile. Eligible cases included all lung cancer cases admitted to public hospitals in Regions I, II and III of Chile from November 1994 to July 1996. Eighty to ninety per cent of all cancer patients in the north of Chile are admitted to public hospitals, and a total of 151 cases participated. Controls were selected from all patients admitted to any public hospital in the study region and frequency-matched to cases by age and sex. Two control series were selected: cancers other than lung cancer and non-cancer controls [no response rates were indicated for cases and controls]. Potential biases in control selection were assessed by several approaches including comparisons with geographical distribution of the general population based on census data. Information regarding residential history, socioeconomic status, occupational history (to ascertain employment in copper smelting) and smoking was obtained by questionnaire interview. Historical exposure to arsenic in

drinking-water was estimated by linking information on residential history with a database of information on arsenic concentrations in public water supplies collected for the years 1950–94. Arsenic concentrations in the year prior to 1950 were based on concentrations in the 1950s. Average concentration of arsenic in the place of residence was assigned to each subject on a year-by-year basis for the period 1930–94. Population coverage of public water systems in the main cities in Regions I and II was over 90% and was between 80 and 90% in the major cities of Region III. The coverage in smaller cities varied between 64 and 91%. Odds ratios were calculated using unconditional logistic regression, adjusted for age, sex, socioeconomic status, smoking and working in a copper smelter. Results from the analysis based on average exposures during 1930–94 and using all controls showed an increase in the odds ratio with concentration of arsenic. Evidence for a synergistic effect of arsenic in water and smoking was found for those who both smoked and had high concentrations of arsenic in their drinking-water (results not shown).

(*e*) *USA*

Cohort study

Lewis *et al.* (1999) reported the association between arsenic in drinking-water and lung cancer mortality in a cohort of residents of Millard County, UT, where the median concentration of arsenic in drinking-water ranged from 14 to 166 µg/L. The SMRs for lung cancer for both men and women were below unity. [Limitations of this study have been cited in Section 2.1.4.]

2.3 Skin cancer

The recognition of arsenic as a carcinogen originally came from case series describing skin cancers following ingestion of arsenical medicine, and exposure to arsenical pesticide residues and arsenic-contaminated drinking-water. Hutchinson (1888) noted skin cancers among patients treated for psoriasis and other ailments with arsenic-containing compounds (e.g. Fowler's Solution containing 1% potassium arsenite). Neubauer (1947) summarized 143 skin cancer cases among arsenic-treated patients. Over 50% of the skin cancers developed in patients treated for 10 years or less and lesions developed after 3–40 years, and on average after 18 years. Clinical reports have described an association of chronic arsenicism with skin cancer in vineyard workers of the Moselle region, Germany (Roth, 1957; Grobe, 1977). Numerous cases of skin cancer have been documented from communities with arsenic-contaminated drinking-water. These include, but are not limited to, case reports from Silesia (Neubauer, 1947), North America (Wagner *et al*., 1979), Taiwan, China (Yeh, 1973), Argentina (Bergoglio, 1964), Mexico (Cebrían *et al*., 1983), Chile (Zaldívar, 1974; Zaldívar *et al*., 1981) and, more recently, Bangladesh (Kurokawa *et al.*, 2001), West Bengal, India (Saha, 2001) and Malaysia (Jaafar *et al.*, 1993). The characteristic arsenic-associated skin tumours include squamous-cell carcinoma arising in keratoses (including Bowen disease) and multiple basal-cell carcinomas

(e.g. Neubauer, 1947; Neuman & Schwank, 1960; Yeh *et al.*, 1968). Therefore, this section focuses on these non-melanoma skin cancers. In addition, ecological studies of skin cancer based on mortality rates in areas with low exposure to arsenic such as the USA or exposure imputed from soil levels are not considered here. Findings of epidemiological studies on arsenic in drinking-water and risk for skin cancer are summarized in Table 25.

2.3.1 *Taiwan, China*

(*a*) *Ecological studies*

(i) *Study based on prevalence of skin cancer*

In 1965, Tseng *et al*. (1968) completed a skin cancer prevalence survey on the south-west coast of Taiwan, a region known to have arsenic-contaminated artesian wells that were introduced into the region in 1910–20. A house-to-house examination was conducted of family members from 37 villages: 10 in Chai-yi County, 25 in Tainan County and two in a suburb of Tainan City. The study covered a total population of 40 421 inhabitants. A total of 428 skin cancers were identified, 238 of which were sent for histopathological review. The study was based on clinical diagnoses. In the survey region, 142 water samples from 114 wells were tested for arsenic. Arsenic concentrations ranged from 1 μg/L to 1820 μg/L, and the majority of wells in the endemic region contained between 400 and 600 μg/L arsenic. Skin cancer prevalence was computed according to the median arsenic concentrations per village, categorized as < 300 μg/L, 300–600 μg/L and > 600 μg/L. Villages with either wide-ranging arsenic concentrations or residents who no longer drank the water were deemed to be indeterminate in the analysis. Prevalence rates of skin cancer (based on clinical diagnosis) for inhabitants residing in low- (< 300 μg/L), medium- (300–600 μg/L) and high- (> 600 μg/L) arsenic areas represented over an eightfold difference from the highest to the lowest category.

(ii) *Studies based on incidence of skin cancer*

Guo *et al*. (1998, 2001) correlated incidence rates of skin cancer with levels of arsenic in well-water for 243 townships in Taiwan (with a total of about 11.4 million residents). Skin cancers were identified from the National Cancer Registry Program from 1980 to 1987 by a hospital-based registry covering both clinical and pathological diagnoses of skin cancers (reporting is not mandatory by law) (Guo *et al*., 1998). Arsenic concentrations were provided by a national survey of wells conducted by the Taiwan Provincial Institute of Environmental Sanitation and published in 1977. The investigators modelled the percentage of the population living in townships with drinking-water concentrations of < 50, 50–89, 90–169, 170–329, 330–640 and > 640 μg/L arsenic. The models assume that the same number of individuals drank from each well within a township. The results for all skin cancers combined estimated a relative risk for the highest versus lowest exposure category of about 14 in men and 19 in women, with no excess detected in the other categories (Guo *et al*., 1998).

Table 25. Summary of epidemiological studies on arsenic in drinking-water and risk for skin cancer

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Ecological studies						
Taiwan						
Tseng *et al.* (1968)	40 421 residents from 37 villages (SW)	Prevalence ≥ 20 years of age	Median arsenic concentrations of wells in village of residence (μg/L) < 300 300–600 > 600	428	Prevalence (per 1000) 2.6 10.1 21.4	Prevalence based on clinical examination of all households. Excludes villages with wells no longer in use or with variations in arsenic concentration (range, 1–1820 μg/L; most wells contained 400–600 μg/L arsenic)
Chen *et al.* (1985)	4 neighbouring townships on the SW coast	Mortality 1968–82	Areas hyperendemic (21 villages), endemic (25 villages) and not endemic (38 villages) for Blackfoot disease, corresponding to high, medium and low exposure	46 men 49 women	SMR (95% CI) 534 (379–689) 652 (469–835)	Mortality rates in all Taiwan as standard
Chen *et al.* (1988a)	Region endemic for Blackfoot disease (SW)	Mortality 1973–86	Median arsenic concentrations of well-water (μg/L) < 300 300–600 > 600	 Men Women Men Women Men Women	SMR 1.6 1.6 10.7 10.0 28.0 15.1	Age-standardized to the 1976 world standard population

Table 25 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Wu *et al*. (1989)	42 villages in region endemic for Blackfoot disease (SW)	Mortality 1973–86	Median arsenic concentrations of well-water in village of residence (μg/L) in 1964–66	19 men 17 women	SMR	Age-standardized to the 1976 world standard population
			< 300	Men	2.03	
			300–600		14.01	
			> 600		32.41 ($p < 0.001$)	
			< 300	Women	1.73	
			300–600		14.75	
			> 600		18.66 ($p < 0.001$)	
Chen & Wang (1990)	314 precincts and townships	Mortality 1972–83	Average arsenic concentrations	NS	Increase (β) in mortality rate per 100 000 per 0.1 μg/L increase:	Multiple regression adjusted for age and indices of urbanization and industrialization. Mortality rates standardized to the 1976 world standard population
				Men	β (SE) = 0.9 (0.2)	
				Women	β (SE) = 1.0 (0.2)	
Guo *et al*. (1998)	243 townships, 11.4 million residents	Incidence 1980–87	Arsenic concentration in wells Exposure categories: > 50, 50–89, 90–169, 170–329, 330–640 and > 640 μg/L	952 men 595 women	Risk difference of 0.34/100 000 ($p < 0.01$) associated with a 1% increase in arsenic concentrations > 640 μg/L Relative risk of highest versus lowest exposure category: 14.21 in men; 19.25 in women No excess risk for other categories	Rates standardized using the 1976 world standard population. Model assumes that same number of individuals use each well.
Tsai *et al*. (1999)	Four townships (SW)	Mortality 1971–94	Area endemic for Blackfoot disease		Age- and sex-adjusted SMR (95% CI)	
				66 men	4.8 (3.7–6.2)	Local standard
					5.97 (4.6–7.6)	National standard
				68 women	5.7 (4.4–7.2)	Local standard
					6.8 (5.3–8.6)	National standard

Table 25 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Guo *et al*. (2001)	243 townships, 11.4 million residents	Incidence 1980–89	Concentration of arsenic in well-water: Exposure categories (µg/L) arsenic	2369 (1415 men, 954 women)	Rate difference association with a 1% increase in residents with categories of arsenic (µg/L):	Cancers identified through National Cancer Registry. Models include age and urbanization index. Models assume same number of individuals use each well. BCC, basal-cell carcinoma SCC, squamous-cell carcinoma *$p < 0.05$ **$p < 0.01$
			Intercept	764 BCC Men	0.779	
				Women	–0.002	
			50–89	Men	0.004	
				Women	–0.012	
			90–169	Men	–0.017	
				Women	0.018	
			170–329	Men	0.006	
				Women	0.004	
			330–640	Men	–0.024	
				Women	0.016	
			> 640	Men	0.128**	
				Women	0.027	
			Intercept	736 SCC Men	0.821	
				Women	1.488	
			50–89	Men	0.024	
				Women	–0.006	
			90–169	Men	–0.026	
				Women	0.006	
			170–329	Men	0.073**	
				Women	0.016	
			330–640	Men	–0.100**	
				Women	–0.064*	
			> 640	Men	0.155**	
				Women	0.212**	
				182 melanoma	No increase associated with melanoma	

Table 25 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Guo *et al.* (2001) (contd)			Three categories of township: (1) No well with arsenic > 40 µg/L; (2) Some wells > 40 µg/L but none > 640 µg/L; (3) More wells > 640 µg/L than between 320 and 640 µg/L		Dose–response relationship between basal-cell and squamous-cell skin cancer in both men and women and in all age categories (except for basal-cell < 30 years of age, which had few subjects). No consistent increase in melanoma incidence by exposure category	
Mexico						
Cebrián *et al.* (1983)	Two rural populations in Lagunera region; 2486 residents	Prevalence (time frame not specified)	Town of El Salvador de Arriba: high exposure to arsenic (410 µg/L); town of San Jose del Vinedo: low exposure (5 µg/L)	4	High exposure: 1.4% (4 cases in 57 households and 296 individuals); low exposure: 0% (0 cases in 68 households and 318 individuals)	Epidermoid or basal-cell carcinomas detected on physical exam of every 3rd household
Chile						
Zaldívar *et al.* (1974)	City of Antofagasta	Incidence of cutaneous lesions of chronic arsenic poisoning, 1968–71	Concentration of arsenic fell from 580 µg/L in 1968–69 to 8 µg/L in 1971		Incidence rates: Men: 145.5/100 000 in 1968–69, 9.1/100 000 in 1971; women: 168.0/100 000 in 1968–69 and 10.0/100 000 in 1971	
Rivara *et al.* (1997)	Regions II and VIII	Mortality 1976–92	Exposed group: Antofagasta in region II (arsenic concentration in drinking-water, 40–860 µg/L; 1950–92) Unexposed group: region VIII, no arsenic contamination (reference)	NS	SMR (95% CI) 3.2 (2.1–4.8)	
Smith *et al.* (1998)	Region II, northern Chile	Mortality 1989–93, age ≥ 30	Annual average arsenic concentrations ranging 43–569 µg/L in 1950–94	20 men 7 women	SMR (95% CI) 7.7 (4.7–11.9) 3.2 (1.3–6.6)	Age-standardized to the national rates of Chile in 1991

Table 25 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
USA						
Berg & Burbank (1972)		Mortality 1950–67	Trace metals in water supplies from 10 basins throughout the USA; concentration of arsenic in water, Oct. 1962–Sept. 1967		No correlation	
Morton *et al*. (1976)	Lane County, OR	Incidence 1958–71	Mean arsenic concentration in municipal water system and single-family systems	3039	Correlation of arsenic content in drinking-water: squamous-cell carcinoma: 0.151 for men and –0.20 for women; basal-cell carcinoma: –0.064 for men and 0.10 for women	Non-melanoma cases identified by review of pathology reports
Wong *et al*. (1992)	Four counties in Montana	Incidence 1980–86	Two contaminated counties (copper smelter and copper mines); two control counties	Around 2300 in the 4 counties	Age-adjusted skin cancer incidence higher in control counties	Overall incidence rates for exposed counties within range observed for other US locations
Cohort studies						
Taiwan						
Chen *et al*. (1988b)	Four townships (SW)	Mortality 1968–83, all ages	Diagnosis of Blackfoot disease as a surrogate for high exposure to arsenic	7	SMR 28.46 ($p < 0.01$) (national standard) 4.51 ($p < 0.05$) (local standard)	871 people who developed Blackfoot disease after 1968 were followed for 15 years. National standard used for the age- and sex-standardized rates of the general Taiwanese population.
Hsueh *et al*. (1997)	Three villages in Putai township (SW)	Incidence 1989–92, age, ≥ 30 years	Duration of residence in area endemic for Blackfoot disease (years) ≥ 33 34–43 44–53 > 53	 1 4 8 20	Relative risk (95% CI) 1.0 5.01 (0.5–48.1) 4.9 (0.6–41.6) 6.8 (0.9–53.7) (p for trend = 0.07)	654 subjects (275 men and 379 women) without skin cancer followed with dermatological examinations. Total of 2239 person–years. Relative risk adjusted for age, sex and level of education

Table 25 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Hsueh *et al.* (1997) (contd)			Duration of consumption of artesian well-water (years)			
			0	1	1.0	
			1–15	1	1.2 (0.4–19.7)	
			16–25	8	3.9 (0.5–32.1)	
			> 25	23	8.9 (1.1–72.9) (p for trend < 0.05)	
			Average concentration of arsenic in drinking-water (mg/L)			
			0	1	1.0	
			0.01–0.70	12	3.3 (0.4–35.8)	
			0.71–1.10	13	8.7 (1.1–65.5) (p for trend < 0.05)	
			Unknown	7	4.8 (0.6–40.4)	
			Cumulative exposure to arsenic (mg/L–years)			
			0	1	1.0	
			0.1–10.6	2	2.8 (0.3–31.9)	
			10.7–17.7	5	2.6 (0.3–22.9)	
			> 17.7	18	7.6 (0.95–60.3) (p for trend = 0.06)	
			Unknown	7	5.1 (0.6–44.4)	
			Level of serum β-carotene (μg/mL)	16 cases (61 controls)	OR (95% CI)	OR adjusted for age, sex, cumulative exposure to arsenic, serum cholesterol and triglyceride levels, cigarette smoking and alcohol drinking Incidence 14.74/1000 person–years
			≤ 0.14		1.0	
			0.15–0.18		0.4 (0.1–2.9)	
			> 0.18		0.01 (0.0–0.4) (p for trend < 0.01)	

Table 25 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Case–control studies						
USA						
Karagas *et al.* (2001b, 2002)	New Hampshire	Incidence 1993–96	Concentration of arsenic in toenails (μg/g)		OR (95% CI)	OR adjusted for age and sex
					Squamous-cell carcinoma	284 cases, 524 controls
			0.009–0.089	155	1.0	
			0.090–0.133	64	0.9 (0.6–1.3)	
			0.134–0.211	33	0.98 (0.6–1.6)	
			0.212–0.280	14	1.1 (0.55–2.2)	
			0.281–0.344	5	1.0 (0.3–3.0)	
			0.345–0.81	13	2.1 (0.9–4.7)	
					Basal-cell carcinoma	587 cases, 524 controls
			0.009–0.089	281	1.0	
			0.090–0.133	156	1.01 (0.8–1.4)	
			0.134–0.211	92	1.06 (0.7–1.5)	
			0.212–0.280	22	0.7 (0.4–1.3)	
			0.281–0.344	10	0.8 (0.3–1.8)	
			0.345–0.81	26	1.4 (0.7–2.8)	
Nested case–control study						
Taiwan						
Hsueh *et al.* (1995)	Three villages in Putai Township (SW)	Prevalence	Duration of residence in area endemic for Blackfoot disease (years)		OR (95% CI)	OR adjusted for age and sex; 1081 residents (468 men, 613 women) underwent a physical examination.
			≤ 45	2	1.0	
			46–49	11	5.2 (1.1–25.8)	
			≥ 50	53	8.5 (1.96–37.2)	
					p for trend < 0.05	

Table 25 (contd)

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments
Hsueh *et al.* (1995) (contd)			Duration of drinking artesian well-water (years)			
			≤ 13	2	1.0	
			14–25	15	5.1 (1.03–24.98)	
			≥ 60	52	6.4 (1.4–27.9)	
					p for trend < 0.05	
			Average exposure to arsenic (ppm)			
			0	2	1.0	
			0–0.70	20	3.5 (0.7–17.0)	
			> 0.71	30	5.0 (1.1–23.8)	
			Cumulative exposure to arsenic (ppm–years)			
			≤ 4	1	1.0	
			5–24	22	8.9 (1.1–73.8)	
			≥ 25	28	13.7 (1.7–111.6)	
			Chronic hepatitis B carrier and liver function status:			
			Non-carrier with normal liver function	41	1.0	
			HBsAg carrier with normal liver function	13	1.1 (0.56–2.2)	
			Non-carrier with liver dysfunction	3	2.1 (0.54–7.7)	
			HBsAg carrier with liver dysfunction	4	8.4 (2.37–29.9)	
					p for trend < 0.05	

SMR, standardized mortality ratio; CI, confidence interval; NS, not specified; OR, odds ratio

In a second study, the incidence rates of each major histological type of skin cancer (basal-cell, squamous-cell and melanoma) were modelled using the previously defined exposure categories (Guo *et al*., 2001). The model included the percentage of residents in categories of age (30–49, 50–69 and > 69 years) and urbanization index as covariates. In this analysis, they found a statistically significant increase in squamous-cell skin cancer in the highest category (> 640 μg/L arsenic) in both men and women. Similarly, for basal-cell carcinoma, there was also a positive association in the highest exposure category. Melanoma was unrelated to any category of exposure to arsenic. In a post-hoc analysis, the investigators created three exposure groups: townships with no well containing levels of arsenic above 40 μg/L, townships with some wells containing more than 40 μg/L arsenic but none above 640 μg/L and townships with more wells containing more than 640 μg/L than between 320 and 640 μg/L. A dose–response relation between basal-cell and squamous-cell skin cancer rates was observed in both men and women and in all age categories (except for basal-cell cancer below age 30 years, which had few subjects). Again, no association was seen for melanoma. [The Working Group noted that the reporting of incident skin cancer may have been incomplete.]

(iii) *Studies based on mortality from skin cancer*

A series of studies conducted in Taiwan, China (Chen *et al*., 1985, 1988a; Wu *et al*., 1989; Chen & Wang, 1990; Tsai *et al*., 1999) (described in Section 2.1.1) analysed skin cancer mortality in relation to levels of arsenic in well-water. The overall SMRs in the four counties were 534 in men and 652 in women, with 100 as the referent value. There was also a gradient of increasing SMRs for skin cancer in areas not endemic or hyperendemic for Blackfoot disease (Chen *et al*., 1985). A subsequent report (Chen *et al*., 1988a) presented SMRs for skin cancer grouped by the median levels of arsenic in well-water measured in 1962–64 into < 300, 300–600 and > 600 μg/L. The age-standardized mortality rates for skin cancer increased in the three categories for both genders (Chen *et al*., 1988a). Wu *et al*. (1989) published age-adjusted mortality rates from skin cancer for the years 1973–86 for the four townships endemic for Blackfoot disease plus 15 villages in the townships of Yensui and Hsiaying. Using the same data on well-water contents and the classification described above, skin cancer mortality rates also increased in men and women with increasing median concentrations of arsenic. Subsequently, Chen and Wang (1990) used data on wells measured from 1974 to 1976 from 314 precincts and townships throughout Taiwan. Based on a multiple regression analysis (adjusted for urbanization and age), a 0.1-μg/L increase in arsenic corresponded to an increase of 0.9 (SE, 0.2) and 1.0 (SE, 0.2) per 100 000 in skin cancer mortality in men and women, respectively. More recently, Tsai *et al*. (1999) computed SMRs for the period 1971–94 for the four townships endemic for Blackfoot disease by applying both local (Chiayi County) and national (Taiwan) rates as the standards. The SMRs for skin cancer were approximately 5.0 for men and women, using both local and national standards.

(*b*) *Cohort studies*

Chen *et al*. (1988b) conducted a retrospective cohort study of 871 patients who met clinical criteria of Blackfoot disease after January 1968. From 1968 to 1983, seven death certificates identified the underlying cause of death as skin cancer. SMRs for skin cancer were computed using both the area endemic for Blackfoot disease and the whole of Taiwan as the population standards. The age-standardized observed versus expected number of skin cancer deaths was around 28 using Taiwan as the standard and 4.5 using the Blackfoot disease townships as the standard. [Use of the national population as the standard may provide a better estimate of excess risk than use of the local population for whom arsenic concentrations in well-water were elevated.]

Hsueh *et al*. (1997) established a cohort of residents living in three villages (Homei, Fuhsin and Hsinming) in Putai Township, one of the regions of the south-west coast of Taiwan endemic for Blackfoot disease. Arsenic-contaminated well-water had existed in these villages for over 50 years, with reported values ranging from 700 to 930 μg/L. The government introduced a new water system in the 1960s, with relatively low penetration until the 1970s. Well-water remained in use for agriculture and aquaculture. The 1571 residents aged 30 years or older who lived for at least 5 days a week in the villages were recruited to take part in the study. Of these, 1081 (68.8%) participated in a physical examination (468 men and 613 women). The 1015 study subjects who did not have a prevalent skin cancer comprised the cohort. Of these, 275 men and 379 women (64%) underwent regular examinations for dermatological conditions. Thirty-three incident skin cancers developed during the follow-up period from September 1989 through December 1992, with a total of 2239 person–years and a rate of 14.74/1000 person–years. Public health nurses interviewed cohort members on length of residence, history of drinking well-water and other potentially confounding factors. An index for cumulative exposure to arsenic was derived for each subject using concentrations of arsenic in well-water for each village of residence measured in the 1960s. These data were multiplied by the duration of consumption of well-water in each village of residence and totalled for each residence. Dermatologists diagnosed clinically the skin cancers that occurred in the cohort, and 91% of clinically diagnosed carcinomas were confirmed histologically. Fasting blood samples and urine samples were collected at the time of interview. Serum was analysed for β-carotene and urine for arsenic metabolites from 16 skin cancer cases [48%] and 61 age- and sex-matched controls. Cox proportional hazard regression was used to analyse data on exposure to arsenic in relation to incidence of skin cancer adjusted for age, sex and educational level. Conditional logistic regression analysis was used to assess the effects of β-carotene and urinary metabolites on the risk for skin cancer. Risk for skin cancer was significantly related to duration of living in the area endemic for Blackfoot disease, duration of consumption of artesian well-water, average concentration of arsenic and index for cumulative exposure to arsenic. There was evidence of a reduced risk for skin cancer in the highest two tertiles of β-carotene versus the lowest tertile after adjustment for multiple potential confounders. Also, compared with controls, cases of

skin cancer had higher total urinary concentration of arsenic, percentage of MMA and ratio of MMA to inorganic arsenic and a lower percentage of DMA and ratio of DMA to MMA (not shown in Table 25).

Hsueh *et al*. (1995) conducted a nested case–control study within the cohort study of Hsueh *et al*. (1997). A total of 66 prevalent skin cancers were identified after clinical examination. Age- and sex-adjusted prevalence odds ratios were computed for the same variables of exposure to arsenic included in the cohort analysis: duration of living in the area endemic for Blackfoot disease, duration of drinking artesian well-water, and average and cumulative exposure to arsenic. Significant increases in risk for each exposure group were shown. In addition, a significantly elevated risk for skin cancer was observed among chronic hepatitis B carriers with liver dysfunction.

2.3.2 *Mexico*

Ecological study based on prevalence of skin cancer

Cebrían *et al*. (1983) reported results from a household survey of two rural Mexican towns in the Region of Lagunera. Towns were selected on the basis of levels of arsenic in drinking-water, one town with a high level of arsenic (average, 410 µg/L) and the other with a low level of arsenic (average, 5 µg/L). The towns are located 37 km apart, and their populations were of comparable size (1488 and 998 inhabitants, respectively) and socio-economic and environmental conditions. A questionnaire and physical examination were administered to all family members of every third household in each community. Seventy-five per cent of the residents had lived in these communities since birth. After clinical diagnosis, prevalence of epidermoid or basal-cell carcinoma (referred to as ulcerative lesions) was 1.4% in the exposed town, whereas no case was observed in the control town. The 20 water samples tested from the exposed town between 1975 and 1978 had arsenic concentrations ranging from 160 to 590 µg/L (standard deviation [SD], 114 µg/L), indicating significant variability. The control town showed little variability (SD, 7 µg/L) in the 18 samples collected over the same period.

2.3.3 *Chile*

Ecological study based on incidence of cutaneous lesions

Zaldívar *et al.* (1981) investigated the incidence of cutaneous lesions (leukoderma, melanoderma, hyperkeratosis, and squamous-cell carcinoma) in residents of Antofagasta in arsenic-contaminated Region II from 1968 to 1971. Among 457 patients, about 70% were children aged 0–15 years. Incidence rates decreased from 1968–69 to 1971 due to a filter plant which started operation in 1970.

Ecological studies based on mortality from skin cancer

In an ecological analysis, Rivara *et al*. (1997) compared mortality rates from skin cancer in 1976–92 between Antofagasta and the unexposed control Region VIII of Chile.

The SMR for skin cancer was 3.2 (95% CI, 2.1–4.8). In a later study, Smith *et al*. (1998) compared sex- and site-specific mortality for the years 1989–93 in Region II of Chile with national mortality rates. The SMR for skin cancer was 7.7 (95% CI, 4.7–11.9) among men and 3.2 (95% CI, 1.3–6.6) among women.

2.3.4 *USA*

(*a*) *Ecological study*

Berg and Burbank (1972) showed no correlation between trace metals from 10 water basins throughout the USA and mortality rates in 1950–67, using concentrations of arsenic measured in 1962–67.

Morton *et al*. (1976) studied the incidence of histologically confirmed basal-cell and squamous-cell skin cancers (*in situ* and invasive) for the period 1958–71 in Lane County, OR, USA. They identified skin cancers by reviewing the pathology records of facilities serving residents of the county and the biopsy files of two of five dermatologists. Water samples were tested from selected points throughout the county from public water systems and from a number of single-family systems. Single-family systems were reported to have been over-sampled in regions suspected of having a problem with arsenic. Within a given region, arsenic values ranged from undetectable to 2150 µg/L. The correlation between census tract estimates of arsenic in drinking-water and incidence of squamous-cell carcinoma was 0.151 in men and –0.20 in women; for the incidence of basal-cell carcinoma, the correlation was –0.064 in men and 0.10 in women. [A major weakness of the study is the misclassification of exposure because of widely varying concentrations of arsenic within a census tract.]

Wong *et al.* (1992) studied approximately 2300 incident cases of skin cancer in four counties in Montana (two contaminated and two controls) in 1980–86. Contamination arose from copper smelters and mines. No difference in incidence rates was observed between exposed counties and the rest of the country.

(*b*) *Case–control studies*

Karagas *et al*. (1998, 2001b, 2002) designed a case–control study of basal-cell and squamous-cell skin cancers in the population of New Hampshire to evaluate the effects of low to moderate levels of exposure to arsenic. About 40% of the population relied on private, unregulated water systems; over 10% of the private supplies contained levels of arsenic above the WHO recommended level of 10 µg/L and 1% of supplies overall contained > 50 µg/L. A biomarker of internal dose was chosen to determine exposure levels. Earlier studies had indicated the reliability of concentrations of arsenic in toenails as a measure of exposure > 1 µg/L arsenic through drinking-water (Karagas *et al*., 1996, 2000) and reproducibility of concentrations over a period of 3–6 years (Garland *et al*., 1993; Karagas *et al.*, 2001a). Cases of basal-cell and squamous-cell skin cancer diagnosed from 1 July 1993 to 30 June 1995 were identified through a statewide network of dermatologists, dermatopathologists and pathologists, with participation rates of over 90% (Karagas *et al.*,

2001b). Because of the high incidence of basal-cell carcinoma, incident cases of basal-cell carcinoma were randomly selected in a 2:1 ratio to cases of squamous-cell carcinoma. To minimize detection bias, cases of squamous-cell carcinoma were restricted to invasive disease only (cases of in-situ carcinomas were excluded). A 2:1 ratio of controls to squamous-cell carcinoma cases was randomly selected from population lists (driver's licence files for cases < 65 years and Medicare enrollment lists for cases ≥ 65 years), frequency-matched to the combined distribution of the basal-cell and squamous-cell carcinoma cases. To be eligible to participate, subjects were required to speak English and have a working telephone. Of the 1143 potential case subjects, 896 took part in the study (78%) and, of the 820 potential controls, 540 (66%) enrolled. The analysis included the 587 cases of basal-cell carcinoma, 284 cases of squamous-cell carcinoma and 524 controls (97% of subjects) who contributed a toenail sample for arsenic analysis. Study participants underwent a personal interview to obtain information on confounding factors such as exposure and sensitivity to sun, history of radiation treatment and other medical and lifestyle factors. Age- and sex-adjusted odds ratios were computed using logistic regression analysis according to percentiles of arsenic concentrations in toenails based on the control distribution. In this categorical analysis, concentrations of arsenic appeared to be unrelated to risk for squamous-cell and basal-cell carcinomas except for the highest category (the top 97th percentile; concentrations above 0.344 μg/g) versus concentrations below the median.

An analysis using continuous exposure variables was presented separately (Karagas *et al*., 2002). A quadratic and two-segment linear model fitted the data for both squamous-cell carcinoma and basal-cell carcinoma. The point at which the dose–response appeared to increase was at 0.105 μg/g (95% CI, 0.093–0.219 μg/g) for squamous-cell carcinoma using a maximum likelihood estimation of the change point for the two-segment linear model. After the change point, a 1% increase in arsenic concentration in toenails was related to a 0.61% increase in risk for squamous-cell carcinoma. The quadratic model for both squamous-cell carcinoma and basal-cell carcinoma produced a consistent nadir or change point of 0.088 and 0.091, respectively. However, it was not possible to estimate a two-segment model for basal-cell carcinoma because of sparse data at the extremes. Based on a regression analysis of concentrations of arsenic in water and toenails, a change point of 0.105 μg/g in toenails translated to 1–2 μg/L in water, with the 95% confidence interval ranging from < 1 to 10–20 μg/L.

2.4 Other organ sites

Studies on cancer at other organ sites are summarized in Table 26.

Neubauer (1947) summarized cancers that had been reported in patients treated with medicinal arsenic. His report of 143 published cases included patients who developed cutaneous tumours and other malignancies such as cancers of the stomach (one case), tongue (two cases, one who also had cancer of oral mucosa), oesophagus (two cases), uterus (one case) and urethra (two cases including one papilloma of the ureter). Among patients who had not developed cutaneous tumours, other reported malignancies included

Table 26. Summary of epidemiological studies of arsenic in drinking-water and risk for other cancers

Reference	Location	End-point	Exposure	Site	No. of cases	Study outcome	Comments
Ecological studies							
Taiwan							
Chen *et al.* (1985)	84 villages on the SW coast	Mortality 1968–82, all ages	Endemic area for chronic arsenic toxicity (Blackfoot disease)		Men	Age- and sex-adjusted SMR (95% CI)	SMRs for a total of 11 sites. Prostate not investigated; mid-year population: 141 733 in 1968, 120 607 in 1982; national rate in 1968–82 used as the standard for estimation of SMR
				Colon	54	1.6 (1.2–2.0)	
				Small intestine	17	2.98 (0.6–3.4)	
				Leukaemia	45	1.4 (1.0–1.8)	
					Women		
				Colon	61	1.7 (1.3–2.1)	
				Small intestine	5	0.97 (0.1–1.8)	
				Leukaemia	22	0.9 (0.5–1.3)	
Chen *et al.* (1988a)	42 villages on the SW coast	Mortality 1973–86, all ages	Median level of arsenic in drinking-water grouped into 3 strata, 1962–64	Prostate			899 811 person–years, rate per 100 000, age-standardized to 1976 world population
			General population			Age-adjusted SMR	
			< 300 µg/L			1.5	
			300–600 µg/L			0.5	
			> 600 µg/L			5.8	
						8.4	

Table 26 (contd)

Reference	Location	End-point	Exposure	Site	No. of cases	Study outcome	Comments
Wu *et al*. (1989)	42 villages (SW)	Mortality 1973–86, age ≥ 20 years	Median level of arsenic in drinking-water grouped into 3 strata, 1962–64			SMR	Age-adjusted mortality. All results are non-significant. Men, 257 935 person–years; women, 234 519 person–years; rate per 100 000, age-standardized to 1976 world population
			< 30 µg/L	Prostate	9 M	0.95	
				Leukaemia	11 M	4.87	
					7 F	3.03	
				Nasopharynx	11 M	3.58	
					7 F	1.59	
				Oesophagus	15 M	7.62	
					4 F	1.83	
				Stomach	46 M	25.6	
					21 F	6.71	
				Colon	17 M	7.94	
					21 F	9.05	
				Uterine cervix	6 F	0.91	
			300–600 µg/L	Prostate	9 M	9.00	
				Leukaemia	11 M	6.52	
					7 F	4.55	
				Nasopharynx	11 M	8.16	
					7 F	5.81	
				Oesophagus	15 M	9.37	
					4 F	3.64	
				Stomach	46 M	17.82	
					21 F	18.72	
				Colon	17 M	8.30	
					21 F	8.16	
				Uterine cervix	6 F	5.46	

Table 26 (contd)

Reference	Location	End-point	Exposure	Site	No. of cases	Study outcome			Comments
Wu *et al.* (1989) (contd)			> 600 µg/L	Prostate	9 M	9.18			
				Leukaemia	11 M	2.69			
					7 F	0.00			
				Nasopharynx	11 M	8.58			
					7 F	4.89			
				Oesophagus	15 M	6.55			
					4 F	0.00			
				Stomach	46 M	56.42			
					21 F	5.98			
				Colon	17 M	12.5			
					21 F	17.21			
				Uterine cervix	6 F	3.92			
Chen & Wang (1990)	42 villages on the SW coast	Mortality 1972–83, all ages	National survey of 83 656 wells (1974–76); average arsenic content for each of 314 precincts or townships			Percentiles of age-adjusted mortality rate/100 000 person–years			
					Men	*25th*	*50th*	*75th*	
				Oesophagus		3.6	6.0	9.2	
				Stomach		14.8	10.2	28.8	
				Small intestine		0.6	1.1	1.9	
				Colon		4.2	5.6	7.2	
				Rectum		1.9	2.7	3.9	
				Pancreas		1.3	2.1	3.0	
				Nasal cavity		1.1	1.3	2.6	
				Larynx		1.1	1.7	2.8	
				Bone/cartilage		1.1	1.8	2.9	
				Prostate		0.9	1.4	2.3	
				Brain		0.7	1.1	1.8	
				Leukaemia		1.3	2.1	2.7	
					Women	*25th*	*50th*	*75th*	
				Oesophagus		1.1	1.8	2.8	
				Stomach		7.2	10.0	13.7	
				Small intestine		0.6	0.9	1.6	
				Colon		3.6	5.5	6.9	

Table 26 (contd)

Reference	Location	End-point	Exposure	Site	No. of cases	Study outcome			Comments
Chen & Wang (1990) (contd)				Rectum		1.5	2.3	3.3	
				Pancreas		1.4	2.1	2.7	
				Nasal cavity		0.6	1.0	1.6	
				Larynx		0.5	0.9	1.5	
				Bone/cartilage		1.0	1.7	2.5	
				Breast		2.7	4.4	6.2	
				Cervix uteri		3.8	6.2	8.3	
				Ovary		0.8	1.4	2.0	
				Brain		1.0	1.5	2.2	
				Leukaemia		1.1	1.7	2.4	
Tsai *et al*. (1999)	Four townships (SW)	Mortality 1971–94, all ages	Endemic area for chronic arsenic toxicity		*Men*	SMR (95% CI)			SMRs with national reference, unless otherwise stated; *SMRs with local reference Men, 1 508 623 person–years; women, 1 404 759 person–years; national rates in 1971–94 used as the standard for SMR estimation
				Pharynx	24	1.1 (0.7–1.7)			
				Oesophagus	69	1.7* (1.3–2.1)			
				Stomach	195	1.4* (1.2–1.5)			
				Intestine	15	2.1 (1.2–3.5)			
				Colon	91	1.4 (1.1–1.7)			
				Rectum	46	1.2 (0.9–1.7)			
				Nasal cavity	40	3.7 (2.6–5.0)			
				Larynx	30	1.8 (1.2–2.5)			
				Bone	41	2.3 (1.7–3.2)			
				Prostate	48	1.96 (1.4–2.6)			
				Brain	19	1.1 (90.7–1.8)			
				Lymphoma	56	1.4 (1.1–1.8)			
				Leukaemia	67	1.3 (1.04–1.7)			
					Women				
				Pharynx	10	2.2 (1.1–4.1)			
				Oesophagus	12	0.8 (0.4–1.4)			
				Stomach	111	1.4* (1.2–1.7)			
				Intestine	8	1.3 (0.5–2.5)			
				Colon	83	1.4* (1.1–1.8)			
				Rectum	33	1.5* (1.03–2.11)			
				Nasal cavity	29	5.1 (3.4–7.3)			
				Larynx	13	3.8 (2.0–6.4)			
				Bone	34	2.2 (1.5–3.1)			
				Brain	21	1.8* (1.1–2.7)			
				Lymphoma	35	1.4 (1.0–2.0)			
				Leukaemia	40	1.1 (0.8–1.4)			

Table 26 (contd)

Reference	Location	End-point	Exposure	Site	No. of cases	Study outcome	Comments
Chile							
Rivara *et al.* (1997)	Regions II and VIII, northern Chile	Mortality 1950–92	Arsenic-contaminated Region II	Larynx		Relative risk (Region II versus Region VIII), 3.4 (95% CI, 1.3–8.6)	Population: 411 000 in Region II, 1 700 000 in Region VIII. Antofagasta (Region II) versus Region VIII.
USA							
Berg & Burbank (1972)	10 water basins	Mortality 1950–67	Trace metals in water supplies (As, Be, Cd, Cr, Co, Fe, Pb, Ni)			Probability of a positive association	
				Larynx		0.024	
				Eye		0.009	
				Myeloid leukaemia		0.042	
Australia							
Hinwood *et al.* (1999)	Victoria	Incidence 1982–91	Median arsenic concentration in drinking-water ranging 1–1077 µg/L		*Obs. no.*	SIR (95% CI)	State rates in 1982–91 used as the standard for estimation of SIR
				Prostate	619	1.1 (1.05–1.2)	
				Melanoma	477	1.4 (1.2–1.5)	
				Breast	762	1.1 (1.03–1.2)	
				Chronic myeloid	40	1.5 (1.1–2.1)	

Table 26 (contd)

Reference	Location	End-point	Exposure	Site	No. of cases	Study outcome		Comments
Case–control study								
Canada								
Infante-Rivard *et al.* (2001)	Québec province	Incidence 1980–93	Trihalomethanes, metals (As, Cd, Cr, Pb, Zn) and nitrates in drinking-water during prenatal and postnatal periods	Childhood acute lymphocytic leukaemia				Adjusted for maternal age and level of education
						OR (95% CI)		
			Arsenic exposure index		*Exposed cases*	*Prenatal period*	*Postnatal period*	
			Average level (> 95th versus ≤ 95th percentile [5 µg/L])		Prenatal, 18 Postnatal, 20	0.9 (0.5–1.8)	1.4 (0.7–2.8)	
			Cumulative exposure (> 95th versus ≤ 95th percentile		Prenatal, 20 Postnatal, 19	0.7 (0.4–1.3)	1.1 (0.6–2.2)	
Cohort studies								
Japan								
Tsuda *et al.* (1989)	Nakajo-machi town, Niigata Prefecture, 281 residents	Mortality 1959–87	High dose of arsenic contamination (through a factory) of well-water used for drinking (1955–59)	Uterus	17 deaths from all cancers in the entire cohort	Among the residents in high-exposure areas (low, < 0.05 ppm; medium, 0.05–0.5 ppm; high, ≥ 0.5 ppm), significant excess mortality from cancer of the uterus over expected value based on mortality for Niigata Prefecture and for all Japan		

Table 26 (contd)

Reference	Location	End-point	Exposure	Site	No. of cases	Study outcome			Comments
Tsuda *et al.* (1995)	454 residents living in Namikicho and Nakajo-machi in Niigata Prefecture	Mortality 1959–92	High-dose arsenic contamination (through a factory) of well-water used for drinking (1955–59)	Uterus		Arsenic concentration (ppm)		SMR (95% CI)	113 persons who drank from industrially contaminated wells in 1955–59, then followed for 33 years; rates in Niigata Prefecture in 1960–89 used as the standard for estimation of SMR
					0	< 0.05		0.0 (0–8.0)	
					0	0.05–0.99		0.0 (0–37.6)	
					2	≥ 1		13.5 (2.4–48.6)	
					2	Total		3.0 (0.5–11.1)	
USA									
Garland *et al.* (1996)	Nested case–control in the Nurses' Health Study Cohort, USA	Incidence 1984–86	Exposure to 5 metals (As, Cu, Cr, Fe, Zn) through any route measured	Breast, diagnosed from 1984 to 1986, 459 matched controls	Total, 433	Quin-tile	Cut-point (μg/g)	Odds ratio	95% CI	Multivariate logistic regression models controlled for age, date of nail return, smoking, age at first birth, parity, history of benign breast disease, history of breast cancer in mother or sister, age at menarche, menopausal status, body mass index and alcohol consumption
					54	1	< 0.059	1.0		
					67	2	0.059–0.078	1.2	0.7–1.98	
					56	3	0.079–0.103	1.01	0.6–1.7	
					62	4	0.104–0.138	1.1	0.7–1.9	
					69	5	> 0.138	1.1	0.7–1.9	
Lewis *et al.* (1999)	Millard County, UT	Mortality	Exposure to arsenic in drinking-water	Prostate	50				SMR	Exposure index relies on ecological measures of arsenic concentration, median value for the community. State rates in 1950–92 used as the standard for estimation of SMR
						All men (μg/L–years)			1.5 (95% CI, 1.07–1.9)	
						Low (< 1000)			1.07	
						Medium (1000–4999)			1.70 ($p < 0.05$)	
						High (≥ 5000)			1.65	

SMR, standardized mortality ratio; CI, confidence interval; M, male; F, female; SIR, standardized incidence ratio; OR, odds ratio

cancers of the breast (two cases, one case who had keratoses present), pancreas (one case who had keratoses present) and mouth (one patient who had treatment to the mouth for syphilis). A report of seven cases of cancer following treatment with Fowler's solution (Jackson & Grainge, 1975) included one case of bilateral breast cancer and one case of colon cancer. Multiple skin cancers were present in both cases. The literature also includes cases of meningioma and intestinal malignancies associated with ingestion of arsenic (IARC, 1987). [Case reports have helped to identify the role of ingestion of arsenic in the occurrence of skin cancer and could provide leads to occurrences of other malignancies. However, without an appropriate comparison group, it is unclear whether any of the cases represent an excess over the norm.]

2.4.1 *Taiwan, China*

Ecological studies

Chen *et al*. (1985) (described in Section 2.1.1) reported SMRs in the four-county region in South-West Taiwan that is endemic for Blackfoot disease using mortality rates for the whole country as the standard. The analyses were based on mortality data obtained from the Department of Health for the period 1968–82. To estimate dose, SMRs were computed for regions that were hyperendemic (21 villages), endemic (25 villages) and not endemic (38 villages) for Blackfoot disease. Age-standardized mortality rates for the four counties were elevated compared with national rates for cancer of the colon in both men and women. Age- and sex-standardized mortality rates for colon cancer were higher in endemic areas than in non-endemic areas, but were lower in the hyperendemic areas compared with other areas. SMRs for leukaemia were of borderline statistical significance in men and close to unity in women. The SMR for cancer of the small intestine also was increased in men but not in women, and was not statistically significant in either sex [Prostate cancer was not investigated in this report.] (Chen *et al*., 1985). A subsequent report used the median concentrations of arsenic in well-water measured in 1962–64 grouped into levels of < 300, 300–600 and ≥ 600 µg/L. A dose-related gradient in age-adjusted mortality was noted for prostate cancer. In the ≥ 600-µg/L group, the age-standardized mortality rate for prostate cancer was 5.6 times higher than that of the general population of Taiwan (Chen *et al*., 1988a) (study described in Section 2.1.1).

Wu *et al*. (1989) (study described in Section 2.1.1) published age-adjusted mortality rates for the years 1973–86 in 27 townships in the four counties endemic for Blackfoot disease together with 15 additional villages in the townships of Yensui and Hsiaying. Using the same data on well-water content and the classification scheme described above (Chen *et al*., 1988a), a dose-related trend in mortality from prostate cancer was again observed (Mantel-Haenszel test for trend, $p < 0.05$). The authors also noted dose-related increases in mortality rates from nasopharyngeal and colon cancer in men, which, however, were not statistically significant. In this analysis, leukaemia and oesophageal, stomach or uterine cancers did not appear to be related to levels of arsenic (Wu *et al*., 1989).

In a later study, Chen and Wang (1990) (described in Section 2.1.1) used data on arsenic in well-water measured from 1974 to 1976 in 314 precincts and townships throughout Taiwan. Based on a multiple regression analysis (adjusted for urbanization and age), mortality rates from prostate cancer significantly increased with higher average level of arsenic. Age-adjusted mortality rates for cancers of the nasal cavity also correlated with average arsenic concentration in men and women for all precincts and townships and for the south-western townships. Cancers of the oesophagus, stomach, small intestine, colon, rectum, pancreas, larynx, bone and cartilage, breast, cervix, ovary and brain and leukaemia were not significantly correlated. [The regression estimates were only presented for statistically significant results.]

Based on data from death certificates for the period 1971–94, Tsai *et al*. (1999) (described in Section 2.1.1) computed SMRs for the four townships that are endemic for Blackfoot disease using local (Chiayi County) and national (Taiwan) rates as the standard. Applying national rates, SMRs were elevated for cancers of the intestine, colon and prostate in men, cancers of the nasal cavity and larynx in both men and women, lymphoma in men and women, leukaemia in men and cancers of the pharynx and bone in women. These SMRs were similarly elevated using the local mortality rates as the standard. In addition, using the local rates as the standard, higher SMRs were found for cancers of the oesophagus in men, cancers of the stomach in men and women and cancers of the colon, rectum and brain in women for the four townships.

[Data from South-West Taiwan indicate a consistent pattern of increases in mortality from prostate cancer in areas with high contamination by arsenic, and there is evidence of a dose-related effect. These studies do not specifically address the issue of dose of exposure, nor do they raise issues of latency and duration. These issues cannot be addressed using mortality as an end-point for prostate cancer since the disease has a low case-fatality rate. One possible source of bias is that prostate cancer often goes undetected, and a higher mortality rate in regions with known exposure to arsenic could occur if screening for cancer deaths is enhanced in the region.]

2.4.2 *Chile*

Ecological study

Rivara *et al*. (1997) compared the mortality rates for various cancers in 1976 between Antofagasta in Region II and the non-contaminated Region VIII. An elevated risk of cancer of the larynx was observed in the arsenic-exposed Region II. Among the various other cancers (17 sites) investigated, no other elevated SMRs were reported.

2.4.3 *Japan*

Cohort studies

From about 1945 to 1959, wells in the small town of Nakajo-machi in Niigata Prefecture became contaminated with arsenic (up to 3000 µg/L) from a factory producing

King's yellow (As_20_3). Two uterine cancer deaths occurred from 1959 to 1992 in the highest exposure category (≥ 500 µg/L), with an SMR for uterine cancer of around 3.0 using the age- and cause-specific mortality rates from Niigata Prefecture (Tsuda *et al*., 1989, 1995). [No other cancer sites were discussed.]

2.4.4 *North America*

(*a*) *Cohort studies*

Garland *et al*. (1996) conducted a nested case–control study in the USA to investigate the relationship between concentrations of arsenic and other trace elements in toenails and the incidence of breast cancer. Cases and controls were selected from the Nurses' Health Study cohort comprising 121 700 nurses aged 30–55 years living in 11 states of the USA. Toenail samples were obtained from 72% of 94 115 cohort members in 1982. A total of 62 641 women provided toenail clippings and did not have a diagnosis of breast cancer as of 1982. The nested study was based on the 433 women who had a diagnosis of breast cancer reported in mailed questionnaires in 1984 and 1986 and an age-matched control group. Compared with the quintile, the adjusted odds ratio for breast cancer was 1.1 (95% CI, 0.7–1.9) for the highest quintile of arsenic.

Lewis *et al*. (1999) reported SMRs for various cancers using a retrospective cohort of residents from Millard County, UT, USA. Of the multiple types of cancers examined, mortality was only elevated for prostate cancer [The limitations of this study have been cited in Section 2.1.4.].

(*b*) *Case–control studies*

Infante-Rivard *et al*. (2001) conducted a population-based case–control study of childhood leukaemia (occurring before the age of 9 years) in Québec Province, Canada. Cases included individuals who were newly diagnosed with childhood leukaemia from 1980 to 1993. Of 510 eligible cases, 491 participated (96.3%) and, of 588 controls, 493 took part (83.8%). The investigators sought drinking-water test data from 1970 onward through a postal questionnaire that yielded usable data from 112 of 202 municipalities (55%). Additional data was provided from the Ministry of Municipal Distribution Systems in 1986. Further analysis of tap-water was performed by the study investigators and covered 103 of the municipalities. These data were linked to information on residential history derived from interviews with the subjects' parents, and the value used for exposure to arsenic was that of the subjects' municipalities of residence for the closest year when data were available. Values from multiple test results were averaged over a given year, and individuals with private water systems were assigned the arsenic value of their municipality of residence. Separate exposure variables were computed for subjects' pre- and postnatal periods and included average arsenic levels and cumulative exposure. A logistic regression analysis included maternal age and level of schooling. The odds ratio for childhood leukaemia above versus less than or equal to the 95th percentile (5 µg/L arsenic) was 0.9 (95% CI, 0.5–1.8) for prenatal exposure and 1.4 (95% CI, 0.7–2.7) for postnatal exposure.

For cumulative exposure (above versus less than or equal to the 95th percentile), the odds ratios were 0.7 (95% CI, 0.4–1.3) for prenatal exposure and 1.1 (95% CI, 0.6–2.2) for postnatal exposure. [The study does not provide evidence of a link between childhood leukaemia and exposure to arsenic through drinking-water either prenatally or postnatally. However, the drinking-water concentrations were relatively low (95% were below 5 μg/L) and the estimates were imprecise. Furthermore, the exposure estimates are subject to misclassification, but there is no discussion on the variability of arsenic concentrations within municipalities and the fraction of residents that used private systems that were assumed to contain the same concentrations of arsenic as the public systems.]

2.4.5 *Australia*

Ecological study

In an ecological study using incidence data from the Victoria Cancer Registry for the years 1982–91, Hinwood *et al.* (1999) calculated SMRs for 14 cancer sites (in addition to liver, lung, bladder and kidney) in 22 postcode areas characterized by a level of arsenic in water > 0.01 mg/L in most areas. Incidence rates for all of Victoria were used as the standard. Cancer sites that showed elevated rates with 95% CIs that excluded 1.0 were prostate, melanoma, breast and chronic myeloid leukaemia. [The Working Group noted that no information was presented on the actual use of water contaminated with arsenic for drinking by the population.]