2. Studies of Cancer in Humans

2.1 Studies among specific occupational groups

A summary of the epidemiological findings reviewed in this section is presented in Tables 79 (cohort studies) and 80 (population-based case–control studies).

2.1.1 *Battery manufacturing workers*

Fanning (1988) obtained the cause-specific distribution of 867 deaths (in-service deaths and pensioner deaths) occurring in male workers in the United Kingdom who were considered to have been exposed to high or moderate levels of lead whilst engaged in lead battery manufacturing. This distribution was compared with that of 1206 male decedants

who had been employed either by other companies that participated in the same pension scheme, or in the lead battery factory but with little potential for exposure to lead. The deaths occurred during the period 1926–85 and the study incorporated data reported previously by Dingwall-Fordyce and Lane (1963) and Malcolm and Barnett (1982). After adjusting for age by 10-year-age groups, there were no significantly elevated proportional mortality odds ratios for cancer risk in relation to lead-exposed employment. A slightly elevated risk was suggested for cancer of the stomach.

There has been an extended study of lead battery and lead smelter workers in the USA (Cooper & Gaffey 1975; Cooper, 1976; Kang *et al*., 1980; Cooper, 1981; Cooper *et al*., 1985; Cooper, 1988; Wong & Harris, 2000). The original cohort (Cooper & Gaffey, 1975) included 4680 battery workers from 10 plants; the most recent update (Wong & Harris, 2000) relates to a reduced cohort of 4518 battery workers. All subjects manufacturing lead batteries were employed for at least 1 year during the period 1947–70, and the most recent follow-up has been analysed for the period 1947–95. There were 195 battery workers (4.3%) who were untraced on the closing date of the study. Exposure data were limited but blood lead and urinary lead measurements were taken, mainly after 1960. For lead battery workers with three or more blood lead measurements, the mean blood concentration was 63 μg/dL and, for those with 10 or more urinary lead measurements, the mean urine concentration was 130 μg/dL. Standardized mortality ratios (SMRs) were calculated after comparison with the mortality rates for the male population in the USA, and were adjusted for age and calendar period. For all cancers, the overall SMR was 104.7 (624 observed; 95% CI, 96.6–113.2). There was a significantly elevated SMR for stomach cancer (152.8; 45 observed; 95% CI, 111.5–204.5) and non-significantly elevated SMR for lung cancer (113.9; 210 observed; 95% CI, 99.0–130.4). [The Working Group noted that it is possible that ethnicity, dietary habits, prevalence of *Helicobacter pylori* infection, or socioeconomic status played a role in the excess of stomach cancer.] Findings were also reported for a nested case–control study of stomach cancer, using 30 cases and 120 age-matched controls from a single large battery factory. [The authors noted a large percentage of Italian- and Irish-born members of the study population (23% of the controls in the case–control study). Being Italian- or Irish-born was associated with a twofold excess risk for stomach cancer in this population. The Working Group considered that confounding by place of birth (which is not available for the whole cohort) would probably account for only a proportion of the 1.5-fold excess reported for this whole population.] The nested case–control study did not show any significantly increased odds ratios or trends for any of the three exposure indices that were investigated (duration of employment at the plant, duration of employment in intermediate or high exposure areas of the plant, [crudely] weighted cumulative exposure). [The Working Group noted that the analysis by duration of employment needs to be interpreted with caution, especially among workforces that were subject to active surveillance and potential removal from work.]

Table 79. Cohort studies on cancer risk among occupational groups exposed to lead or lead compounds

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Battery factory workers								
Fanning (1988) United Kingdom	Proportional mortality study; 2073 men; frequency-matched by 10-year age group; 1926–85	Low (1206 men) and high (867 men) exposure groups; defined by job–exposure matrix				**PMOR**		Limited to deaths in service and in pensioners
			All sites		195	0.95		
			Stomach		31	1.34		
			Lung		76	0.93		
Wong & Harris (2000) USA	4518 men employed for > 1 year during 1947–70; follow-up 1947–95; vital status, 95.7%; cause of death, 99.5% (death certificates)	No exposure data; bio-monitoring 1947–72: urinary lead (2275 men), blood lead (1863 men); mean blood lead, 63 µg/dL (n = 1083); mean urinary lead, 130 µg/dL (n = 1550)				**SMR**		Expected deaths based on male mortality rates in the USA
			All sites		624	104.7	96.6–113.2	
			Lung		210	113.9	99.0–130.4	
			Stomach		45	152.8	111.5–204.5	
			Large intestine		59	103.9	79.1–134.0	
			Rectum		14	84.7	46.3–142.1	
			Central nervous system		10	75.0	35.9–137–9	
			Kidney		7	50.2	20.2–103.4	
Lead smelter workers								
Wong & Harris (2000) USA	2300 men employed in 6 smelters for > 1 year during 1947–70; follow-up, 1947–95; vital status, 93%; cause of death, 99.5% (death certificates)	No exposure data; bio-monitoring 1947–72: urinary lead (2275 men), blood lead (1863 men); mean blood lead, 80 µg/dL (n = 254); mean urinary lead, 173 µg/dL (n = 1550)				**SMR**		Expected deaths based on male mortality rates in the USA
			All sites		273	101.8	90.1–114.6	
			Lung		107	121.5	99.5–146.8	
			Stomach		15	133.4	74.6–220.0	
			Large intestine		22	89.0	55.8–134.7	
			Rectum		8	123.0	53.1–242.4	
			Central nervous system		5	74.5	24.2–173.9	
			Kidney		6	92.3	33.9–201.0	
McMichael & Johnson (1982) Australia	241 male smelter workers employed 1–30 years, diagnosed with lead poisoning 1928–59, followed through 1977; 140 deaths identified through death registration records	Lead poisoning; mean urinary lead, 173 µg/L	All sites	Lead-poisoned workers versus other workers	9	**SPMR** 0.59		Reference group: 695 deceased smelter workers without lead poisoning

Table 79 (contd)

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Steenland *et al.* (1992) USA	1990 male smelter workers employed > 1 year, at least 1 day at the smelter 1940–65; subcohort with heavier exposure (n = 1436); vital status ≤ 31 December 1979 (95.5%); cause of death, 96.3%	Mean blood lead, 56 µg/dL (n = 173); mean air lead, 3.1 mg/m^3 (n = 203); mean air arsenic, 14 µg/m^3 (n = 89)				**SMR**		Further follow–up of the cohort from Selevan *et al.* (1985)
			All sites	Total cohort	192	98	84–112	National standard population
			Stomach		15	136	75–224	No information on smoking
			Lung		72	118	92–148	
			Colorectal		9	48	22–90	
			Kidney		9	193	88–367	
			All sites	Subcohort with high lead exposure	137	98	81–115	
			Stomach		10	128	61–234	
			Lung		49	111	82–147	
			Colorectal		8	59	25–116	
			Kidney		8	239	103–471	
Gerhardsson *et al.* (1986) Sweden	Retrospective cohort study; 3832 men followed up 1950–81; subcohort of 437 workers employed ≥ 3 years in high-exposure jobs, 1950–74; based on median value of the cumulative blood lead concentration, subcohort further divided into high (n = 218) and low (n = 219) mean blood lead (high > 478.5 µg × yr/dL > low) and high (n = 288) and low (n = 149) peak blood lead (high > 70 µg × yr/dL > low)					**SMR**		National and regional standards specified for cause, sex, age and calendar period
			All sites	Cohort	270	[114]	[100–128]	Potential exposure to arsenic, chromium and nickel; cohort update in Lundström *et al.* (1997)
				Subcohort	23	[87]	[55–131]	
				High mean blood lead	15	[100]	[56–165]	
				High peak blood lead	16	[89]	[51–145]	
			Lung	Cohort	90	[218]	[176–269]	
				Subcohort	8	[160]	[69–315]	
				High mean blood lead	5	[172]	[56–402]	
				High peak blood lead	4	[118]	[32–301]	
			Stomach	Cohort	46	[143]	[105–191]	
				Subcohort	3	[94]	[19–274]	
				High mean blood lead	2	[111]	[13–401]	
				High peak blood lead	3	[136]	[28–399]	

Table 79 (contd)

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Lundström *et al*. (1997) Sweden	3979 workers employed > 1 year 1928–79; sub-cohort of 1992 workers from the lead department and other lead-exposed departments; mortality, 1955–87; vital status, 88.5%; incidence, 1958–87	Blood lead level 1950–69 (AES) and 1967–87 (AAS); mean blood lead in 1950, 62 µg/dL; mean blood lead in 1987, 33 µg/dL		Total cohort	(*n* = 3979)	**SMR**		Follow-up of the cohort reported in Gerhardsson *et al.* (1986) Regional standard specified for cause, sex, age and calendar period Multifactorial exposure pattern and lack of smoking data
			All sites		126	120	100–150	
			Lung		39	280	200–380	
				Highest	(*n* = 1026)			
			All sites	exposed	55	120	90–150	
			Lung	subgroup	19	280	180–450	
		≥ 15 year latency period		Total cohort	(*n* = 2353)	**SIR**		
			All sites		172	110	90–120	
			Lung		42	290	210–400	
			Central nervous system		6	110	40–230	
			Gastrointestinal		31	80	50–110	
			Kidney		7	90	40–190	
				Highest	(*n* = 650)			
			All sites	exposed	83	110	90–140	
			Lung	subgroup	23	340	220–520	
			Central nervous system		4	160	40–420	
			Gastrointestinal		15	80	50–130	
			Kidney		3	90	20–250	
		Lead-only workers or lead department and other lead-exposed departments; ≥ 15 year latency period		Total cohort	(*n* = 1005)	**SIR**		
			All sites		44	90	60–120	
			Lung		14	310	170–520	
			Central nervous system		2	110	10–380	
			Gastrointestinal		6	50	20–110	
			Kidney		0	0	0–150	

Table 79 (contd)

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Lundström et *al*. (1997) (contd)				Highest exposed subgroup	(*n* = 163)			
			All sites		19	120	80–200	
			Lung		7	510	200–1050	
			Central nervous system		1	190	10–1050	
			Gastrointestinal		2	50	10–190	
			Kidney		0	0	0–500	
Englyst *et al*. (2001) Sweden	3979 workers in primary copper and lead smelter; follow-up 1958–87; subcohort (1): 710 workers employed in lead department and other departments during work history; subcohort (2): 383 workers from subcohort (1) only employed in lead department	Estimate based on cumulative blood lead index		Subcohort (1)		**SIR**		Workers also exposed to arsenic. County population reference. Same cohort as Lundström *et al*. (1997)
			All sites		47	100	70–130	
			Lung		10	240	120–450	
			Kidney		2	90	10–320	
			Central nervous system		1	60	2–360	
				Subcohort (2)				
			All sites		18	120	70–190	
			Lung		5	360	120–830	
			Kidney		1	130	3–720	
			Central nervous system		0	0	0–650	
Gerhardsson *et al*. (1995) Sweden	664 male secondary lead smelter workers employed > 3 months 1942–87; incidence 1969–89	Blood lead sampling starting 1969				**SIR**		Regional standard population: county rates specified for cause, sex, age and calendar year
			All sites		40	127	91–174	
			Stomach		3	188	39–550	
			Kidney		1	80	2–448	
			Central nervous system		1	75	2–420	
			Respiratory tract		6	132	49–288	
Cocco *et al*. (1996) Italy	1345 male lead and zinc smelting plant workers followed 1973–91; subcohort of 1222 with known G6PD[a] phenotype	Mean blood lead 1988–92 and mean environmental lead in 1991		Total cohort		**SMR**		Regional reference (Sardinia) Possible healthy worker effect; smoking not addressed
			Lung		2	[57]	[7–206]	
			Stomach		2	[333]	[40–1204]	
						Standardized mortality rates × 10^{-4}		
			All sites	Wild-type G6PD	10	25.7	21.4–30.6	
				G6PD-deficient	2	17.9	4.3–30.1	

Table 79 (contd)

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Cocco *et al.* (1997) Italy	1388 male lead smelter workers, employed > 1 year 1932–71; mortality follow-up 1950–92; vital status 97.3%; cause of death 96%	Lead concentration in respirable dust; air arsenic below level of detection (23/24 samples); geometric mean air lead, 48 µg/m^3				**SMR**		National reference (1950–92)
			All sites		149	69	58–81	
			Lung		35	62	43–86	
			Stomach		17	49	29–79	
			Brain		4	125	34–319	
			Kidney		5	142	46–333	
			All sites		132	93	78–110	Regional reference (1965–92)
			Lung		31	82	56–116	
			Stomach		14	97	53–162	
			Brain		4	217	57–557	Exposure to other agents, e.g. cadmium; no smoking data
			Kidney		4	175	48–449	
Ades & Kazantzis (1988) United Kingdom	4173 zinc–lead–cadmium smelter workers; employed > 1 year; all staff employed 1 January 1943 + all staff subsequently employed < 1970; born < 1940; 0.7% lost to follow-up; 3.2% emigrated; ≥ 10 years follow-up	Mean blood lead in cadmium plant, 28 µg/dL (3% of cohort); 59 µg/dL in furnace (10% of cohort); 56 µg/dL in sinter (8% of cohort) Years employed	Lung			**SMR**		Regional standard population. Exposure to lead highly correlated with exposure to arsenic.
				Overall	182	125	107–144	
				Duration of employment (years):				
				1–4	43	86	62–116	
				5–9	23	107	68–161	
				10–19	36	122	86–170	
				20–29	44	190	138–256	
				30–39	28	142	94–205	
				≥ 40	8	292	126–575	
	Nested case–control study with 174 lung cancer cases and 2717 controls frequency-matched on age, employment start date, surviving the case. Subjects followed up < 10 years excluded to allow for latency	Job–exposure matrix; ordered exposure categories	Lung			**RR**		Estimated RR associated with 10 years employment at each exposure level; no. of cases working at least 1 year
				Background	57	1.25		
				Low	73	1.28		
				Medium	72	1.36		
				High	27	1.54		

Table 79 (contd)

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Lead chromate pigment production								
Sheffet *et al.* (1982) USA	1946 men (1296 Caucasian and 650 non-Caucasian) employed ≥ 1 month in a pigment plant 1940–69; followed until 1979	Exposure to chemical dust air samples (airborne chromium)		Caucasian				National standard population. Adjusted to include cases with unknown cause of death
			All sites		50	1.03		
			Lung		21	1.6		
			Stomach		5	2.0		
			Large intestine		2	0.5		
				Non-Caucasian				
			All sites		25	1.01		
			Lung		10	1.6		
			Stomach		3	1.6		
			Large intestine		0	0.0		
Davies *et al.* (1984a) United Kingdom	1152 male pigment workers first employed 1933, 1949, 1947 and followed until 1981; factories A and B exposure to zinc and lead chromate; factory C exposure to lead chromate only	Jobs categorized into exposure grades: high, medium and low	Lung	Date of first employment		**SMR**		High and medium exposure combined. Reference: specially compiled quinquennial national rates.
				Factory A				
				1932–45	13	222	120–380	Adjusted for duration of service
				1946–54	8	223	100–440	
				1955–mid-1963	2	100	10–360	
				mid-1963–67	0	–		
				Factory B				
				1948–60	6	373	140–810	
				1961–67	5	562	180–1310	
				Factory C				
				1946–60	1	48	0–270	
Davies *et al.* (1984b) United Kingdom	57 male pigment workers with non-fatal clinical lead poisoning; followed from date of poisoning or earliest available record, through 31 December 1981	Not estimated	Lung			**SMR**		Same factories as in Davies *et al.* (1984a) National reference
					4	145	[39–370]	

Table 79 (contd)

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Glass workers								
Cordioli *et al.* (1987) Italy	468 workers in the glass industry employed ≥ 1 year 1953–1967 and followed until 1985; vital status 98.3%	Not estimated				**SMR**		National standard population
			All sites		28	127	[84–184]	
			Lung		13	209	[111–357]	
			Larynx		4	449	[122–1150]	
			Stomach		2	61	[7–220]	
Sankila *et al.* (1990) Finland	Cohort of 3749 (1803 men and 1946 women) employed ≥ 3 months in 2 glass factories, followed 1953–86; subcohort of 235 glass blowers (201 men and 34 women)	Not estimated		Total cohort		**SIR**		National standard population
			Stomach		34	93	64–129	
			Kidney		3	35	7–102	
			Central nervous system		6	60	22–131	
			Lung		69	128	99–162	
			Colon		7	46	19–96	
			Rectum		14	113	62–189	
			Lung		5	85	28–198	
			Stomach	Subcohort of glass blowers	6	231	85–502	
			Skin		3	625	129–1827	
Wingren & Englander (1990) Sweden	625 male art glassworkers employed ≥ 1 month 1964–85	Air measurements of lead				**SMR**		County reference. Smoking status lower than in the general population
			All sites		26	138	[90–202]	
			Lung		6	240	[88–522]	
			Colon		4	250	[68–640]	
Miners								
Cocco *et al.* (1994a) Italy	4740 men employed ≥ 1 year 1932–71 in 2 lead/zinc mines; mortality 1960–88; vital status 99.5%; cause of death 99.4%	Not estimated				**SMR**		Regional reference Exposure to silica and radon Includes 1741 subjects of the study reported by Carta *et al.* (1994).
			All sites		293	94	83–105	
			Lung		86	95	76–117	
			Stomach		27	94	62–137	
			Bladder		17	115	67–184	
			Intestine and rectum		12	64	33–112	
			Peritoneum; retro-peritoneum		6	367	135–798	
			Kidney		7	128	52–264	
			Nervous system		8	117	50–230	

Table 79 (contd)

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Cocco *et al.* (1994b) Italy	483 women employed ≥ 1 year 1932–71 in the same 2 lead/zinc mines as in Cocco *et al.* (1994a); mortality 1951–88; vital status 96.0%	Not estimated	All sites		32	70	48–99	National reference; availability of death records not mentioned
			Lung		6	232	85–505	
			Stomach		2	32	4–115	
Newspaper printers								
Bertazzi & Zocchetti (1980) Italy	700 men employed ≥ 5 years before 1955 in production department of newspaper plant; mortality 1956–75; vital status 96.7%	Not estimated				**SMR**		National reference
			All sites		51	123	[92–162]	Increase in lung cancer risk confined mainly to packers and forwarders possibly exposed to vehicle exhausts
			Lung		13	148	[79–253]	
			Duration of employment (years):					
			≤ 9		2	167	[20–602]	
			10–19		5	106	[34–247]	
			≥ 20		6	207	[76–450]	
			Digestive organs and peritoneum		19	120	[72–188]	
Michaels *et al.* (1991) USA	1261 men members of typographical union, employed 1 January 1961, followed-up 1961–84, vital status 96.9%	Not estimated				**SMR**		Regional standard (New York City rates)
			All sites		123	84	69–100	Lead phased out during 1974–78; before: low-level exposures documented from other printing industry plants (ranging from < 2% to 40% of the occupational standard)
			Lung		37	89	62–122	
			Stomach		5	55	18–128	
			Bladder		8	151	65–297	
			Leukaemia and aleukaemia		5	104	34–244	

Table 79 (contd)

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Organic lead								
Sweeney *et al.* (1986) USA	Retrospective study; 2510 men (2248 Caucasian and 262 non-Caucasian) employed at chemical plant (tetraethyl lead manufacture) > 1 day 1952–77; vital status 99.3%, cause of death 98.7%	Not estimated						National reference.
		Employment 1952–77, all workers combined	Lung		14	112	68–1.75	One brain tumour appeared to be a metastasis according to pathology reports.
			Larynx		2	364	65–1145	
			Brain and central nervous system		4	213	73–487	
			Lymphatic		4	85	36–343	
		Employment 1952–60, Caucasian only	Lung		13	122	73–194	
			Brain		3	186	51–482	
		Employment prior to 1960 and 15 year latency; duration of employment	Respiratory		14	154	[84–258]	
				< 10 years	6	199	[73–432]	
				> 10 years	8	132	[57–260]	
Fayerweather *et al.* (1997) USA	Case–control study in a tetraethyl lead manufacturing site; 735 male cases and 1423 controls matched on age, sex, payroll class; 1956–87; company mortality registries and employment rosters	Employment in tetraethyl lead areas (ever versus never)		Exposed		**OR**		90% CI
			Digestive	Ever	45	1.3	0.9–1.9	Incidence among active workers only
				Cumulative exposure:				Quartiles of cumulative exposure (low, medium, high, very high) defined as no. of years × rank weight of exposure, ranking variables originating from a variety of sources
				High	10	1.3	0.7–2.7	
				Very high	16	2.2	1.2–4.0	
			Rectum	Ever	9	3.7	1.3–10.2	
				Cumulative exposure:				
				High to very high	7	5.1	1.6–16.5	
			Colon	Ever	16	1.3	0.7–2.5	
				Cumulative exposure:				
				High to very high	8	1.7	0.8–4.0	

Table 79 (contd)

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Biomonitoring								
Anttila *et al.* (1995) Finland	20 741 workers (18 329 men, 2412 women) with monitored blood lead; 1973–83; 2318 industrial plants or workplaces	Highest blood lead (μmol/L)		Blood lead (μmol/L)		**SIR**		Men only [test for trend borderline significant]
			Lung, trachea	< 1.0	25	70	50–110	
				1.0–1.9	35	140	100–190	
				2.0–7.8	11	110	60–200	
			Stomach	< 1.0	11	100	50–190	Men only
				1.0–1.9	11	140	70–250	OR for estimated mean lifetime blood lead ≥ 0.8 μmol/L: 1.1 (95% CI, 0.4–3.2), based on 14 cases
				2.0–7.8	1	30	0–180	
			Kidney	< 1.0	4	60	20–150	Men only
				1.0–1.9	5	100	30–240	OR for estimated mean lifetime blood lead ≥ 0.8 μmol/L: 0.5 (95% CI, 0.2–1.7), based on 7 cases
				2.0–7.8	0	0	0–200	
			Nervous system	< 1.0	8	130	60–260	Men only
				1.0–1.9	6	130	50–270	
				2.0–7.8	3	160	30–460	
		Highest blood lead (μmol/L)				**RR**		Internal comparison; Poisson regression
			Lung, trachea	< 1.0	26	1.0	ref	
				1.0–1.9	36	2.0	1.2–3.2	
				2.0–7.8	11	1.5	0.8–3.1	
	Nested case–control study 1973–90; 53 cases and 156 controls matched on sex, year of birth and vital status	Cumulative exposure (μmol × yr/L)	Lung			**OR**		Test of trend NS
				0	16	1.0	ref	Includes pleural cancer
				1–6	6	0.9	0.2–3.6	Adjusted for smoking
				7–17	15	1.2	0.4–3.1	
				18–70	16	1.4	0.6–3.7	

Table 79 (contd)

Reference, location	Cohort description	Assessment or indices of exposure to lead	Cancer site	Exposure categories	No of cases or deaths	Relative risks	95% CI	Comments
Anttila *et al.* (1996) Finland	Same cohort as Anttila *et al.* (1995)	Blood lead (µmol/L)	Nervous system			**SIR**		Entire cohort analysis
				≤ 0.9	12	[90]	[47–158]	
				1.0–1.9	10	[130]	[62–239]	
				2.0–7.8	4	[138]	[38–353]	
	Nested case–control study 1973–90 with 26 cases and 200 controls matched on sex, year of birth and vital status	Highest blood lead (µmol/L)	Nervous system			**OR**		Internal comparison, 200 controls
				0.1–0.7	7	1.0	ref	
				0.8–1.3	9	1.4	0.5–4.1	
				1.4–4.3	10	2.2	0.7–6.6	
				p for trend		0.17		
			Glioma			**OR**		Internal comparison, 125 controls. Adjusted for year of first personal measurement
				0.1–0.7	1	1.0	ref	
				0.8–1.3	8	6.7	0.7–347	
				1.4–4.3	7	11.0	1.0–626	
				p for trend		0.037		
		Cumulative exposure (year × µmol/L)	Glioma			**OR**		49 controls Adjusted for year of first personal measurement
				0	1	1.0	ref	
				1–6	2	2.0	0.1–116	
				7–14	2	6.2	0.1–816	
				15–49	5	12.0	0.9–820	
				p for trend		0.02		
		Lifetime mean lead (µmol/L)	Glioma	0.1–0.7	1	1.0	ref	49 controls Adjusted for gasoline and cadmium exposure
				0.8–1.3	5	3.5	0.4–171	
				1.4–3.4	4	23.0	0.8–2441	
				p for trend		0.041		
		Duration of occupational exposure to lead (years)	Glioma	0	1	1.0	ref	49 controls Adjusted for gasoline and cadmium exposure
				1–9	1	0.9	0–122	
				10–19	3	3.7	0.2–244	
				20–42	5	6.9	0.6–400	
				p for trend		0.029		

AAS, atomic absorption spectroscopy; AES, atomic emission spectroscopy; RR, relative risk; PMOR, proportional mortality odds ratio; SMR, standardized mortality ratio; SPMR, standardized proportional mortality ratio; SIR, standardized incidence ratio; OR, odds ratio; NS, not significant; [....] calculated by the Working Group

[a] G6PD, glucose-6-phosphate dehydrogenase

Table 80. Population-based case–control studies on cancer risk in relation to exposure to lead or lead compounds

Reference, location and years of study	Characteristics of cases and controls	Assessment or indices of exposure to lead	Cancer site	No. of cases	Odds ratio	95% CI	Comments
Multiple cancer sites							
Siemiatycki (1991) Canada 1979–85	Men aged 35–70 years, resident in the Montreal metropolitan area; hospital records and population files (multi-site cancer and population controls available); response rates: cancer cases 82%, population controls 72% [others not available]; incident cases histologically confirmed	Expert assessment					90% CI; cancer controls for all exposures and sites, except lead fumes and lung cancer (population controls)
		Lead compounds:					
		Any[a]	Lung	326	1.1	0.9–1.4	
		Substantial[b]		42	1.5	1.0–2.2	
		Any	Lung, squamous-cell	146	1.3	1.0–1.6	
		Substantial		18	1.5	0.8–2.6	No data on central nervous system/brain cancer
		Any	Stomach	126	1.2	1.0–1.6	
		Substantial		17	1.8	1.1–2.8	
		Any	Bladder	155	1.3	1.0–1.6	
		Substantial		17	1.1	0.7–1.8	
		Any	Kidney	88	1.2	1.0–1.6	
		Substantial		6	0.8	0.4–1.7	
		Lead dust:					
		Any	Stomach	5	4.7	1.9–11.7	
		Substantial		3	21.6	3.2–99.9	
		Lead oxides:					
		Any	Lung	22	1.9	1.1–3.4	
		Substantial		8	2.2	0.8–5.7	
		Lead carbonate: any	Lung, adenocarcinoma	7	1.9	0.9–4.0	
		Lead chromate: any	Lung	26	1.6	1.0–2.7	
			Bladder	17	1.8	1.1–3.1	
			Kidney	6	2.1	1.0–4.5	
		Lead fumes: any	Lung, oat-cell	12	1.8	1.0–3.2	
			Lung, squamous-cell	16	1.8	0.9–3.6	
			Stomach	10	1.7	0.9–3.0	
			Pancreas	7	1.9	1.0–3.8	
			Non-Hodgkin lymphoma	13	1.8	1.1–3.0	

Table 80 (contd)

Reference, location and years of study	Characteristics of cases and controls	Assessment or indices of exposure to lead	Cancer site	No. of cases	Odds ratio	95% CI	Comments
Stomach							
Cocco *et al.* (1999b) USA 1984–96	Population-based study; 24 states; 41 957 deaths (20 878 Caucasian men, 14 125 Caucasian women, 4215 African-American men, 2739 African-American women) aged ≥ 25 years at the time of death; 2 controls per case, having died from non-malignant diseases	Occupation and industry titles on death certificates plus job–exposure matrix	Stomach				Matching by geographic region, race, sex and age (5-year)
		High probability of lead exposure:					
		Caucasian men		1503	0.92	0.86–0.99	
		African-American men		453	1.15	1.01–1.32	
		White women		65	1.53	1.10–2.12	
		African-American women		10	1.76	0.74–4.16	
		High intensity of lead exposure:					
		Caucasian men		290	1.10	0.95–1.27	
		African-American men		52	0.81	0.59–1.13	
		Caucasian women		37	1.02	0.68–1.51	
		African-American women		3	1.25	0.30–5.23	
Cocco *et al.* (1998b) USA 1984–92	Same design as in Cocco *et al.* (1999b); 1056 cases (1023 Caucasian men and 33 African-American men) and 5280 controls	Occupation and industry titles on death certificates + job–exposure matrix	Stomach				Gastric cardia cancer. [Intercorrelation with other exposures not described]
		High probability of exposure with intensity:					
		Unexposed		841	1.0		
		Low		77	1.3	1.0–1.8	
		Medium		10	1.1	0.5–2.2	
		High		1	–	–	
Kidney							
Partanen *et al.* (1997) Finland 1977–78	Population-based study; 408 incident cases (male and female) aged ≥ 20 years and 819 controls matched on year of birth, sex, survival status; response rate 69% (cases), 68% (controls)	Summary indicators 1920–68; industrial hygienist	Kidney	4	2.77	0.49–15.6	Lead + inorganic lead compounds; adjusted for smoking, coffee consumption and obesity

Table 80 (contd)

Reference, location and years of study	Characteristics of cases and controls	Assessment or indices of exposure to lead	Cancer site	No. of cases	Odds ratio	95% CI	Comments
Pesch *et al.* (2000) Germany 1991–95	Population-based study; 935 cases (570 men, 365 women); 95% histologically confirmed; 4298 controls (2650 men, 1648 women) matched by region, sex and age; response rates 84–95% (cases), 63–75% (controls)	Two job–exposure matrices (lead and lead compounds) used for jobs held > 1 year	Renal-cell carcinoma				Adjusted for age, study centre and smoking
		Job–exposure matrix 1[c]:					
		Men					
		Substantial		29	1.5	1.0–2.3	
		High		71	1.2	0.9–1.6	
		Medium		84	1.2	1.0–1.6	
		Women					
		Substantial		11	2.6	1.2–5.5	
		High		14	1.0	0.6–1.9	
		Medium		8	0.7	0.4–1.6	
		Job–exposure matrix 2[d]:					
		Men					
		Substantial		30	1.3	0.9–2.0	
		High		81	1.2	0.9–1.6	
		Medium		69	0.9	0.7–1.2	
Brain and nervous system							
Cocco *et al.* (1998a) USA 1984–92	Population-based study; 24 states; 27 060 deaths (Caucasian and African-American men and women) and 108 240 controls who died from non-malignant diseases (aged ≥ 35 years)	Occupation and industry titles on death certificates plus job–exposure matrix: *High intensity and high probability of lead exposure*:	Brain				The group with high intensity (estimated mean blood lead > 1.4 µmol/L) and high probability of exposure comprised typesetters and compositors.
		Caucasian men		14	2.1	1.1–4.0	Adjusted for age, marital status, residence (urban versus rural) and socioeconomic status
		Caucasian women		4	1.4	0.4–4.2	
Cocco *et al.* (1999a) USA 1984–92	Same design as in Cocco *et al* (1998a), 12 980 women	Occupation and industry titles on death certificates plus job–exposure matrix	CNS	366	1.1	1.0–1.2	Reference: no exposure
			Meningioma	9	1.9	1.0–3.9	

Table 80 (contd)

Reference, location and years of study	Characteristics of cases and controls	Assessment or indices of exposure to lead	Cancer site	No. of cases	Odds ratio	95% CI	Comments
Hu, J. *et al.* (1998), Heilongjiang Province, China 1989–95	Hospital-based study; 218 cases histologically confirmed (139 astrocytoma and 79 other brain glioma, male and female) 436 controls with non-neoplastic non-neurological diseases, matched on sex, age, residence (rural/urban); 100% response rates for cases and controls	Self-reported exposure to lead	Glioma	0		[4 controls]	
Hu, J. *et al.* (1999), Heilongjiang Province, China 1989–96	Same design as in Hu, J. *et al.* (1998) 183 cases, 366 controls	Self-reported exposure to lead Men Women	Meningioma	 6 10	 7.20 5.69	 1.00–51.72 1.39–23.39	Adjusted for income, education, fruit and vegetable consumption (men), further adjusted for smoking (women)
Other primary sites							
Risch *et al.* (1988) Canada 1979–82	Population-based study; 835 cases histologically confirmed (male and female) and 792 controls, response rates 67% and 53%, respectively; cases and controls matched by year of birth, sex and area of residence	Partially self-reported exposure to lead compounds, men Ever exposed OR for trend per 10 years of duration Exposed ≥ 6 months 8–28 years before diagnosis	Bladder	 61	 2.00 1.76 1.45	 1.16–3.54 0.91–3.51 1.09–2.02	Adjusted for lifetime cigarette consumption; exposure during full-time job ≥ 6 months

Table 80 (contd)

Reference, location and years of study	Characteristics of cases and controls	Assessment or indices of exposure to lead	Cancer site	No. of cases	Odds ratio	95% CI	Comments
Kauppinen *et al.* (1992) Finland 1976–78 1981	Population-based study; 344 cases histologically confirmed (male and female), 476 stomach cancer controls and 385 coronary infarction controls, matched to cases by age and sex; 71% response rates for both cases and controls	*Job–exposure matrix*: Low exposure to lead and its compounds	Liver	52	0.91	0.65–1.29	Men and women combined
		Expert assessment: Any exposure to lead and its compounds		6	1.14	0.44–2.98	Adjusted for alcohol consumption; no cases with heavy exposure; moderate exposure, OR 2.28 (95% CI, 0.68–7.67; 5 cases)

CNS, central nervous system; OR, odds ratio
[a] Any, any exposure
[b] Substantial exposure
[c] Job–exposure matrix 1: British
[d] Job–exposure matrix 2: German

2.1.2 *Lead smelter workers*

The extended study of lead battery and lead smelter workers in the USA (Cooper & Gaffey, 1975; Cooper, 1976; Kang *et al*., 1980; Cooper, 1981; Cooper *et al*., 1985; Cooper, 1988; Wong & Harris, 2000) originally included 2352 lead smelter workers from six plants (Cooper & Gaffey, 1975); the most recent update (Wong & Harris, 2000) relates to a reduced cohort of 2300 smelter workers. All lead smelter workers were employed for at least 1 year during the period 1947–70, and the most recent follow-up has been analysed for the period 1947–95. There were 161 lead smelter workers (7.0%) who were untraced on the closing date of the study. Lead exposure data were limited, but blood lead and urinary lead measurements were taken, mainly after 1960. For smelter workers with three or more blood lead measurements, the mean blood concentration was 80 µg/dL and, for those with 10 or more urinary lead measurements, the mean urine concentration was 173 µg/dL. Other exposures may have included cadmium, arsenic and sulfur dioxide. SMRs were calculated after comparison with the mortality rates for the male population in the USA, and were adjusted for age and calendar period. For all cancers, the overall SMR was 101.8 (273 observed; 95% CI, 90.1–114.6). There were non-significantly elevated SMRs for stomach cancer (133.4; 15 observed; 95% CI, 74.6–220.0) and lung cancer (121.5; 107 observed; 95% CI, 99.5–146.8). SMRs were also shown for the lead battery workers and smelter workers combined in relation to three categories of duration of employment (< 10 years, 10–19 years, ≥ 20 years). Positive trends were not found for cancer of the stomach or cancer of the lung. Corresponding findings were not shown separately for smelter and battery workers.

Rencher *et al*. (1977) studied the mortality at a large copper smelter in western USA during the period 1959–69. Death certificates were used to determine the causes of death. The death pattern was compared with regional (state) death rates. [The Working Group did not report the results because the methods of analysis rendered the study uninterpretable and person–time was not defined.]

In a study at a lead smelter in Australia (McMichael & Johnson, 1982), 241 male workers diagnosed with lead poisoning during the period 1928–59 were identified. The list was cross-checked against death registration records in South Australia for the period 1930–77, thereby identifying 140 deaths. Age-standardized proportional mortality rates (SPMR) were calculated after comparison with the mortality pattern in 695 other workers in non-office production jobs at the same smelter, and with the male population in Australia. The SPMR for all cancer mortality was 0.59, based on nine cancer deaths. [The Working Group noted that the low SPMR for cancer may be explained by a very high SPMR for chronic nephritis.]

Selevan *et al*. (1985) studied mortality in a cohort of 1987 men employed between 1940 and 1965 at a primary lead smelter in the USA. Other exposures included zinc, cadmium, arsenic, sulfur dioxide and, in some departments, airborne free silica. In an extended follow-up study of this cohort (Steenland *et al*., 1992), 1990 male hourly-paid smelter workers were identified. They had worked in a lead-exposed department for at

least 1 year, with at least 1 day of employment at the smelter between 1940 and 1965. The vital status of the cohort was determined via the Social Security Administration and the National Death Index. The population of the USA was used as a reference group. For all cancers, the overall SMR was 98 (192 observed; 95% CI, 84–112). There were non-significantly elevated SMRs for stomach cancer and lung cancer. In the subcohort (1436 subjects) with heavier exposure to lead (departments with mean airborne lead concentrations in 1975 that exceeded 0.2 mg/m^3), the SMRs were similar. Eight of the nine kidney cancer deaths occurred in the subcohort with heavier exposure to lead (SMR, 239; 95% CI, 103–471). Analyses by duration of exposure failed to show any significant positive trends with site-specific cancer risks. Detailed data about individual lead exposures were lacking as well as information about potential confounders such as concomitant exposure to cadmium, arsenic and other exposures at the primary smelter. However, some data were available. In 1975, the mean airborne arsenic concentration was 14 μg/m^3, whereas the mean airborne lead concentration was 3.1 mg/m^3. These means were based on 89 and 203 personal 8-h samples, respectively. [This level of arsenic exposure is approximately an order of magnitude lower than that seen in most of the historical cohort studies of arsenic-exposed workers that have shown lung cancer excesses (Steenland *et al*., 1996). No lung cancer excess was seen in workers with similar average exposure levels (between 7 and 13 μg/m^3) in copper smelters studied by Enterline *et al*. (1987). Similarly, little or no lung cancer excess was seen among workers with this level of exposure in another copper smelter in the USA studied by Lubin *et al*. (2000).] Data on smoking were lacking.

In a study in Sweden (Gerhardsson *et al*., 1986), 3832 male workers first employed before 1967 at a primary copper smelter in northern Sweden were followed from 1950 to 1981. A subcohort of 437 workers employed for more than 3 years in jobs with high lead exposure had a mean blood lead concentration of 58 μg/dL in 1950, which had decreased to 34 μg/dL in 1974. Workers were also potentially exposed to carcinogenic substances such as arsenic, chromium and nickel. A significant excess of lung cancer and stomach cancer mortality was observed in the whole cohort but was not sustained in the high-exposure subcohort.

In a follow-up study at the same smelter (Lundström *et al*., 1997), the total cohort was extended to comprise 3979 workers who had been employed for at least 1 year during the period 1928–79 and who had been monitored for blood lead concentrations since 1950. A subcohort of 1992 workers was defined by excluding workers ever employed in the roaster departments, machine shop and any other departments with appreciable exposures to arsenic and nickel. This subcohort comprised workers from the lead department and other lead-exposed departments. Airborne concentrations of arsenic ranged from 0.35 to 1.5 mg/m^3 at the roasters during the late 1940s and decreased to 0.1–0.5 mg/m^3 during the 1950s; those of sulfur dioxide ranged from 70 to 560 mg/m^3 during the 1940s and decreased to 5–10 mg/m^3 during the 1960s. [This subcohort is described in the paper as one of ‘lead-only workers’, but these workers would have been exposed to some degree to arsenic and nickel.] Expected mortality in 1955–87 and cancer incidence in 1958–87

were calculated relative to county rates, specified for cause, sex, 5-year age groups and calendar year. Information on mortality was obtained from the Cause-of-Death Register at Statistics Sweden. The death certificates were coded according to the 8th revision of the International Classification of Diseases (ICD-8). Information on the incidence of malignant tumours was gathered from record linkage with the National Swedish Tumour Registry, established in 1958. The most highly-exposed subgroup was selected on the basis of a cumulative blood lead dose, which was calculated by summing the annual mean blood lead values for each worker during the period of employment (≥ 207 μg×yr/dL). For the total cohort (*n* = 3979), the overall SMR for all cancers was 120 (126 observed; 95% CI, 100–150). There was a significantly elevated SMR for lung cancer (280; 39 observed; 95% CI, 200–380). The SMR for lung cancer in the most highly-exposed subgroup (*n* = 1026) was 280 (19 observed; 95% CI, 180–450). For cancer incidence in the total cohort (with a 15-year minimum latency period), the overall standardized incidence ratio (SIR) for all cancers was 110 (172 observed; 95% CI, 90–120). There was a significantly elevated SIR for lung cancer (42 observed; SIR, 290; 95% CI, 210–400). The SIR for lung cancer in the most highly-exposed subgroup was 340 (23 observed; 95% CI, 220–520). The risk estimates for lung cancer were further elevated in the subgroup of 'lead-only workers' with the highest exposure (7 observed; SIR, 510; 95% CI, 200–1050). No significantly elevated SIRs were observed for other malignancies. [The multifactorial exposure pattern and the lack of smoking data make it difficult to separate the effects of lead from the effects of other agents, in particular arsenic, in the working environment.]

This cohort from Sweden (described above) was further analysed by Englyst *et al*. (2001) forming two subcohorts from the original cohort of 3979 male smelter workers (Lundström *et al*., 1997). Subcohort 1 consisted of 710 workers who had been employed in the lead department. Subcohort 2 was nested within subcohort 1 and the subcohort of the 1992 workers defined by Lundström *et al*. (1997) and consisted of 383 workers who had been employed in the lead department at any time but never in the arsenic plant, nickel plant, the roaster department or the machine shop. SIRs for 1958–87 were calculated relative to county rates. The lung cancer incidence was raised in both lead subcohorts. Incidence for all cancers was close to expectation. A detailed study of company records revealed that nine of the 10 lung cancer cases in subcohort 1 and four of the five lung cancers in subcohort 2 had also had some considerable exposure to arsenic. [The Working Group noted that such information on exposure to arsenic was not available for the rest of the cohort.]

Gerhardsson *et al*. (1995) studied the mortality and cancer incidence among workers exposed to lead at a secondary lead smelter in southern Sweden. There was no known concomitant exposure to arsenic, hexavalent chromium, nickel or cadmium. Annual mean blood lead values declined during the follow-up period, from 62 μg/dL in 1969 to 33 μg/dL in 1985. The cohort consisted of 664 male lead smelter workers who had been employed for at least 3 months from 1942 to 1987. The causes of death in 1969–89 were obtained from Statistics Sweden. Death certificates were coded according to ICD-8.

Yearly cancer incidence from 1969 to 1989 was obtained from the National Swedish Tumour Registry, with calendar year-, sex- and 5-year age group-specific incidences for the county population. For all cancers, the overall SIR was 127 (40 observed; 95% CI, 91–174). There were non-significantly elevated SIRs for stomach cancer and cancers of the respiratory tract. [The Working Group noted that the results must be interpreted with caution due to small numbers and lack of data on smoking.]

In a study of 1345 male smelter workers at a lead and zinc smelting plant in south-western Sardinia, Italy, mortality was followed from 1973 to 1991 (Cocco *et al.*, 1996). Death certificates were provided for all deceased subjects by the local health units. SMRs were calculated after comparison with death rates in the general male population in Sardinia. No significant excess of mortality was noted for any single cancer site. There were two deaths from stomach cancer and lung cancer mortality was lower than that expected. The overall SMR was not presented. [The study interpretation is hampered by limited numbers of expected deaths, lack of detailed information about individual exposures to lead, zinc and other substances at the smelter, as well as a lack of data on smoking.]

Cocco *et al*. (1997) also studied 1388 lead workers from another lead smelter in Italy. An industrial hygiene survey carried out in 1977–78 reported concentrations of cadmium in respirable dust below the limit of detection (1 μg/m^3) in 9/39 samples and below 10 μg/m^3 in 28/39 samples. In addition, concentrations of arsenic were reported to be below the limit of detection (1 μg/m^3) in 23/24 samples; the remaining reading was 3 μg/m^3 in the agglomeration area. Concentrations of lead in respirable dust had a wide range of values (1–1650 μg/m^3) with a geometric mean for all work areas of 48 μg/m^3. Vital status of the workers was followed from 1950 to 1992. Fifty-five per cent of the cohort members had died by the end of follow-up. Death certificates were available for 96% of the deceased men. The underlying causes of death were coded according to the 9th revision of the International Classification of Diseases (ICD-9). SMRs were calculated for specific causes of death after comparison with national and regional reference rates. On the basis of national rates, mortality for all cancers, stomach cancer and lung cancer were lower than expected. On the basis of regional rates for a more limited period of follow-up (1965–92), mortality rates for all cancers, stomach cancer and lung cancer were close to those expected.

Lung cancer mortality was investigated in a cohort study of men employed at a zinc–cadmium smelter in the United Kingdom (Ades & Kazantzis, 1988). The study comprised all hourly-paid male workers employed at the smelter on 1 January 1943 and those who subsequently started work before 1970. All subjects were born before 1940 and worked for at least 1 year before 1970. Average arsenic concentrations assessed by static samplers between 1981 and 1983 ranged from 1 to 3 μg/m^3 in the sinter and from 4 to 7 μg/m^3 in the furnace. Airborne cadmium exposure before 1970 was assessed to be 200 μg/m^3 in the sintering plants and 80 μg/m^3 in the cadmium plant. By 1977, these concentrations had decreased to 15 μg/m^3 in both departments. Biological monitoring results showed mean blood lead concentrations of 28 μg/dL in the cadmium plant workers, 59 μg/dL in the furnace workers (10% of the cohort) and 56 μg/dL in the sinter workers

(8% of the cohort). In total, 4173 men were followed up for more than 10 years. SMRs were calculated using regional comparisons. The SMR for lung cancer was 125 (182 observed; 95% CI, 107–144). The lung cancer mortality was positively related to duration of employment. On the basis of a matched case–control study nested in this cohort, the cumulative arsenic and lead exposure (both estimated crudely in terms of 'level–decades'), but not cumulative cadmium exposure, were positively related to lung cancer mortality. [It was not possible, however, to elucidate the independent relationships for arsenic, lead or other concomitant exposures at the smelter.]

2.1.3 *Lead chromate pigment production*

Workers producing lead chromate pigments have been the subject of two cohort studies focused on possible lung carcinogenicity resulting from exposure to hexavalent chromium, which was classified as Group 1 human carcinogen by IARC (IARC, 1990). [It is not possible to separate the effects of chromium on the lung from those of lead in these studies, limiting their usefulness in the evaluation of the carcinogenicity of lead.]

Sheffet *et al*. (1982) studied mortality among 1296 white and 650 non-white men in a pigment plant producing lead and zinc chromates in the USA who were employed for at least 1 month between 1940 and 1969, and followed through 31 March 1979. Moderate exposure was defined as work in jobs with an average exposure of 0.5–2 mg/m^3 airborne chromium, while high exposure was defined as > 2 mg/m^3 airborne chromium; 76% of the cohort had high or moderate exposure. A statistically significant relative risk of 1.6 (95% CI, 1.1–2.2; 31 deaths) for lung cancer was found among male employees, increasing to a significant 1.9 for those exposed for at least 2 years to moderate or high exposure. Stomach cancer had a SMR of 2.0 (95% CI, 0.9–3.6; 8 deaths). SMRs varied depending on whether or not those decedents with cause of death unknown (15%) were excluded from the observed count of lung cancers or added in proportion corresponding to the distribution of observed deaths with known causes. [SMRs for other cancers were calculated, but numbers were small and there were no significant findings.]

Davies *et al*. (1984a) studied 1152 men at three pigment plants in the United Kingdom; two of the plants produced zinc and lead chromates, the third only lead chromate. Workers had at least 1 year of employment between the beginning of complete plant records (1933, 1949 and 1947 for the three plants) and 1967 (with the exception of a few late entrants 1968–74), and were followed up until 1981. Exposure was categorized into high, medium and low grades: jobs in dry departments and full-time stove drying with heavy exposure to chromate-containing dust (high); slight or occasional exposure to chromate, including jobs in management, laboratory, shops, maintenance, etc. (low); and other jobs, e.g. wet departments, men going all over the factories (medium). There was a statistically significant excess of lung cancer mortality at the two factories producing zinc and lead chromate, but no excess was observed at the plant producing only lead chromate, despite small numbers. The authors speculated that zinc chromate was responsible for the lung cancer excess at the first two plants. No quantitative data on exposure were given, although it was mentioned

that lead concentrations were high enough to result in frequent lead poisoning until the 1950s.

Davies *et al*. (1984b) studied 57 men with documented lead poisoning who were part of the larger cohort of workers at three pigment plants (Davies *et al*., 1984a; see above). There were four cases of lung cancer (SMR, 145; 95% CI, 39–370). [Due to small numbers, this study is essentially non-informative regarding cancer risk among these highly-exposed workers.]

2.1.4 *Workers in glass production*

Glass work involves smelting and foundry work, and glass blowing, grinding and polishing with potentially high exposures to lead but also to a variety of other metals (arsenic, cadmium, chromium, antimony, copper), as well as some exposure to silica and, to a lesser extent, possible exposure to asbestos used in insulation. An earlier Working Group (IARC, 1994) concluded that the manufacture of art glass, glass containers and pressed ware entails exposures that *are probably carcinogenic to humans (Group 2A)* and that occupational exposures in flat-glass and special glass manufacture *are not classifiable as to their carcinogenicity to humans (Group 3)*.

Numerous linkage studies on occupation and cancer have been conducted. Some gave positive results for glass workers and lung cancer (Milne *et al*, 1983; Lynge *et al*., 1986; Levin *et al*., 1988) or brain cancer (Mallin *et al*., 1989).

(*a*) *Cohort studies*

Cordioli *et al*. (1987) studied 468 male workers with at least 1 year of employment in a glass factory in Italy between 1953 and 1967 and followed them for mortality until 1985. A SMR for lung cancer of 209 [95% CI, 111–357] was observed, based on 13 lung cancer deaths. An excess of laryngeal cancer was also observed (SMR, 449 [95% CI, 122–1150]), based on four cases.

Sankila *et al*. (1990) studied 3749 workers (1803 men, 1946 women) employed for at least 3 months in two glass factories in Finland and followed them for cancer incidence from 1953–86. An excess of lung cancer was found (SIR, 128; 95% CI, 99–162; 69 cases, 62 men and seven women). The authors noted that a similar excess of lung cancer was found when comparing industrial workers in general with the general population in Finland, suggesting confounding by smoking as a possible explanation of the observed excess. An excess of stomach cancer (SIR, 231; 95% CI, 85–502; six cases) and skin cancer (SIR, 625; 95% CI, 129–1827; three cases) was found in the subcohort of glass blowers ($n = 235$), but no excess of lung cancer was observed in this group.

Wingren and Englander (1990) studied 625 male glass workers employed in Sweden for at least 1 month between 1964 and 1985, for cancer incidence and mortality. Slag from blow pipes contained lead, manganese and nickel. Mortality was emphasized in the results because the follow-up period covered by incidence was shorter, and the incidence results tended to parallel the mortality results. Both national and county (local) standards were

used, with county rates being considerably lower for lung cancer. Lung cancer was found in excess using national rates (SMR, 144; 95% CI, 52–311) as well as country rates (SMR, 240; 95% CI, [88–522]), based on small numbers (six lung cancer deaths). Colon cancer (SMR, 250; 95% CI, [68–640]; four deaths) was also elevated, based on county rates. Smoking status was known for 60 workers employed in the 1960s, showing a lower proportion of smokers than in the general population.

(*b*) *Case–control studies*

There have been three case–control studies of glass workers in Sweden, conducted by the same authors, based on death certificates and with some overlapping data (Wingren & Axelson, 1985; 1987; 1993). Initially, three rural parishes in which glass works were common were studied from 1950 to 1982. The initial investigation was expanded to 11 parishes, which included most of the glass works in Sweden, again studying the period 1950–82. To assess past and present exposure, a questionnaire regarding use of different metals was sent to 13 existing glass works of which seven replied. Cancer was not more common in the parishes than in the whole of Sweden in cohort analyses, but in case–control analyses (controls were non-cardiovascular, non-cancer deaths) based on occupation on the death certificate [no information was given on how many were missing], glass workers had elevated odds ratios. There was an excess of lung cancer (odds ratio, 1.7; 90% CI, 1.1–2.5; 21 exposed cases), stomach cancer (odds ratio, 1.5; 90% CI, 1.1–2.0; 44 exposed cases) and colon cancer (odds ratio, 1.6; 90% CI, 1.04–2.5; 18 exposed cases). More detailed data on jobs were available for about half of those who died, and analyses by specific job title suggested that the excess of stomach and colon cancer appeared most strongly among glass-blowers, while the excess of lung cancer was about the same among glass blowers and glass workers without specified job title. However, all glass workers used several metals, which were often used in combination, and it was difficult to identify particular metals as being responsible for particular cancer excesses. Measurement of lead in several worksites showed high air concentrations, with a mean of 61 μg/m^3 in one foundry for heavy crystal glass.

2.1.5 *Studies in miners*

Carta *et al.* (1994) followed mortality among active male employees in two lead and zinc mines in Sardinia, Italy. The study was performed particularly to test the relationships between silica and radon exposures and lung cancer risk. Later, Cocco *et al.* (1994a,b) enlarged the study to include male (n = 4740) and female (n = 483) workers in the mines with at least 1 year of employment between 1932 and 1971. Follow-up of the male cohort was from January 1960 to the end of November 1988, and eligible subjects were men who were still employed on 1 January 1960 or who had worked for a minimum of 12 months during 1960–71. In the study among female workers, follow-up was from 1951 to 1988, and eligible subjects were women who were alive at the onset of follow-up. Vital status was known for 99.5% of the male and 96% of the female cohort members,

and death certificates were available for all deceased members. In both mines, the ores mainly consisted of *blende* and *galena* (zinc and lead sulphides). The concentrations of in-air respirable dust averaged 2.5 and 2.6 mg/m^3 in 1962–70 and 1.6 and 1.8 mg/m^3 from 1971 onwards in the two mines, respectively. Dust concentrations at surface workplaces were less than 1 mg/m^3 in the 1970s. Expected rates were derived from the regional rates in the study among men and from the national rates in the study among women. Among men, the overall SMR was 104 (1205 observed; 95% CI, 98–110). The SMR for deaths from all cancers was 94 (293 observed; 95% CI, 83–105) and 95 (86 observed; 95% CI, 76–117) for lung cancer. Except for cancers of the peritoneum and retroperitoneum (SMR, 367; six deaths observed; 95% CI, 135–798), none of the cancer sites studied had a significantly increased SMR. In the study among women, 163 deaths occurred in total (SMR, 78; 95% CI, 67–91); the SMR for lung cancer was 232 (95% CI, 85–505; six deaths observed). Information on lifetime smoking habits were available for 1741 male employees included in a cross-sectional survey in 1973 (Carta *et al.*, 1994). About 65% were current smokers. Further details on exposures to lead were not available.

2.1.6 *Newspaper printers*

Two studies among newspaper printers are described here; these studies aimed at describing explicitly long-term exposures to lead in cohorts not exposed to other known carcinogens (such as other metals, benzene, organic solvents). Other studies of printing workers potentially exposed to lead have not been reviewed in this monograph.

Bertazzi and Zocchetti (1980) studied mortality among workers in a newspaper plant in Milan, Italy. Male workers employed in the production department as of 31 December 1955 and having at least 5 years of employment were considered eligible (n = 700). Mortality follow-up covered the years 1956–75. Follow-up and tracing was successful for 96.7% of the eligible workers. Persons not traced were assumed to be alive at the end of the follow-up period. The expected numbers were calculated using the national rates. For 10 deaths, no specific cause was mentioned on the death certificate. The overall SMR was 108 (199 deaths observed; 95% CI, 94–124). The SMR for any cancer was 123 (51 deaths observed; 95% CI, 92–162), that for lung cancer was slightly elevated (SMR, 148; 13 deaths observed; 95% CI, 79–253) and that for cancers of the digestive organs and peritoneum was 120 (19 observed; 95% CI, 72–188). There were two deaths from brain cancer (expected number not given). SMRs for lung cancer were 167 (two deaths observed), 106 (five deaths observed) and 207 (six deaths observed) in the groups for whom length of employment was 5–9, 10–19 and 20 or more years, respectively. Risk for lung cancer was highest among packers and forwarders (SMR, 250; six deaths; 95% CI, 92–544), who were possibly exposed to vehicle exhausts. Among compositors and stereotypers, who were thought to be the group most probably exposed to moderate concentrations of lead, no excess mortality was found but the study size was small (for lung cancer, there was one death observed and two expected). [The Working Group noted that no data were available on exposure to lead for this cohort.]

Michaels *et al*. (1991) followed mortality among 1261 newspaper printers in New York, USA. The cohort was composed of male members of a typographical union employed at two newspaper printing plants on 1 January 1961. The cohort consisted primarily of compositors and make-up workers, and exposure to lead was assumed to be similar in both groups. No measurements were reported from these two plants, but the authors described measurements of airborne lead at other printing plants in the USA in 1942 as varying from < 1 μg/m^3 to 20 μg/m^3, i.e. below the occupational standard of 50 μg/m^3. According to a survey in 11 plants in the USA in the 1970s, airborne lead concentrations were generally < 10 μg/m^3, most of them < 1 μg/m^3. Of the 1309 male members potentially eligible for the study, 48 (3.7%) were not traced and were excluded. Vital status was known for 1222 subjects (96.9% of the traced). Those with unknown vital status were assumed to be alive at the end of follow-up. Follow-up through death certificates was carried out until December 1984. New York City mortality rates were used as the reference. The overall SMR was 74 (498 deaths observed; 95% CI, 68–81); the SMR for any cancer was 84 (123 deaths observed; 95% CI, 69–100) and that for lung cancer was 89 (37 observed; 95% CI, 69–100). There were no clear increases in SMRs for any of the primary cancer sites studied. [The Working Group noted that the hot lead process was phased out of newspaper printing during the period 1974–78.]

2.1.7 *Exposure to organic lead*

Organo-lead compounds such as tetraethyl and tetramethyl lead have been used historically as components in gasoline. Gasoline engine exhaust has been previously evaluated as *possibly carcinogenic to humans* (Group 2B) (IARC, 1989). Studies on gasoline are not further reviewed here as there are mixed exposures and the effects of lead cannot be characterized separately. A cohort study and a nested case–control study of workers employed in the manufacture of tetraethyl lead are described below.

Sweeney *et al.* (1986) investigated the mortality of 2510 men employed at a chemical plant in east Texas, USA. Tetraethyl lead was produced during the study period from 1952 to 1977, together with ethylene dichloride and chloroethane. Vinyl chloride monomer was also manufactured from 1960 to 1975. Other chemicals (ethylene dibromide, ethylene, inorganic lead, dyes) were used in the manufacturing processes of tetraethyl lead. Male employees who had worked at least 1 day at the factory between 1952 and 1977 were eligible from company records and workers' union files. More than 50% of the total workforce had been employed at the plant for at least 5 years. Vital status was ascertained for 99.3% of the cohort members. Expected numbers were calculated from the national rates by ethnicity, age groups and 5-year calendar periods. Mortality from all causes of death was lower than expected (SMR, 74; 156 observed; 95% CI, 64–84). The SMR for malignant neoplasms was 103 (38 deaths observed; 95% CI, 77–135). The SMR for lung cancer was 112 (14 observed; 95% CI, 68–175). There was a slight excess of laryngeal cancers (SMR, 364; two deaths observed; 95% CI, 65–1145) and of brain and central nervous system tumours (SMR, 213; four deaths observed; 95% CI, 73–487). Among white men

employed between 1952 and 1960, when the manufacture of tetraethyl lead was the principal process, the SMR for lung cancer was 122, based on 13 deaths (95% CI, 73–194) and the SMR for brain tumours was 186 (three deaths observed; 95% CI, 51–482). When deaths among male workers employed before 1960 were restricted to those deaths occurring 15 or more years after first employment, the SMR for respiratory cancers was 154 (14 observed; 95% CI, 84–258); for length of employment < 10 years, the SMR was 199 (six observed; 95% CI, 73–432); and for employment > 10 years, the SMR was 132 (eight observed; 95% CI, 57–260). [There were no further details on mortality by employment at departments using tetraethyl lead or with other chemical exposures.]

Fayerweather *et al*. (1997) reported a case–control study among employees who worked at a tetraethyl lead manufacturing company in New Jersey, USA. The plant began producing tetraethyl lead in 1923 and production was closed in 1991; thereafter, the tetraethyl lead plant was involved in lead remediation. The study subjects, 735 male cases of cancer other than non-melanoma of the skin, and 1423 controls matched by year of birth, sex, and most recent payroll class, were drawn from the cancer and mortality registries of the company and from employment rosters. Neoplasms that occurred during 1956–87 were included. The cancer registry mainly covered active workers; workers who left the company were missing from the registry (but those who left the active workforce and were put on the company's disability rolls were included in the registry). The mortality registry covered all active and pensioned employees since 1957. Information on ever having worked in the tetraethyl lead area, years of employment in tetraethyl lead manufacture, rank (degree) of exposure to tetraethyl lead and cumulative exposure to tetraethyl lead were estimated using employment information from the personnel records, industrial hygiene data and records of biological measurements available at the factory. Tetraethyl lead exposure ranks were based on job titles. Employees manufacturing tetraethyl lead could have been exposed both to organic and inorganic lead compounds, but it was not possible to distinguish between these in the exposure assessment because of insufficient data. Exposure (ever/never) to other known or suspected carcinogens (such as aromatic amines, nitriles, benzene, asbestos, radioactive materials) was also assessed. Smoking histories were available from reports of periodical pulmonary function tests for 38% of the cases and 51% of the controls. Cases and controls for whom there was no available information on employment from personnel records were excluded. Odds ratios for cancer of the digestive tract were elevated for the group who had ever worked in the tetraethyl lead manufacturing area compared with the group who had never worked in that area (odds ratio, 1.3; 45 cases observed; 90% CI, 0.9–1.9); the risk was increased for high (odds ratio, 1.3; 90% CI, 0.7–2.7) and very high (odds ratio, 2.2; 90% CI, 1.2–4.0) estimated cumulative exposure. Further latency analyses, adjustments for smoking, and exposure to aromatic amines, radioactive materials and asbestos did not markedly change the results. Risk for rectal cancer was increased (odds ratio, 3.7; nine cases observed; 90% CI, 1.3–10.2), and was associated with high cumulative exposure to tetraethyl lead. The odds ratio for colon cancer was 1.3 (16 observed; 90% CI, 0.7–2.5) and was moderately elevated for the highest cumulative exposure category. [Not all workers exposed to

organic lead were followed-up, e.g. workers who had terminated their employment without pension eligibility. Losses in tracing and follow-up were not described in this study. Quantitative information on the exposure categories was not available. Detailed results on other primary cancer sites were not reported.]

2.1.8 *Workers biologically monitored for blood lead concentrations*

Anttila and co-workers (Anttila, 1994; Anttila *et al.*, 1995, 1996) studied mortality and cancer incidence among a worker population biologically monitored for occupational exposure to lead. The biological monitoring programme was undertaken by the Institute of Occupational Health in Finland in order to evaluate the uptake of lead, with the aim particularly to prevent lead poisoning. The database included 63 700 blood lead measurements performed during 1973–83 on workers in approximately 2318 industrial plants or workplaces from all over Finland. Personal identity was traced for 97.0% of the measurements (those for whom the identity could not be traced were excluded). The study population included 20 741 employees, 18 329 men and 2412 women. In the cohort analyses, follow-up was done through cause-of-death records, and records from the nationwide cancer registry from 1973 to 1988. In addition to the cohort follow-up, a nested case–control study was performed, extending the incidence follow-up to 1990. The case–control study included 10 common primary cancer sites and controls were selected from monitored workers not registered for cancer. Controls were matched with the cases by sex, year of birth, age and vital status. In the case–control study, information on occupational histories and on smoking and alcohol consumption were requested from the study subjects or their next-of-kin using a postal questionnaire. Lifetime exposures to lead, and eight other groups of occupational carcinogens, were estimated by an industrial hygienist; the assessment was blinded as to the case–control status. Assessment of lifetime exposures to lead was based on a combination of average individual blood lead values and exposure profiles within lead-exposed worker groups/industries.

Yearly median concentrations of blood lead decreased from 1.4 μmol/L in 1973 to 0.7 μmol/L in 1982 among men and from 1.0 μmol/L to 0.3 μmol/L among women. The blood lead concentrations exceeded 1.0 μmol/L (the administrative reference value of 'occupationally unexposed' during that time) in 9100 (42%) of the employees. Workers monitored most regularly for blood lead concentrations were from the lead battery industry (about 1300 employees from five plants), lead smelting and metal scrap business (692 employees from 36 plants), metal foundries (419 employees from 30 plants), railroad equipment machine shops (434 employees from 14 plants) and manufacture of some industrial chemicals (100 employees from seven plants). Lead-exposed employees monitored less frequently were those working, for example, in automobile repair shops and related industries (1290 employees from 292 workplaces), the graphics industry (1238 employees from 166 plants), the manufacture of glass, pottery, PVC plastics and paints (1220 employees from 68 plants), shipyards (1113 employees from 23 plants) and miscellaneous metal and engineering (2844 employees from 335 plants) (Anttila, 1994).

Altogether 1082 deaths (1007 men and 75 women; SMR, 84; 95% CI, 79–89) and 469 incident cancer cases (SIR, 99; 95% CI, 90–108) were observed in the cohort follow-up. Three exposure categories, based on the highest personal blood lead concentration, were used: low, < 1.0 μmol/L; intermediate, 1.0–1.9 μmol/L; and high, 2.0–7.8 μmol/L. [Compared with many other occupational cohorts, there were rather low levels of exposure to lead in this cohort and small numbers of highly-exposed employees; there were only a few cancer cases among women.] In the low exposure group, the SIR for any cancer was 80 (95% CI, 70–100; $p < 0.05$); the SIRs were 120 (95% CI, 100–140) and 100 (95% CI, 70–140) in the intermediate and high exposure categories, respectively. The SIRs for lung cancer were, respectively, 70 (95% CI, 50–110), 140 (95% CI, 100–190) and 110 (95% CI, 60–200) for the three groups. [The Working Group noted that the reference population has a deficit in all cancers and lung cancer incidence, which affects internal comparisons.] In the internal comparison, there was a twofold risk for lung cancer (relative risk, 2.0; 95% CI, 1.2–3.2) for the intermediate and a 1.5-fold risk (relative risk, 1.5; 95% CI, 0.8–3.1) in the high exposure groups, compared with the low exposure group [no *p*-value for trend available]. Additional analyses were done by cumulative exposure for which the *p*-value for trend was not statistically significant (Anttila *et al.*, 1995).

In the nested case–control study on lung cancer, there were initially 121 male cases and 363 controls. The final population was restricted to 53 cases and 156 controls for whom complete occupational histories were obtained. The nested case–control analyses gave results similar to those of the cohort analyses. There was a positive trend, although not statistically significant, of odds ratios increasing with increasing cumulative exposure to lead, with odds ratios for lung cancer being 0.9, 1.2 and 1.4 for three groups of estimated lifetime cumulative exposure to lead of 1–6, 7–17 and 18–70 μmol/L × year as compared with the unexposed, adjusted for smoking and vital status. Compared with non-adjusted results, the odds ratio for lung cancer increased slightly in the highest exposure group and remained unaltered in the intermediate category when adjusted for smoking and vital status, suggesting that smoking was not a confounder in the internal comparison. In this study (Anttila *et al.*, 1995), a significant fourfold difference was reported between the risk for lung cancer for raised blood lead alone and raised blood lead with estimated co-exposure to exhaust. [The Working Group noted that information on exposure to engine exhaust was of limited quality and the results were difficult to interpret.] There were no clear increases in risk for stomach or kidney cancer associated with lead exposure.

In a further study on brain and nervous system cancers in the same cohort (Anttila *et al.*, 1996), the observed/expected numbers of brain and other nervous system cancers were 12/13.3, 10/7.7 and 4/2.9 over three categories of blood lead (< 1.0, 1.0–1.9, 2.0–7.8 μmol/L). Internal analyses using Poisson regression showed 1.6-fold (95% CI, 0.7–3.8) and 1.8-fold (95% CI, 0.6–5.8) risks for the intermediate and high blood lead categories in comparison with the low. Histology-specific risk estimates could be computed only in the case–control design. There was a statistically significant increase in the risk for gliomas in the high blood lead category (*p*-value for trend = 0.037; 16 gliomas in total), whereas there were no associations between exposure to lead and cancers with other or unknown histo-

logy (10 cases; *p*-value for trend = 1.00). Among those subjects for whom lifetime exposures could be assessed (including 10 of the glioma cases), the risk was associated with the estimated level and duration of lifetime occupational exposure to lead as well as with the cumulative exposure (*p*-values for trend = 0.041, 0.029 and 0.020, respectively).

2.1.9 *Register linkage studies*

McLaughlin *et al.* (1987) studied the occurrence of meningioma in men using the Cancer–Environmental Registry of Sweden, which linked cancer incidence from 1961–79 with 1960 census information on employment. Analyses included all intracranial and intraspinal meningiomas ($n = 1092$), 98% of which were coded as histologically benign. Among glassmakers, a regionally-adjusted fivefold risk was observed (6 cases; SIR, 5.2; $p < 0.01$).

Navas-Acién *et al*. (2002; discussed in a letter to the editor by Costa, 2003) investigated occupational risks for gliomas and meningiomas in Sweden. The study was based on a linkage of census records with cancer registry files, and exposures were estimated based on the occupational and industrial titles in the 1970 census. A job–exposure matrix was used that classified probability (no/possible/probable) of exposure, based on estimated proportions of exposed workers. Possible exposure meant that between 10 and 66% of the subjects were exposed at a level > 10% of the threshold limit value. Probable exposure meant that more than 66% of the subjects were exposed. The job–exposure matrix was aimed to be representative for the labour force in Sweden. There were 3363 gliomas and 1166 meningiomas in men, and 1561 gliomas and 1273 meningiomas in women in the follow-up from 1971 to 1989, including those aged 25–64 years at the beginning of follow-up. Risk for glioma in men with possible exposure to lead was not increased (10 cases; relative risk, 1.08; 95% CI, 0.58–2.01; adjusted for age, period, geographical category, town size and other chemical exposures); there were no cases with probable exposure to lead. Risk for meningioma was elevated (seven cases; relative risk, 2.36; 95% CI, 1.12–4.96) for possible exposure to lead; no cases had probable exposure. There were fewer than four cases exposed to lead in the female study population, and the risk estimates were not reported. [The Working Group noted that it is difficult to be confident about the exposure classification.]

Wesseling *et al.* (2002) carried out a study on brain and nervous system cancer risk among women in Finland, based on linkage of census and cancer registry data. Occupation titles were drawn from the 1970 census, and follow-up was performed from 1971 to 1995 among a cohort of 413 887 women with blue-collar occupations. There were 693 cases of brain and nervous system cancers, 43% of which were meningiomas, 29% gliomas and 28% of other types. In a Poisson regression model with multiple agents, adjusted for year of birth, period of diagnosis, and turnover rate, exposure to lead was not statistically significantly elevated: the SIR for low exposure (blood lead < 0.3 μmol/L) was 1.24 (95% CI, 0.95–1.62) and the SIR for medium/high exposure (blood lead > 0.3 μmol/L) was 1.27 (95% CI, 0.81–2.01).

2.1.10 *Population-based case–control studies*

(*a*) *Multiple cancer sites*

A population-based case–control study of cancer associated with occupational exposure among male residents of Montreal, Canada, aged 35–70 years, included histologically-confirmed cases of several types of cancer newly diagnosed between 1979 and 1989 in 19 hospitals (Siemiatycki, 1991). Interviews were carried out with 3730 cancer patients (response rate, 82%) and 533 age-stratified controls from the general population (response rate, 72%). The main cancer sites included were oesophagus, stomach, colon, rectum, pancreas, lung, prostate, bladder, kidney, skin melanoma and non-Hodgkin lymphoma. For each cancer site analysed, two controls were available: a population control and a control selected among cases of cancer at other sites. The interview was designed to obtain lifetime job histories and information on potential confounders. Each job was reviewed by a team of chemists and industrial hygienists who translated the jobs into occupational exposures using a checklist of 293 substances found in the workplace. For exposure to lead compounds or various other forms of lead, no excess risk of cancer was seen for most of the primary sites examined. For substantial exposure to lead compounds, there was a statistically significant 1.8-fold increase in the risk of stomach cancer and a statistically significant 1.5-fold increase in the risk of lung cancer. Substantial exposure to lead dust was associated with an increased risk of stomach cancer, but there were only three exposed cases. The odds ratio for kidney cancer for any exposure to lead was 1.2 (90% CI, 1.0–1.6; 88 exposed cases) and that for substantial exposure was 0.8 (90% CI, 0.4–1.7; six cases). For other forms of exposure to lead, there were smaller numbers, and there were some excess risks reported only with the category 'any exposure'. [The Working Group noted that this study reported significant associations between estimated exposure to lead compounds and both stomach cancer and (to a lesser extent) lung cancer. However, the study involved multiple comparisons of exposures and cancer sites, as well as some uncertainties in exposure classifications, and so reliance has been placed in this monograph primarily on the results from cohort studies of lead-exposed populations.]

(*b*) *Stomach*

Cocco *et al.* (1999b) reported a population-based case–control study on occupational risk factors for stomach cancer associated with 12 workplace exposures, based on information from a national surveillance programme for occupational diseases at the National Cancer Institute, USA. The main study included 41 957 deaths from stomach cancer during 1984–96. Two controls per case were selected from those who died from non-malignant diseases; controls were matched to cases by geographic region, race, sex and 5-year age group. An investigation of deaths from cancers of the gastric cardia (ICD-9 code 151.1), including 1056 cases during 1984–92 and 5280 controls, was also undertaken (Cocco *et al*., 1998b). The study classified probability and intensity of exposures to lead with help of a job–exposure matrix composed from occupational and industry titles reported as the 'usual' occupation and industry on the death certificate. Overall, risk for stomach cancer

was not increased among Caucasian men with either increasing probability or intensity of exposure to lead. There were some slight increases in the risk among African-American men, Caucasian women and African-American women with high probability of lead exposure. Risk for gastric cardia cancer was slightly elevated with increasing probability or intensity of exposure to lead. There was only one case, however, in the group with high probability and intensity and the risk estimate was not provided. [The reliability of the lead exposure data and intercorrelations with other exposures were not described.]

(*c*) *Kidney*

A population-based case–control study among residents of Finland (Partanen *et al*., 1991) was conducted in 1977–78 involving 672 incident cases of primary renal adenocarcinoma and 1344 controls matched on age, sex and survival status. A questionnaire including information on job history, smoking and obesity was sent to all participants or to the next-of-kin of deceased participants. Response rates for cases and controls were 69% and 68%, respectively. After exclusion of non-eligible subjects, 408 cases and 819 controls remained in the study. Summary indicators of occupation were calculated for the period 1920–68 to allow for a 10-year latency and occupational histories were scored by an industrial hygienist. The annual exposure to lead and inorganic lead compounds was categorized as background (< 0.001 mg/m^3), low (0.001–0.05 mg/m^3), high (> 0.05 mg/m^3) and 'not known'. Four cases of kidney cancer (all men) had been exposed to lead and inorganic lead compounds. After adjusting for smoking, coffee consumption and obesity, an odds ratio of 2.77 (95% CI, 0.49–15.6) was observed in subjects with at least 5 years of high- or low-level exposure before 1968, or less than 5 years of exposure but at least 1 year of high-level exposure during 1920–68, versus background exposure. When the white-collar and farming occupations were excluded, the odds ratio was 5.6 (95% CI, 0.6–54.8).

A population-based case–control study on renal-cell cancer from 1991 to 1995 (Pesch *et al*., 2000) enrolled 935 cases from five regions in Germany and 4298 population controls, matched to the cases by region, sex and age. Information on occupational history and other risk factors was collected in face-to-face interviews. The response rates were 84–95% and 63–75% for cases and controls, respectively. Information on occupational risk factors was based on two job–exposure matrices (British and German) and used on every job task held for at least 1 year. For each job title and job task the exposure matrix provided an expert rating in terms of the probability and the intensity of exposure to an agent. Slight increases were suggested in the renal-cell cancer risk for estimated exposures to lead, with some dose–response patterns. [Descriptions of tasks with estimated exposures were not provided. Inter-correlations or confounding from other occupational exposures were not tested. It was not possible to check whether differential response rates between cases and controls affected the results.]

(*d*) *Brain and nervous system*

A population-based case–control study using information from a national surveillance programme for occupational diseases at the National Cancer Institute, USA, classified

probability and intensity of exposures to lead with help of a job–exposure matrix composed from occupational and industry titles (Cocco *et al*., 1998a). No information on the duration of exposure was available. Cases were 27 060 Caucasian and African-American subjects (14 655 men and 12 405 women) who died during the period 1984–92 from cancer of the brain at age 35 years or older. Four controls per case were selected from among subjects who died from non-malignant diseases. When all levels of exposure to lead were combined, brain cancer risk did not increase with increasing probability of exposure. When all probabilities of exposure were combined, there was no overall increase in the risk by exposure level, except among the African-American population (for most of whom low probability of exposure was coded, however, if the estimated level was medium or high). The risk estimate for brain cancer with high probability and level of exposure to lead was 2.1 (95% CI, 1.1–4.0; 14 cases observed) among Caucasian men and 1.4 (95% CI, 0.4–4.2; four cases observed) among Caucasian women. Among Caucasian men, the category with high probability and level of exposure appeared to be only one occupational group, i.e. typesetters and compositors. In a later study on central nervous system tumours in women in the USA, Cocco *et al*. (1999a) reported a slightly increased risk for meningiomas (odds ratio, 1.9; 95% CI, 1.0–3.9; nine cases observed) for any versus no exposure to lead.

Hu, J. *et al*. (1998) performed a hospital-based case–control study on risk factors for glioma in the province of Heilongjiang, China. Altogether 218 consecutive incident cases of primary glioma diagnosed between 1989 and 1995 were identified from six hospitals, and two controls were recruited per case from patients with non-neoplastic, non-neural disease. The reported response rates were 100% for both cases and controls. Based on self-reported exposure (request to describe chemical or other occupational exposures using a pre-specified list of agents), there was no increase in the risk related to lead exposure (no cases and four controls). The study was extended to December 1996 with 183 cases of meningioma and 366 controls (Hu *et al*., 1999). This study suggested an increased risk for meningioma with exposure to lead. [Only self-reported exposure was available. Occupations or exposure levels among lead-exposed respondents were not detailed.]

(*e*) *Other primary sites*

Risch *et al*. (1988) conducted a population-based case–control study of bladder cancer during 1979–82 in Canada. Cases aged 35–79 years diagnosed through the tumour registry or hospital files were eligible (n = 1251) and population controls were used (n = 1483). Information on occupational history and jobs held in some pre-selected industries, together with self-reported exposure to fumes, dusts, smoke or chemicals, were collected for 835 (67%) eligible cases and 792 (53%) controls through face-to-face interviews. Information on family, medical and residential histories, use of tobacco, socioeconomic factors and diet was also collected. Among men who had worked full-time for at least 6 months, exposure to lead compounds was associated with risk for bladder cancer (twofold risk among ever exposed, adjusted for smoking) and there was a trend with duration of exposure/employment as estimated per 10 years. [Exposure to lead was not reported among women. Exposures were partially self-reported. It was not clearly stated if the information on work tasks

was used in defining exposure status in the assessment. It was not possible to check whether the differential response rate affected the results.]

Kauppinen *et al*. (1992) conducted a population-based case–control study on primary liver cancer and occupational exposures in Finland. Cases were drawn from 1976–78 and 1981 from the files of the nationwide cancer registry (cases from 1979–80 had been used in another study by the same group); two reference groups were formed from patients with stomach cancer in 1977 and persons who had died from coronary infarction. There were 344 liver cancer cases, 476 controls with stomach cancer and 385 controls with coronary infarction. Controls were matched to cases by age and sex. Information on work history was collected, with the aid of a postal questionnaire, from the closest next-of-kin traced for the study subjects. Response rates were 71% for both cases and controls. Exposure assessment was made using a job–exposure matrix and by a team of occupational hygienists. In the analyses using the job–exposure matrix, no association between the risk for liver cancer and exposure to lead and lead compounds was seen (odds ratio, 0.91; 95% CI, 0.65–1.29 for a combined group of low level or probability of exposure). Based on the hygienists' assessments, the odds ratio for any exposure to lead was also close to unity (1.14; 95% CI, 0.44–2.98 after adjustment for alcohol consumption). No cases and four controls had had heavy exposure to lead (they were all typesetters with more than 10 years of employment) and five cases had had moderate exposure (odds ratio, 2.28; 95% CI, 0.68–7.67). Moderate exposure was defined as a duration of at least 10 years with low-level exposure or a duration of less than 10 years with high-level exposure; the group included workers in plumbing, welding and crystal glass manufacture. [Comparison between stomach cancer and infarction controls as to their exposures to lead was not available.]

2.1.11 *Meta-analyses*

Fu and Boffetta (1995) reviewed reports of 16 cohort studies and 13 case–control studies (nested and population-based) relating to lead exposure and cancer risk. Meta-analyses were performed for all cancers (12 studies), stomach cancer (10 studies), lung cancer (15 studies), kidney cancer (five studies) and bladder cancer (five studies). [The Working Group noted that most of the studies included in the meta-analyses of Fu and Boffetta (1995) and Steenland and Boffetta (2000) (see below) have been considered in this monograph. Neither meta-analysis included exposures to organo-lead or in the mining industry, both of which are discussed in detail in this volume. The meta-analysis of Fu and Boffetta (1995) included two studies of oil mist exposure in the printing industry (Goldstein *et al*., 1970; Pasternack & Ehrlich, 1972), which have not been discussed here. These two studies lacked specific lead exposure data, did not adjust for smoking nor for other occupational exposures and did not have appropriate reference groups.] Fu and Boffetta (1995) included only the most recent publications if several reports were available for the same study population. Fixed-effect models were used; random-effect models were also applied when there was significant heterogeneity in a set of relative risks. The meta-

analysis was limited to overall study findings (SMRs from cohort studies, and odds ratios from case–control studies); quantitative data or analyses in relation to categories of cumulative exposure were not considered. The meta-analyses (fixed-effect models) provided significantly elevated summary relative risks for all cancers (relative risk, 1.11; 95% CI, 1.05–1.17), stomach cancer (relative risk, 1.33; 95% CI, 1.18–1.49), lung cancer (relative risk, 1.29; 95% CI, 1.10–1.50) and bladder cancer (relative risk, 1.41; 95% CI, 1.16–1.71). A non-significantly elevated risk was shown for kidney cancer (relative risk, 1.19; 95% CI, 0.96–1.48). Significant heterogeneity in the set of study-specific relative risks was only shown for lung cancer ($p < 0.001$) but a highly significant summary relative risk was also obtained for this cancer from a random-effect model (odds ratio, 1.29; 95% CI, 1.10–1.50). When meta-analysis was restricted to studies conducted in industries involving higher lead exposures (battery and smelter industries), significantly elevated summary relative risks were shown for all cancers (five studies: relative risk, 1.08; 95% CI, 1.02–1.15), stomach cancer (four studies: relative risk, 1.50; 95% CI, 1.23–1.83) and lung cancer (random-effect model applied to three studies: relative risk, 1.42; 95% CI, 1.05–1.92). A non-significantly increased relative risk was shown for kidney cancer (three studies: relative risk, 1.26; 95% CI, 0.70–2.26). [Most of the studies included in this meta-analysis were of occupational groups with exposure to carcinogens such as chromium and arsenic as well as lead. Most of the studies were cohort studies entailing comparison with the general population without adjustment for potential confounding from smoking or diet. Many of the cohort studies did not report data for all of the cancers of interest and there is considerable scope for publication bias for the meta-analyses of kidney and bladder cancer; however, this is not an issue for the lung cancer findings.]

In their review of lead and cancer in humans, Steenland and Boffetta (2000) included a meta-analysis of eight cohort studies of highly exposed workers. Four studies analysed cancer mortality (of which one study used a nested case–control design); the remaining four studies analysed cancer incidence (cancer registrations). The results of meta-analyses for all cancers ($n = 1911$) and cancers of the lung ($n = 675$), stomach ($n = 181$), kidney ($n = 40$) and brain ($n = 69$) were presented. The investigators first determined whether there was significant heterogeneity in each set of cause-specific relative risks (estimated by overall site-specific SMRs, summary relative risks or odds ratios obtained from internal comparison). There was an absence of such heterogeneity for all cancers, and cancers of the stomach, kidney and brain. Therefore, fixed-effect models were used for these groupings of cancer sites to combine relative risks across the studies. A significantly elevated relative risk was shown for cancer of the stomach (relative risk, 1.34; 95% CI, 1.14–1.57) but not for kidney cancer (relative risk, 1.01; 95% CI, 0.72–1.42), brain cancer (relative risk, 1.06; 95% CI, 0.80–1.40) or all cancers (relative risk, 1.04; 95% CI, 1.00–1.09). There was significant heterogeneity in the set of relative risks for lung cancer and the investigators applied a random-effect model, leading to an overall relative risk of 1.30 (95% CI, 1.15–1.46). A previous study (Englyst *et al*., 1999) had shown that there was significant arsenic exposure in the outlier study (Lundström *et al*., 1997), and exclusion of this study led to a much lower summary relative risk for lung cancer (1.14;

95% CI, 1.04–1.25). [This meta-analysis is limited to overall summary findings; quantitative data or possible dose–response effects within the eight studies were not available for meta-analysis. It was not possible to adjust for potential confounders such as smoking and occupational exposure to arsenic and other chemicals.]

2.2 Studies based on general population (environmental) exposures

Studies in the general population involve exposures to lead in the environment which are usually much lower than lead exposures in occupational studies, sometimes by as much as an order of magnitude. Exposure effects at low doses can differ from those at high doses with regard to the type of cancer. Furthermore, low-dose effects may involve biological mechanisms different from those involved in high-dose effects, even for the same cancer site. Nevertheless, when considering the same cancer site, in general, one should expect that higher doses should cause more disease than lower doses.

Five ecological studies deal with exposure to lead and cancer. Correlations between levels of trace metals in water supplies and cancer mortality in the USA were investigated by Berg and Burbank (1972). Lung cancer mortality rates for Caucasian men and women in the former 'Tri-State mining district' of the USA (Cherokee County, KS; Jasper County, MO and Ottawa County, OK) were investigated by Neuberger and Hollowell (1982). Correlations between lead concentrations (and other aspects of air pollution) and lung cancer incidence rates (standardized for age, sex and race) were investigated in 1973–76 by Vena (1983) for 125 census tracts in New York State, USA. Correlations between blood lead concentrations and age were investigated by Hussain *et al*. (1990) for cancer patients and other residents of the Lahore district in India. Relationships between mineral and trace elements in drinking-water and gastric cancer mortality in 34 municipalities in the Aomori Prefecture of Japan were investigated by Nakaji *et al*. (2001). [The Working Group judged these studies to be uninformative due to the poor classification of exposure and the considerable scope for confounding.]

2.2.1 *Cohort studies*

McDonald and Potter (1996) conducted a mortality study in a cohort of 454 paediatric patients resident in Massachusetts, USA, and diagnosed with lead poisoning at Boston Children's Hospital between 1923 and 1966. Diagnosis of lead poisoning was based on the presence of at least two of the following clinical criteria: (1) history of lead exposure or of lead poisoning in a sibling; (2) radiographic lead lines in the bones; (3) gastrointestinal, haematological and/or neurological symptoms of lead poisoning. Cohort members were traced until 1991 to ascertain mortality; 153 (33.7%) were lost to follow-up. Numbers of observed deaths were compared with those expected, based on population statistics in the USA. Eighty-six deaths were observed (observed/expected, 1.74; 95% CI, 1.40–2.15), 10 of which were due to cancer (observed/expected, 1.14; 95% CI, 0.55–2.10). Seventeen deaths were directly attributed to lead poisoning. Mortality from cardiovascular disease

was elevated (observed/expected, 2.09; 95% CI, 1.29–3.19). [The study is limited by the high percentage of cohort members lost to follow-up.]

2.2.2 *Cohort studies of the general population based on blood lead concentrations*

The National Health and Nutrition Examination Survey (NHANES II) conducted two studies between 1976 and 1980 on the same population in the USA, based on a national probability sample of the civilian non-institutionalized population, aged 6 months to 74 years at baseline (n = 27 801) (Jemal *et al.*, 2002; Lustberg & Silbergeld, 2002) (see also Section 1.6). Data were obtained from standardized questionnaires, physical examinations and laboratory tests. Single blood lead measurements were made for all children below 7 years of age and for a random subsample of half of the subjects aged 7 years or more. Mortality was investigated for the period 1976–92 via internal comparisons of rates for those with high blood lead concentrations versus those with low blood lead concentrations [a single blood lead estimation may misrepresent long-term exposure].

Jemal *et al*. (2002) restricted their analyses to 3592 Caucasian subjects (1702 men, 1890 women) aged 30 years or more at baseline. The study had a complex sample design with multistage stratified cluster sampling and sample weighting of study participants. Cox proportional hazard regression models were used to estimate dose–response relationships between blood lead and mortality from all cancers (203 deaths), as well as some specific cancers. Log-transformed blood lead was both categorized into quartiles and treated as a continuous variable in a cubic regression spline. Median blood lead concentrations for the quartiles were 7.3, 10.6, 13.8 and 19.7 μg/dL. In analyses that adjusted for baseline values of age (continuous variable), poverty, annual alcohol and tobacco use, region and year of examination, there were no significant trends between blood lead concentrations (quartile analyses) and risk for cancer mortality in men and women combined (p = 0.16), men (p = 0.57) or women (p = 0.22). None of the examined site-specific cancer risks showed a significant association with blood lead at baseline. For lung cancer (71 deaths), the rate ratio comparing subjects with blood lead concentrations above the median versus below the median, adjusted for smoking and age, was 1.5 (95% CI, 0.7–2.9). Based on five stomach cancer deaths, the relative risk for those with blood lead concentrations above the median versus those below the median was 2.4 (95% CI, 0.3–19.1). [The Working Group noted the strong reported correlation between smoking and baseline blood lead concentration and that adjustment for smoking did not consider duration of smoking, which may have led to some residual confounding.]

NHANES II was used by another research group to analyse associations between blood lead concentrations at baseline and subsequent mortality (Lustberg & Silbergeld, 2002). This report made use of data for non-Caucasian as well as Caucasian subjects. A total of 4292 male and female participants aged 30–74 years with baseline blood lead concentrations were considered; follow-up identified 929 deaths (240 cancer deaths) before the end of 1992. In order to exclude those with high blood lead concentrations due to possible

occupational exposure, the authors did not consider subjects who had blood lead concentrations ≥ 30 μg/dL. [The Working Group noted that elimination of those with highest exposure may weaken dose–response analyses.] In analyses that adjusted for baseline values of age, sex, race, education, income, smoking, body mass index, exercise and location (urban, rural, suburban), there was a positive trend with blood lead concentration for all causes of death (referent < 10 μg/dL; 10–19 μg/dL: relative risk, 1.17; 95% CI, 0.90–1.52; 20–29 μg/dL: relative risk, 1.46; 95% CI, 1.14–1.86), for diseases of the circulatory system (referent < 10 μg/dL; 10–19 μg/dL: relative risk, 1.10; 95% CI, 0.85–1.43; 20–29 μg/dL: relative risk, 1.39; 95% CI, 1.01–1.91) and for all cancers (referent < 10 μg/dL; 10–19 μg/dL: relative risk, 1.46; 95% CI, 0.87–2.48; 20–29 μg/dL: relative risk, 1.68; 95% CI, 1.02–2.78). The only specific cancer for which results were given was lung cancer, for which rate ratios were 1.70 (95% CI, 0.60–4.81) and 2.20 (95% CI, 0.80–6.06), for the middle and high exposure groups, respectively. [The Working Group noted that residual confounding by smoking may have resulted from failure to consider duration in the adjustment for smoking. Data for all cancers show large decreases in rate ratios after control for smoking, suggesting that better control over smoking might lead to further decreases, especially for lung cancer. The Working Group also noted that the generalized increase in all deaths, all cancers and all circulatory diseases with increasing blood lead concentration suggests possible residual confounding by socioeconomic status.]

2.2.3 *Case–control studies*

The possible relationship between laryngeal cancer and subclinical lead intoxication (assessed both by blood lead concentrations and ALAD activity in the blood) has been investigated (Kandiloros *et al*., 1997). A total of 58 patients underwent surgery for cancer of the larynx over a period of 8 months at a hospital in Athens, Greece. After excluding patients with a history of lead intoxication, professional exposure to lead, previous renal or haematological diseases, or with other health problems, a total of 26 patients (24 men, two women) aged 42–75 years were included in the study. All patients had histologically-confirmed squamous-cell laryngeal carcinoma; none of the patients had received chemotherapy. Fifty-three patients with no history of cancer, suffering from other diseases, mainly otitis media, comprised the control group. There was no significant difference in the mean blood lead concentration between the two groups (patients: mean, 8.5 μg/dL; controls: mean, 7.9 μg/dL). However, ALAD activity was significantly lower ($0.001 < p < 0.01$) in the cases (patients: mean, 50.9 U/L; controls: mean, 59.8 U/L). [The Working Group noted that the exclusion of lead-exposed cases may have biased the results and that the ALAD concentration could have been affected by the case–control status.]

The possible relationships between cancer of the gallbladder and biliary concentrations of heavy metals have been investigated (Shukla *et al*., 1998). Cases comprised 38 patients (11 men, 27 women) with histologically-diagnosed cancer of the gallbladder admitted to the surgical unit of the University Hospital, Varanesi, India, from January 1995 to March 1996. Controls comprised 58 patients with gallstones (14 men, 44

women). The mean age of the cases was 53.5 years and that of the controls was 48.3 years. Bile was taken by needle aspiration from the gallbladder of all patients at the time of surgery for estimation of cadmium, chromium and lead concentrations. Statistical comparisons were made using Student's *t*-test. Highly significant differences between cases and controls ($p < 0.001$) were observed for the mean values of all the metals under study (cadmium: cases, 0.19 mg/L; controls, 0.09 mg/L; chromium: cases, 1.26 mg/L; controls, 0.55 mg/L; lead: cases, 58.4 mg/L; controls, 3.99 mg/L). There was no overlap in the observed ranges of biliary lead concentrations (cases, 35–76 mg/L; controls, 0–19 mg/L). [The Working Group noted that age and sex differences in the two groups (cases were on average 5 years older than controls and included a higher percentage of men) were not taken into account, but judged this to be an unlikely explanation of the study findings. The results could indicate that lead exposure is an important risk factor for cancer of the gallbladder, but no attempt was made to determine whether the cases had been more exposed to lead than had the controls. Alternatively, the lead concentration findings may reflect a consequence of gallbladder cancer or gallstones.]

At a hospital clinic in Lucknow, India, blood lead, zinc and copper concentrations in 17 patients undergoing surgery for cancer of the prostate, 41 patients undergoing surgery for benign hyperplasia of the prostate and 20 controls (men without any symptoms of bladder flow obstruction) were investigated (Siddiqui *et al*., 2002). Patients (mean age: cancer cases, 71.0 years; benign disease, 70.0 years) were older than controls (mean age, 53.1 years) [no information was supplied on how controls were selected]. Mean blood lead concentrations were significantly higher ($p < 0.05$) in patients with prostate diseases (cancer cases, 28.2 µg/dL; benign hyperplasia, 23.4 µg/dL) than in controls (10.2 µg/dL). Blood concentrations of zinc and copper were significantly lower ($p < 0.05$) both in prostate cancer cases and cases of benign hyperplasia than in controls. [The comparisons were unadjusted for age.] None of the subjects reported any previous occupational or accidental exposure to lead. [The Working Group noted that the disease status may have affected the blood lead concentrations.]

2.3 Studies on parental exposure and childhood cancer

2.3.1 *Cohort studies*

Wulff *et al*. (1996) conducted a cancer incidence study among a cohort of 30 644 children born between 1961 and 1990 in the municipality of Skellefteå, Sweden, to determine whether children born to women living near the Rönnskär smelter during pregnancy ($n = 4400$) had an increased incidence of cancer compared with children born to women living at a distance from the smelter ($n = 26\,244$). The Rönnskär smelter is a significant source of environmental pollutants, including lead, arsenic, copper, cadmium and sulfur dioxide. People living in two parishes within a 20-km radius of the smelter (St. Örjan and Bureå) were considered to be the exposed group, based on environmental sampling data. People in all other parishes within the municipality were considered to be unexposed.

Through linkage to the Swedish Cancer Registry, cancer diagnoses were obtained and compared with expected numbers based on national incidence rates in Sweden. Thirteen cases of childhood cancer (four leukaemia, three brain, one kidney, one eye and four other cancers) were identified among children born in the exposed area, versus 6.7 expected (SIR, 195; 95% CI, 88–300). Among children born to women living in the unexposed area, the observed number of cancer cases ($n = 42$) was similar to that expected ($n = 41.8$). [The focus on incidence of disease, the large size of the population and the linkage to national data sets are strengths of this study, but the lack of individual exposure data or blood lead concentrations are weaknesses. The presence of multiple contaminants makes etiological assignment difficult.]

In a study in Norway, Kristensen and Andersen (1992) used multistep register linkage to measure cancer incidence in a cohort of children who were the offspring of men who were members of the Oslo printers' unions. A file of these workers' children was established through linkage with the Central Population Register. Children born between 1950 and 1987 ($n = 12\,440$) were traced for cancer incidence during the years 1965–87 in the Cancer Registry of Norway (193 406 person–years). Thirty-three incident cases of cancer were found. To account for the fact that the use of lead in the Oslo printing industry ended in the mid-1970s, an examination of cancer incidence was undertaken in the subcohort of 3221 children born before 1975. In this group, none developed cancer before age 15 (32 532 person–years) compared with 3.7 expected (upper limit of the 95% CI, 100). [The Working Group noted that exposure was uncertain.]

2.3.2 *Case–control studies*

(*a*) *Wilms' tumour*

In a case–control study of Wilms' tumour incidence (Kantor *et al.*, 1979), 149 children born in Connecticut, USA, aged 0–19 years (80 males, 69 females) with Wilms' tumour recorded in the Connecticut Tumor Registry during the period 1935–73 were compared with 149 matched controls selected from Connecticut birth certificates and matched by sex, race and year of birth. The occupation of the father at the time of the child's birth was determined from the birth certificate and used as an indicator of potential sources of exposure to carcinogens. An association was found between paternal occupations related to lead (driver, motor-vehicle mechanic, service-station attendant, welder, solderer, metallurgist and scrap metal worker) in the children with Wilms' tumour compared with the controls. Fathers of 22 cases and of six controls had been employed in lead-related occupations (odds ratio, 3.7; 95% CI, 1.5–11.1). Fathers of five cases and of one control had been employed in jobs with potential exposure to lead (odds ratio, 5.75). [The Working Group noted that no confidence interval was given and that exposure was uncertain.]

In a case–control study conducted by Wilkins and Sinks (1984a,b), an occupation–exposure linkage system was used to examine the possible association between paternal occupation and Wilms' tumour incidence. The study was undertaken in Ohio, USA, and was based on 62 cases with histologically-confirmed tumours, registered through the Columbus

Children's Hospital Tumor Registry between 1950 and 1981. Cases from certain counties in Ohio were excluded from analysis because they fell outside a particular catchment area. Two controls per case were selected from birth certificate files in Ohio and matched on year of birth, sex and race. Job-related exposure of the father was inferred from the occupational and industry notation on the birth certificates, using a job–exposure matrix developed by Hoar *et al.* (1980). The first part of the study was designed to test the hypothesis that paternal exposure to lead is a risk factor for Wilms' tumour in offspring. There was no statistical difference in the frequency of occupational exposure to lead (odds ratio, 1.1; 95% CI, 0.6–2.0), lead alkyls (odds ratio, 1.3; 95% CI, 0.5–3.3) or lead salts (odds ratio, 0.7; 95% CI, 0.1–4.1) between fathers of children with Wilms' tumour and fathers of controls. Occupations associated with exposure to lead were examined by calculating odds ratios, all of which were greater than unity but not statistically significant. For exposure to lead, the odds ratio was 1.25 (95% CI, 0.56–2.70).

Olshan *et al.* (1990) undertook a case–control study in the USA to examine the possible relationship between Wilms' tumour and paternal occupational exposure. Cases consisted of 200 children with Wilms' tumour diagnosed by histopathological examination, who were registered at selected National Wilms' Tumour Study institutions between 1 June 1984 and 31 May 1986. The National Wilms' Tumour Study registers an estimated 84% of all cases of Wilms' tumour diagnosed in the USA. Disease-free controls ($n = 233$) of the same age (± 2 years) and geographic area were matched to each case using a random-digit dialling procedure. To ascertain history of occupational exposure, the parents of cases and controls completed a self-administered questionnaire that provided information on all jobs held for more than 6 months since 18 years of age. Questionnaires were completed by the parents of 234 cases (61% of eligible cases), but only 200 (52% of eligible) were successfully matched with a control. Questionnaires were completed by parents of 233 controls (52% of eligible). Paternal exposures were assessed for three separate time periods in the period between birth and diagnosis: preconception, during pregnancy and postnatal. Exposure was determined by juxtaposition of each occupational exposure history with a job–exposure matrix developed by NIOSH. Specific analyses linking exposure to lead with the incidence of Wilms' tumour gave odds ratios of 1.07 (37 exposed cases/33 exposed controls; 95% CI, 0.58–1.98) for preconception exposure; 1.14 (24/24; 95% CI, 0.56–2.36) for exposure during pregnancy; and 1.31 (21/22; 95% CI, 0.61–2.77) for postnatal exposure.

(*b*) *Other cancer sites*

Buckley *et al.* (1989) conducted a case–control study to examine the incidence of acute non-lymphocytic leukaemia in relation to parental occupational exposures in children in the USA and Canada under 18 years of age. Of 262 eligible cases, mothers of 204 children (78%) were interviewed successfully. Controls were obtained through random-digit dialling and matched on date of birth (± 2 years for children aged more than 4 years and ± 12 months for children aged 1–3 years) and race. Information on occupational exposure was sought through interview with the mother, and exposures were ascertained either by

direct reporting of chemical name or inference from job title. The fathers of five cases and five controls had been exposed to lead between 1 and 1000 days (odds ratio, 1.0; 95% CI, 0.3–3.5); the fathers of six cases and of none of the controls had had exposure to lead for more than 1000 days (p for trend = 0.03). [The Working Group noted that the positive trend with increasing duration is based on a small number of cases and on retrospective ascertainment of exposure without any blood lead data.]

A case–control study conducted during 1976–87 in the USA included all residents of New York State, excluding New York City, diagnosed with neuroblastoma (Kerr *et al*., 2000). A total of 216 cases aged < 15 years and born to Caucasian mothers was ascertained from the NY State Cancer Registry. Controls were sampled from the NY State Department of Health live birth certificate registry and matched on ethnicity of the mother and age. Telephone interviews were conducted with the mothers during 1992–93 with a completion rate of 85% (final number of cases = 183). Interviews gathered information on gestation, drug use and medical history during pregnancy, parents' lifestyle, occupation, and sociodemographic attributes. Using self-reported occupational exposure and a list of industries and occupations with potential for exposure, exposure certainty indexes were coded for each of 25 physical and chemical agents as: category 1, reported exposure and potential for exposure; category 2, no report of exposure but potential for exposure; category 3, report of exposure but no potential for exposure; category 4 (no reported exposure and no potential for exposure) was used as reference. Odds ratios of 4.7 (95% CI, 1.3–18.2) for self-reported maternal exposure to lead (nine cases, four controls) and 2.4 (95% CI, 1.2–4.8) for self-reported paternal exposure (21 cases, 18 controls) were observed. Odds ratios for categories 1, 2 and 3 for maternal exposure were 3.5 (95% CI, 0.7–22.6), 0.8 (95% CI, 0.4–1.8) and 8.3 (95% CI, 0.8–412.1), respectively, and for paternal exposure, 2.2 (95% CI, 0.9–5.4), 1.0 (95% CI, 0.7–1.6) and 3.3 (95% CI, 1.0–11.5), respectively.