

**Table 2.7. Summary of epidemiological studies of arsenic in drinking-water and bladder and kidney cancers**

Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments	
<i>Ecological studies</i>							
<b>Taiwan</b>							
Chen <i>et al.</i> (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	<i>Bladder</i> Men Women <i>Kidney</i> 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 <i>et al.</i> (1988a)	Area endemic for Blackfoot disease	Mortality 1973–86	Village of residence; median arsenic levels of well-water samples	<i>Bladder</i> Men  Women  <i>Kidney</i> Men  Women		Age-standardized mortality rates per 100,000 3.1 15.7 37.8 89.1 1.4 16.7 35.1 91.5 1.1 5.4 13.1 21.6 0.9 3.6 12.5 33.3	Age-standardized mortality rates per 100 000; 899 811 person-years Reference: world population in 1976

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Wu <i>et al.</i> (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 <i>Group 1</i> (< 300 µg/L) Men (248 728) Women (248 728)  <i>Group 2</i> (300–590 µg/L) Men (138 562) Women (127 502)  <i>Group 3</i> (≥ 600 µg/L) Men (79 883) Women (74 083)	<i>Bladder</i>	Age-adjusted mortality rates per 100 000	Reference: world population in 1976
				Men	22.64 ( <i>p</i> < 0.001)	
				Women	25.60 ( <i>p</i> < 0.001)	
				<i>Kidney</i>		
				Men	8.42 ( <i>p</i> < 0.05)	
				Women	3.42 ( <i>p</i> < 0.001)	
				<i>Bladder</i>		
				Men	61.02 ( <i>p</i> < 0.001)	
				Women	57.02 ( <i>p</i> < 0.001)	
				<i>Kidney</i>		
				Men	18.90 ( <i>p</i> < 0.05)	
				Women	19.42 ( <i>p</i> < 0.001)	
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%.	<b>All 314 precincts and townships</b>		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)
				<i>Bladder</i>		
				Men	3.9 (0.5)	
				Women	4.2 (0.5)	
				<i>Kidney</i>		
				Men	1.1 (0.2)	
				Women	1.7 (0.2)	
				<b>170 south-western townships</b>		
				<i>Bladder</i>		
				Men	3.7 (0.7)	
				Women	4.5 (0.7)	
				<i>Kidney</i>		
Men	1.2 (0.2)					
Women	1.7 (0.3)					

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Chiang <i>et al.</i> (1993)		Incidence 1981–85	Exposure not evaluated Endemic area	<i>Bladder</i>		Incidence per 100 000	Adjusted for age			
				Total	140			23.5		
				Men	81			26.1		
				Women	59			21.1		
				Neighbouring endemic area				Total	13	4.5
				Men	7			4.7		
Women	6	4.3								
All Taiwan		Total	2135	2.3						
Men	1608	3.3								
Women	527	1.2								
Guo <i>et al.</i> (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	<i>Bladder</i>		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				
				Men	1185		0.57 (0.07)			
				Women	363		0.33 (0.04)			
				<i>Kidney</i>						
				Men	158		0.03 (0.02)			
				Women	81		0.142 (0.013)			
Tsai <i>et al.</i> (1999)	4 townships	Mortality 1971–94	Area endemic for Blackfoot disease	<b>Deaths</b>		Local reference (Chiayi-Tainan county) National reference (Taiwan) Local National Local National Local National				
				<i>Bladder</i>						
				Men	312		8.9 (7.96–9.96)			
				Women	295		10.5 (9.4–11.7) 14.1 (12.5–15.8) 17.7 (5.7–19.8)			
				<i>Kidney</i>						
				Men	94		6.7 (5.5–8.3) 6.8 (5.5–8.3)			
Women	128	8.9 (7.4–10.6) 10.5 (8.8–12.5)								

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Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments		
<b>South America</b>								
Hopenhayn-Rich <i>et al.</i> (1996, 1998)	26 counties in the Province of Córdoba, Argentina	Mortality 1986–91	Exposure levels	<b>Deaths</b>		SMR (95% CI)		
				<i>Bladder</i>				
				Low (690 421)	Men		113	0.8 (0.7–0.96)
					Women		39	1.2 (0.9–1.6)
				Medium (406 000)	Men		93	1.4 (1.1–1.7)
					Women		24	1.6(1.0–2.4)
				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)
				<i>Kidney</i>				
				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 <i>et al.</i> (1997)	Chile	Mortality 1950–92	Arsenic-contaminated Region II of northern Chile versus non-contaminated region VIII	Bladder Kidney	SMR (95% CI) 10.2 (8.6–12.2) 3.8 (3.1–4.7)	SMR for period 1976–92		
Smith <i>et al.</i> (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	<i>Bladder</i>		SMR (95% CI)	Population of about 400 000	
				Men	6.0 (4.8–7.4)			
				Women	8.2 (6.3–10.5)			
				<i>Kidney</i>				
Men	1.6 (1.1–2.1)							
Women	2.7 (1.9–3.8)							

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Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments	
Marshall <i>et al.</i> (2007)	Region II, northern Chile	Mortality 1950-2000	High exposure (>800 µg/L) in 1958-1970.	Bladder Men		RR (95% CI)	RR shown for comparison with Region V rates. Results shown for a sample of 3-yr periods between 1950 and 2000.	
				1983-'85	41			5.8 (3.7-9.1)
				1986-'88	47			6.1 (4.0-9.4)
				1989-'91	52			4.7 (3.2-6.9)
				1992-'94	62			5.0 (3.5-7.1)
				1995-'97	56			4.4 (3.1-6.4)
				Women				
				1983-'85	2			8.4 (4.3-16.4)
				1986-'88	3			7.3 (4.4-12.0)
				1989-'91	3			6.6 (4.0-10.9)
				1992-'94	2			13.8 (7.7-24.5)
1995-'97	3	7.6 (4.8-12.1)						
<b>Australia</b>								
Hinwood <i>et al.</i> (1999)	Victoria	Incidence 1982-91	Median arsenic concentration in drinking-water ranged 1-1077 µg/L	Bladder Kidney	303 134	SIR (95% CI) 0.9 (0.8-1.1) 1.2 (0.98-1.4)	State rates used as reference	
<i>Case-control studies</i>								
<b>Taiwan</b>								
Chen <i>et al.</i> (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		

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Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments									
<b>USA</b>															
Bates <i>et al.</i> (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	Cumulative dose (mg)	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								
				47	14	All subjects									
				36	21	1.0									
				39	17	1.6 (0.8–3.2)									
				38	19	0.95 (0.4–2.0)									
						1.4 (0.7–2.9)									
						1.0									
						0.7 (0.3–1.5)									
						0.5 (0.3–1.2)									
						1.0 (0.5–2.1)									
Bates <i>et al.</i> (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)													

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Reference	Location	End-point	Exposure	No. of cases		Study outcome	Comments
Karagas <i>et al.</i> (2004)			Level in toenails (mcg/g)	Controls	Cases		Levels in toenails reflect exposures occurring between 9 & 15 months prior to sample collection. With a constant water source, exposure estimates may extend many years prior.
			0.009-0.059	121	75	1.0	
			0.060-0.086	105	99	1.5 (1.0-2.3)	
			0.087-0.126	109	66	1.0 (0.7-1.6)	
			0.127-0.193	67	37	1.0 (0.6-1.7)	
			0.194-0.277	18	18	1.8 (0.9-3.7)	
			0.278-0.330	10	3	0.5 (0.1-1.9)	
		0.331-2.484	11	14	2.2 (0.9-5.1)		
Steinmaus <i>et al.</i> (2003)			Highest 1-yr daily avg intake	Controls	Cases		Results shown are for analysis with 20-yr lag. Paper also presents results for 5-yr and 40-yr lag. In addition, findings for ever- and never smokers are presented.
			<10 µg	230	127	1.0	
			10-80 µg	53	28	0.9 (0.5-1.6)	
			>80 µg	45	26	1.1 (0.6-1.9)	
			Highest 5-yr daily avg intake	239	130	1.0	
			<10 µg	48	25	0.96 (0.5-1.7)	
			10-80 µg	41	26	1.3 (0.7-2.3)	
			>80 µg	258	139	1.0	
			Highest 20-yr avg intake	34	23	1.2 (0.7-2.3)	
			<10 µg	36	19	1.1 (0.6-2.0)	
			10-80 µg				
			>80 µg	212	123	1.0	
			Cumulative exposure	46	17	0.6 (0.3-1.1)	
<6.4 mg	70	41	1.0 (0.6-1.7)				
6.4-82.8 mg							
>82.8 mg							
<b>S. America</b> Bates <i>et al.</i> (2004)			Exposure quartile 6-40 yrs prior to study (µg/L) (Excluding proxy-well measurements)				
			0-0.5	31	26	1.0	
			0.6-1.2	28	28	0.97 (0.4-2.3)	
			1.3-35	25	31	1.46 (0.7-3.3)	
			>35	29	27	0.97 (0.4-2.3)	

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Reference	Location	End-point	Exposure	No. of cases	Study outcome	Comments						
<b>Europe</b>												
Kurttio <i>et al.</i> (1999)	Areas in Finland in which < 10% of population belong to the municipal drinking-water system	Incidence 1981–95	Concentration of arsenic in water	<i>Short latency</i>	<b>Bladder</b> Relative risk (95% CI)	Case-cohort design Adjusted for age, sex and smoking Short latency: exposure in the 3rd to 9th calendar year prior to the cancer diagnosis Long latency: exposure in the 10th calendar year and earlier prior to the cancer diagnosis						
				< 0.1 µg/L			23	1.0				
				0.1–0.5 µg/L			19	1.5 (0.8–3.1)				
				≥ 0.5 µg/L			19	2.4 (1.1–5.4)				
				Total			61	1.4 (0.95–1.96)				
				<i>Long latency</i>								
				< 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			<i>Short latency</i>	<b>Kidney</b>	Relative risk (95% CI)	Levels in toenails reflect exposure between 9 & 15 months prior to sample collection. With a constant water source, exposure estimates may extend many years prior.		
							< 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)										
<i>Long latency</i>												
< 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)										
Michaud <i>et al.</i> (2002)			Level in toenails (µg/g)		Controls	Cases						
					147	136	1.0					
					72	73	1.10 (0.73-1.64)					
					44	37	0.93 (0.56-1.54)					
				16	20	1.38 (0.68-2.80)						
				14	14	1.14 (0.52-2.51)						

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<i>Cohort studies</i>						
<b>Taiwan</b>						
Chen <i>et al.</i> (1988b)	4 neighbouring townships in area endemic for Blackfoot disease	Mortality 1968–93	Comparison of mortality with general and endemic population	Cancer deaths Bladder 15 Kidney 3	SMR 38.8 [21.7–64.0] 19.5 [4.0–57.0]	95% CI calculated by the Working Group General population as reference
				Bladder 15 Kidney 3	SMR 2.6 [1.4–4.2] 1.6 [0.3–4.7]	Area endemic for Blackfoot disease as reference
Chiou <i>et al.</i> (1995)	4 neighbouring townships in area endemic for Blackfoot disease (BFD)		Cumulative index derived for each subject: $\Sigma (C_i \times D_i)$ . Cumulative exposure (mg/L $\times$ year) 0 0.1–19.9 $\geq 20$  0 0.1–19.9 $\geq 20$	BFD patients 263 Healthy controls 2293 Bladder cancer cases 29	<i>Bladder cancer</i> RR* (95% CI)  1.0 2.1 (0.6–7.2) 5.1 (1.5–17.3) RR** (95% CI) 1.0 1.6 (0.4–5.6) 3.6 (1.1–12.2)	*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

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

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<b>USA</b>							
Lewis <i>et al.</i> (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)	
			Low exposure (< 1000 ppb-years)	Men Women	0.36 1.18	<i>Bladder/other urinary cancers</i>	
			Medium exposure (1000–4999 ppb-years)	Men Women	– –		
			High exposure (≥ 5000 ppb-years)	Men Women	0.95 1.10		
			Total	Men Women	0.4 (0.1–1.2) 0.8 (0.1–2.9)		
			Low exposure (< 1000 ppb-years)	Men Women	2.51 2.36		<i>Kidney cancer</i>
			Medium exposure (1000–4999 ppb-years)	Men Women	1.13 1.32		
			High exposure (≥ 5000 ppb-years)	Men Women	1.43 1.13		
			Total	Men Women	1.8 (0.8–3.3) 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