2. Studies of Cancer in Humans

2.1 Cohort and nested case–control studies by industry

2.1.1 *Coal gasification* (Table 2.1)

Kennaway and Kennaway (1947) analysed the mortality from cancer of the lung and larynx by occupation in England and Wales in 1921–38 that had been reported earlier (Kennaway & Kennaway, 1936). Data on occupation were obtained from death certificates; the population at risk in each occupation was estimated from national census data, which allowed the calculation of age-adjusted expected numbers of cancers by occupation. [Since different sources were used to obtain occupational titles for the numerator and denominator, this may have caused a bias in the estimated risks.] Among gas works labourers, 96 deaths from lung cancer (standardized mortality ratio [SMR], 1.29; 95% confidence interval [CI], 1.04–1.57) and 43 deaths from laryngeal cancer (SMR, 0.90; 95% CI, 0.65–1.22) occurred; among male gas producers, 12 deaths from lung cancer (SMR, 2.03; 95% CI, 1.05–3.55) and two deaths from laryngeal cancer (SMR, 0.59; 95% CI, 0.07–2.12) occurred. No data on tobacco smoking habits were available.

Bruusgaard (1959) analysed causes of death among current and former employees at a Norwegian gas producing plant over a 15-year period, during which 125 deaths occurred. Of these, 12 were from cancers of the respiratory tract, four of which were lung cancers. Among all cancer deaths, the proportion of cancer of the respiratory tract was higher than that in the general population. [This comparison was made on crude death rates that were not adjusted for the age distribution among the gas workers.]

Kawai *et al*. (1967) reported the findings of a cohort study of all 504 generator gas production workers who were employed at a Japanese steel factory until it was closed down in 1953. Earlier publications from the plant included a report of a series of 12 cases of lung cancer among the generator gas workers during 1931–35 (Kuroda & Kawahata, 1936). Mortality in the cohort was followed prospectively until 1965, up to a maximum age of 55 years. Causes of death were obtained from medical records from the two hospitals that served the area. Expected numbers of deaths were obtained by the person–year method that used mortality in a reference cohort of 25 760 steel workers who had not worked at the generator gas plant. Six cases of lung cancer occurred among the gas workers in comparison with 0.18 expected (SMR, 33.33; [95% CI, 12.20–72.60]). [Only eight deaths from lung cancer occurred in the reference cohort, but the authors stated that the age-specific mortality from lung cancer in the reference group did not differ from that among Japanese men in general. However, the precision of the estimates of the expected numbers of cases among the gas workers was low.]

Table 2.1. Cohort and linkage studies of coal gasification workers

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Kennaway & Kennaway (1947), United Kingdom	Register-based national mortality analysis of all deaths in England and Wales, 1921–38	Occupational titles	Lung	Gas works labourers	96	1.29 [1.04–1.57]	No data available on tobacco smoking
				Gas producers (male)	12	2.03 [1.05–3.55]	
			Larynx	Gas works labourers	43	0.90 [0.65–1.22]	
				Gas producers (male)	2	0.59 [0.07–2.12]	
Kawai *et al*. (1967), Japan	503 workers at a generator gas plant in a steel industry followed from 1953 to 1965; the plant was closed down in 1953.	Occupational titles	Lung	Gas generator plant	6	33.3 [12.2–72.6]	Precision in the estimation of expected numbers was low.
Doll *et al.* (1972), United Kingdom	3023 gas manufacturing workers aged 40–65 years employed at, or in recpt of pension from, four gas boards ('original gas boards') followed for mortality from 1953 to 1965; minimum duration of employment, 5 years	Occupational titles at start of study	Lung	Heavy exp. to coal gas (A)	99	1.79 [1.46–2.18]	Tobacco smoking habits studied in a 10% sample of the cohort indicated no excess. No excess of atheros-clerotic heart disease supports that smoking habits were not excessive among the gas workers.
				Low or no exp. (C1)	11	0.75 [0.37–1.34]	
			Bladder	Heavy exp. to coal gas (A)	10	2.35 [1.13–4.33]	
				Low or no exp. (C1)	1	[0.77 (0.02–4.29)]	
			Skin	Heavy exp. to coal gas (A)	3	6.0 [1.24-17.5]	
				Low or no exp. (C1)	0 (not possible to calculate expected number)	–	
	4687 men from four additional gas boards followed for mortality from 1957 (one gas board from 1959) to 1965		Lung	Heavy exp. to coal gas (A)	23	1.34 [0.85–2.01]	
				Intermittent exp. (B)	40	1.72 [1.23–2.35]	
				Low or no exp. (C2)	16	0.53 [0.30–0.86]	
			Bladder	Heavy exp. to coal gas (A)	2	1.53 [0.19–5.54]	
				Intermittent exp. (B)	2	1.07 [0.13–3.85]	
				Low or no exp. (C2)	1	[0.40 (0.01–2.23)]	

Table 2.1 (Contd)

Hansen *et al.* (1986), Esbjerg, Denmark	47 gas production workers employed >1 year any time between 1911 and 1970.; an age-matched reference cohort of 141 persons selected from population registers		Lung		7	**OR** 3.94 (p <0.05)	No data on tobacco smoking habits available; analytical method may not have been appropriate. A shorter time to death from lung cancer was noted among the gas wokers than among the referent cohort (p = 0.01)
Wu (1988), China	3107 workers active in 1971 at any of six coal gas plants followed for mortality until 1982		Lung		[not stated]	**SRR** (90% CI) 3.66 (2.36–5.43)	The short report does not allow an assessment of the validity of the study.
Gustavsson & Reuterwall (1990), Stockholm, Sweden	295 male blue-collar workers from a gas production plant in Stockholm employed > 1 year between 1965 and 1972; followed for mortality from 1966 to 1986 and for cancer incidence from 1966 to 1983	Department	Lung	Entire cohort	4	1.35 (0.36–3.46)	
				Coke-oven department	0 (0.9 expected)	–	
			Nose and sinuses	Entire cohort	2	29.57 (3.57–106.89)	
Berger & Manz (1992), Hamburg, Germany	4908 male employees from a gas- producing plant, employed >10 years between 1900 and 1989 were followed for mortality from 1953 to 1989	Department	Lung	Gas furnace workers	78	2.88 (2.28–3.59)	Data on tobacco smoking available for about 80% of the cohort; no smoking- adjusted SMR for lung cancer was presented. Causes of death were obtained by different methods for the cohort and the national reference group.
				Other labourers	102	0.96 (0.78–1.17)	
				White-collar workers	12	0.45 (0.23–0.79)	
			Stomach	Gas furnace workers	31	1.77 (1.20–2.51)	
				Other labourers	72	1.13 (0.88–1.42)	
				White-collar workers	10	0.57 (0.27–1.05)	
			Colon and rectum	Gas furnace workers	13	1.84 (0.98–3.15)	
				Other labourers	48	1.70 (1.25–22.5)	
				White-collar workers	7	0.92 (0.37–1.90)	

Table 2.1 (Contd)

Martin *et al.* (2000), France	Case–control study nested within a cohort of male workers employed >1 year at a company producing gas and electricity. 310 lung cancer cases occurring between 1978 and 1989 were included, 1225 referents were selected from the cohort.	Industry-specific job–exposure matrix with index of cumulative exposure	Lung	Coal gas production Unexposed Q1 Q2 Q3 Q4	 298 7 7 7 5	 1.0 1.02 (0.21–4.94) 1.59 (0.39–6.49) 0.55 (0.07–4.57) 3.87 (1.15–12.9)	Risks adjusted for exposure to asbestos and socioeconomic status. There may be residual confounding from tobacco smoking.

CI, confidence interval; exp., exposed; OR, odds ratio; Q, quartile; SMR, standardized mortality ratio; SRR, standardized rate ratio

Doll (1952) and Doll *et al*. (1965, 1972) reported mortality among a cohort of British gas workers that originally comprised 11 499 men employed at, or in receipt of a pension from, four British gas boards (North Western, West Midlands, South Eastern and North Thames) in 1953. Men aged 40–65 years with a minimum duration of employment of 5 years were included. Job titles at the start of employment were used to classify the degree of contact with coal gas: coal carbonizing process workers (heavy exposure, Class A); intermittent exposure in gas-producing plants or process work other than in retort houses (intermittent exposure, Class B); process and maintenance workers in chemical and by-product plants (low exposure, Class C1); or pre-payment meter collectors, credit meter readers and gas fitters (low or no exposure, Class C2). For the final follow-up, the cohort was restricted to 3023 men who were classified into Class A or C1. In addition, employees at four other gas boards were included (South Western, North Eastern, Southern and East Midlands), using similar inclusion criteria and exposure classification processes, and thereby increased the number of men in the cohort by 4687. The original cohort was followed for mortality from 1953 to 1965, and workers from the additional gas boards were followed from 1957 (one gas board from 1959) to 1965. Follow-up was nearly 100% complete, and data were missing for only one individual. Underlying causes of death were obtained from death certificates. Age-standardized death rates were calculated and compared within the cohort as well as with the general death rates for England and Wales. Local death rates were also used for some analyses to take into account geographical differences in cancer rates. In the four original gas boards, there was an increased risk for lung cancer among men who were heavily exposed to coal gas (Class A) [SMR, 1.79; 95% CI, 1.46–2.18]. In Class C (with low or no exposure), there was no excess risk for lung cancer [SMR, 0.75; 95% CI, 0.37–1.34]. Ten deaths from bladder cancer occurred in Class A, which was in excess of the expected number [SMR, 2.35; 95% CI, 1.13–4.33], and only one death in Class C1 versus 1.3 expected. Three deaths from skin cancer were observed in Class A, which indicated an excess risk [SMR, 6.00; 95% CI, 1.24–17.50]. In the four additional gas boards, there was increased mortality from lung cancer among both Class A [SMR, 1.34; 95% CI, 0.85–2.01] and Class B [SMR, 1.72; 95% CI, 1.23–2.35] workers. Thus, the excess was higher among intermittently exposed and not statistically significant among regularly exposed workers. [The authors discussed various explanations for this unexpected finding, the most plausible of which appeared to be random variation.] Only two cases of bladder cancer occurred in Class A and two in Class B, which were within the limits of those expected by chance. An internal analysis based on a matched case–control approach indicated that work as a top man or hydraulic mains attendant, both associated with high exposure to coal gas, was especially associated with an increased risk for lung cancer. Smoking habits were studied in a 10% sample of the cohort from the original four gas boards and indicated no excess among the gas workers (Doll *et al*., 1965). [The Working Group noted that the findings of the analysis of atherosclerotic and degenerative heart disease did not indicate that smoking habits were in excess among the gas workers.]

Hansen *et al*. (1986) studied mortality among 47 gas workers in Esbjerg, Denmark, who had been employed for >1 year at any time during 1911–70. A reference cohort was formed by selecting age-matched referents from the population registers of the Municipality of Esbjerg. Three referents were selected per cohort member (141 persons). Dates of death were obtained from population registers, and causes of death were obtained from death certificates. The mortality of gas workers was compared with that of the reference cohort using a Kaplan-Meier survival analysis. Odds ratios were also calculated. Thirty-three of the gas workers and 78 of the referent cohort had died at the end of follow-up. [The Working Group noted that the analytical methods were not sufficiently described. The end of follow-up was not specified but a maximum survival of 60 years was noted.] Mortality from all causes did not differ between gas workers and the reference cohort. However, mortality from cancer, and especially from lung cancer, was higher among the gas workers than the referent cohort (odds ratio, 3.84; p <0.01; and odds ratio, 3.94; p <0.05, respectively). Restriction of the analysis to those with at least 10 years of employment and allowing for a latency of 10 years gave similar results. No data on tobacco smoking were available.

Wu (1988) reported summary results for a number of occupational epidemiological studies in the People's Republic of China. Mortality in a cohort of 3107 workers from six coal gas plants was compared with that in a cohort of steel workers. [The Working Group noted that an increased risk for lung cancer has been observed among steel workers, which may underestimate the true risk.] Workers employed in 1971 were followed for mortality up to 1981, and 234 deaths occurred among gas workers (standardized rate ratio [SRR], 1.29; 90% CI, 1.16–1.44). The SRR among workers in the gas departments of the coal gas plant was increased (SRR, 3.66; 90% CI, 2.36–5.43). [It is not possible to assess the validity of the study from this short report.]

Gustavsson and Reuterwall (1990) studied mortality and cancer incidence among gas workers employed by the Stockholm Gas Company in Sweden. All men who had been employed for at least 1 year between 1965 and 1972 were followed for mortality from 1966 to 1986 and for cancer incidence from 1966 to 1983. In total, 300 individuals were identified from company records; four had emigrated and one could not be traced, and the analyses were based on the remaining 295 workers. Follow-up was carried out via computerized population registers, underlying causes of death were obtained from death certificates and incident cases of cancer were obtained from the national cancer register. Expected numbers of deaths were calculated from gainfully employed men in Stockholm using the person–year method; expected numbers of cancers were based on national cancer rates. Overall mortality was slightly higher among gas workers than in the reference population (84 deaths; SMR, 1.27; 95% CI, 1.01–1.57). Four incident cases of lung cancer occurred which was close to the expected number (standardized incidence ratio [SIR], 1.35; 95% CI, 0.36–3.46). A significant increase in the incidence of cancer of the nose and nasal sinuses was found (SIR, 29.57; 95% CI, 3.57–106.89). [The Working Group noted that this is a rare tumour, and that the observed increase was based on only two cases.]

Berger and Manz (1992) studied mortality among 4908 male workers at a gas production plant in Hamburg, Germany. All male blue- and white-collar workers who had been employed for >10 years during 1900–89 were included and were followed for mortality from 1952 until 1989. Three exposure groups were formed: 789 gas furnace workers (Group I), 3401 workmen in other parts of the plant (Group II) and 718 white-collar workers (Group III). The average duration of employment was 26.7, 26.1 and 38.0 years, respectively. Causes of death were obtained from autopsy records, medical records from hospital or family doctors and statements from relatives. SMRs were computed using the person–year method and two reference cohorts: the general population of Germany and Group III as an internal comparison. Tobacco smoking habits were obtained from occupational health service registers, colleagues, next of kin and the subjects themselves when alive. Of the initial 4928 men, 20 could not be traced and the analyses were based on the remaining 4908. A total of 2240 cohort members had died at the end of follow-up, which was somewhat below the expected number based on national death rates (SMR, 0.83; 95% CI, 0.80–0.87). Gas furnace workers (Group I) showed a highly increased rate of mortality from lung cancer (SMR, 2.88; 95% CI, 2.28–3.59) and from stomach cancer and cancer of the colon and rectum. Mortality from lung cancer was close to the expected rate in Group II (SMR, 0.96; 95% CI, 0.78–1.17), whereas it was lower than that expected among the white-collar workers (SMR, 0.45; 95% CI, 0.23–0.79). A clear relation with duration of employment was observed for lung cancer but not for stomach or colorectal cancer. [The analysis of mortality in relation to duration of employment was published in a non-peer reviewed report (Manz *et al*., 1983).] The authors recognized the methodological problem raised by the fact that causes of death were obtained using different methods within the cohort, including data from next of kin, and national reference rates. An internal analysis using white-collar workers as a reference cohort addressed this question and showed a higher SMR for lung cancer (SMR, 7.28; 95% CI, 5.79–9.03) than that obtained with external rates. [It is questionable whether white-collar workers constitute a suitable reference group.] The analysis of tobacco smoking habits showed a higher rate of smokers among the gas furnace workers (69.2%) than among other labourers (64.1%) and white-collar workers (48.7%). It should be noted that smoking habits could not be obtained for 18, 16 and 22% of Groups I–III, respectively. [It is improbable that all of the high excess of lung cancer among gas furnace workers could be explained by tobacco smoking.]

Martin *et al.* (2000) reported a case–control study of lung cancer nested within a cohort of all men who had been employed for at least 1 year at a French electricity and gas producing company (EDF–GDF) between January 1978 and December 1989. Cases of lung cancer were identified from the company's cancer registry. Using incidence density sampling, four individually age-matched referents per case were selected from the cohort, which resulted in a total of 310 cases and 1225 referents in the study. Occupational exposure to over 20 agents or exposure situations was assessed by a industry-specific job–exposure matrix. The relative risk for lung cancer was estimated by conditional logistic regression with adjustment for exposure to asbestos and

socioeconomic status, which served as a proxy for tobacco smoking habits. The relative risk for lung cancer was increased among workers in coal gas production (odds ratio, 1.64; 95% CI, 0.80–3.40). An analysis of exposure–response based on an index of cumulative exposure showed a statistically significant excess risk in the highest quartile of exposure (odds ratio, 3.87; 95% CI, 1.15–12.9). [There may be residual confounding from tobacco smoking since socioeconomic status is not a good proxy for tobacco smoking habits. Also, adjustment for socioeconomic status may lead to overmatching and result in underestimation of relative risks.]

2.1.2 *Coke production* (Table 2.2)

In the study by Kennaway and Kennaway (1947) (reported in detail in Section 2.1.1), 85 deaths from lung cancer (SMR, 2.84; [95% CI, 2.27–3.52]) and 37 deaths from laryngeal cancer (SMR, 2.13; [95% CI, 1.50–2.93]) occurred among gas stokers and coke-oven chargers. No data on tobacco smoking habits were available.

Reid and Buck (1956) reported a mortality study of British coke workers, in which deaths among coke plant workers from 1949 to 1954 were identified from the Carbonization Department of the National Coal Board. Causes of death were ascertained either from claims to the trade union's funeral fund that required death certificates, or from the General Registrar's Office. The population at risk was estimated from a census in 1952, which allowed estimation of person–years by job category and age group, and was approximately 8000 persons. Expected numbers of deaths were calculated from death rates obtained from 'a large industrial organization' [It was not stated that the death rates were said to be similar to those of the General Post Office]. During the study period, 14 deaths from respiratory cancer occurred [SMR, 1.40; 95% CI, 0.77–2.35]. A proportionate mortality analysis was performed for retired workers but was uninformative due to the small numbers of deaths. [Insufficient details were given regarding the data sources, the methods used to estimate the population at risk and the reference cohort to assess the validity of the study.]

Sakabe *et al.* (1975) reported mortality among 2178 coke-oven workers in Japan who retired (at age 55 years) between 1947 and 1973 from 11 companies, and who were followed for mortality from 1949 to 1973. Expected numbers of deaths were calculated from the general Japanese male population, with adjustment for age. Overall mortality was not reported. Fifteen deaths from lung cancer were observed in comparison with 11.67 expected [SMR, 1.29; 95% CI, 0.72–2.12]. [The methods for tracing the vital status of the retired workers was not reported.]

Davies (1977) reported mortality among 610 coke production workers who were actively employed in May 1954 at two coke plants located at steel industries in South Wales, United Kingdom, and who were followed for mortality until June 1965. The cohort was identified from personnel registers of the companies that also kept information on job departments. Follow-up was achieved through company records, through mail and National Insurance numbers, and underlying causes of death were obtained from death

Table 2.2. Cohort and record linkage studies of coke production workers

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Kennaway & Kennaway (1947), United Kingdom	Register-based national mortality analysis of all deaths in England and Wales 1921–38	Occupational title	Lung Larynx	Gas stokers & coke-oven chargers	85 37	2.84 [2.27–3.52] 2.13 [1.50–2.93]	
Reid & Buck (1956), United Kingdom	Deaths among coke workers of the National Coal Board from 1949 to 1954 obtained from local or national registers; population at risk estimated from a census.	Job department	Respiratory cancer	Coke-oven workers	14	[1.40 (0.77–2.35)]	The validity of the study design and methods is questionable
Sakabe *et al.* (1975), Japan	2178 coke-oven workers who retired 1947–73 followed for mortality from 1949 to 1973		Lung		15	1.29 [0.72–2.12]	The methods for tracing vital status among the retired workers was not reported

Table 2.2 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Davies (1977), Wales, United Kingdom	601 coke production workers in active employment in 1954 at two plants followed for mortality until 1965	None	Lung		8	[0.82 (0.35–1.62)]	Follow-up period limited
Hurley *et al.* (1983), United Kingdom	6767 male manual workers from 14 BSC works and 13 NSF Ltd works in active employment in 1966–67 followed for mortality until 1979	Oven, part-oven, non-oven work; duration of employment	Lung	Non-oven work Part-oven work Oven work	65 33 66	[0.93 (0.71–1.18)] [1.22 (0.84–1.72)] [0.99 (0.76–1.26)]	The period of follow-up was short
Wu (1988), China	21 995 coke plant workers in the steel industry employed before 1965 followed for mortality from 1971 to 1982	Job department	Lung	Entire cohort Coke oven workers	93 40	[2.55 (2.06–3.13)] [4.97 (3.55–6.77)]	Description of methods insufficient

Table 2.2 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Swaen *et al.* (1991), Netherlands	5659 male workers employed for at least 6 months at any of three plants in 1945–69 followed for mortality up to 1984	Job department (coke plant or by-product plant)	Lung	By-product plant	104	1.0 [0.82–1.21]	
				Coke oven	62	1.29 [0.99–1.65]	
			Bladder	By-product plant	20	1.37 [0.84–2.12]	
				Coke oven	7	0.98 [0.39–2.02]	
			Skin	By-product plant	4	15.5 [0.42–3.97]	
				Coke oven	0	–	
Chau *et al.* (1993), Lorraine, France	536 manual workers who retired from two coke plants between 1963 and 1982 followed for mortality up to 1987	Work area	Lung	*All areas*	25	2.38 [1.54–3.51]	Adjustment for tobacco smoking by an indirect method gave ambiguous results
				Coke ovens	2	1.75 [0.21–6.32]	
				Near ovens	8	2.52 [1.09–4.97]	
				By-product area	2	2.37 [0.29–8.56]	
				Workshops	6	4.33 [1.59–9.42]	
				Unexposed areas	6	2.28 [0.84–4.96]	
Franco *et al.* (1993), Carrara, Italy	538 male production workers employed >1 year in 1960–85 followed for mortality up to 1990		Lung		19	1.70 (1.02–2.65)	

Table 2.2 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Costantino *et al.* (1995); Lloyd & Ciocco (1969); Lloyd *et al.* (1970); Lloyd (1971); Redmond *et al.* (1972); Redmond (1983)	5321 coke-oven workers from 12 plants in the USA and Canada in employment any time in 1951–55 (or for two plants, in 1953) followed for mortality up to 1982	Information on job histories, department, work tasks and occupational hygiene measurements used to calculate the individual cumulative exposure to CTPV	Lung	*Years as coke-oven worker* 0 1–5 5–9 10–15 15–19 >20	 203 39 18 26 47 125	 1 (–) 1.33 (0.92–1.89) 1.37 (0.92–2.51) 1.82 (1.26–2.99) 2.91 (2.27–4.52) 2.71 (1.76–2.85)	The use of other steel workers as a reference cohort may reduce the potential for bias due to tobacco smoking, and the clear exposure–response relationship precludes tobacco smoking as an explanation. Especially high risks were noted among non-whites, who also held the most highly exposed jobs

Table 2.2 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Bye *et al.* (1998), Norway	888 male workers employed >1 year in 1962–88 were followed for mortality and cancer incidence up to 1993.	Individual job histories and personal exposure measurements for PAH	Lung	**Lung**		**SIR**	Lagged results
				Unexposed	7	0.82 (0.33–1.70)	
				Cumulative PAH ($\mu g/m^3 \times y$)	5	0.76 (0.25–1.77)	
				<50	0	0 (1.1 expected)	
				50–149	0	0 (0.5 expected)	
				≥150	2	4.82 (0.58–17.41)	
			Stomach	**Stomach**			
				Unexposed	9	2.22 (1.01–4.21)	
				Cumulative PAH ($\mu g/m^3 \times y$)	6	1.72 (0.63–3.74)	
				<50	1	2.74	
				50–149	1	7.40	
				≥150	1	12.61	

BSC, British Steel Corporation; CI, confidence interval; CTPV, coal-tar pitch volatiles; NSF, National Smokeless Fuels; PAH, polycyclic aromatic hydrocarbon; SIR, standardized incidence ratio; SMR, standardized mortality ratio

certificates. Follow-up was complete for all 610 workers. [The follow-up period was short.] Expected numbers of deaths for the entire follow-up period were computed by the person–year method using death rates for England and Wales in 1958–61. A total of 82 deaths occurred in the cohort [SMR, 0.86; 95% CI, 0.68–1.06], eight of which were from lung cancer [SMR, 0.82; 95% CI, 0.35–1.62].

Hurley *et al*. (1983) reported mortality in two cohorts that together constituted a large part of all British coke workers. One cohort comprised all male manual workers at coke production plants owned by the British Steel Corporation (BSC), who were actively employed for the full period 1 January 1966 to 31 July 1967. The second cohort comprised all male manual workers in coke production plants owned by National Smokeless Fuels Limited (NSF) who were employed on 1 January 1967. Information on work histories, including job departments, was obtained from company registers. In total, 6767 men from 14 BSC and 13 NSF works in England, Scotland and Wales were included and followed up to 1979. Follow-up was achieved through population registers. SMRs were calculated by the person–year method using national death rates to calculate expected numbers of deaths. Surveys of tobacco smoking habits were performed among those employed by the BSC in 1971–73 and by the NSF in 1968 and 1973. Follow-up was completed for all but 159 men (2.3%) who were excluded from the analyses which were performed on the remaining 6608 men. Four hundred and three deaths occurred in the BSC cohort and 734 deaths in the NSF cohort, giving a total of 1137 deaths during the follow-up period; 480.2 and 802.5 deaths were expected, respectively, giving a combined SMR for both cohorts of 0.89 (95% CI, 0.84–0.94); 167 deaths were from lung cancer (SMR, 1.17; 95% CI, 1.00–1.37). A subdivision of the cohort into the categories 'non-oven work' (SMR, 0.93; 95% CI, 0.71–1.18; n=65 deaths), 'part oven work' (SMR, 1.22; 95% CI, 0.84–1.72; n=33 deaths) and 'oven work' (SMR, 0.99; 95% CI, 0.76–1.26; n=66 deaths) showed no evidence of a dose–response pattern. Based on a small subset, no trend in the SMR for lung cancer was observed with duration of employment. [The limited data on tobacco smoking did not permit an assessment of the contribution of smoking habits to the increased risk for lung cancer.]

Wu (1988) reported summary results for a number of occupational epidemiological studies in the People's Republic of China. Mortality in a cohort of 21 995 workers employed before 1965 in 19 coke plants in the metallurgical industry in China was compared with that among workers in a primary rolling mill in the steel industry from 1971 to 1982. Among the coke plant workers, 837 deaths occurred (SMR, 1.33; 95% CI, 1.24–1.42); 93 deaths from lung cancer (SMR, 2.55; 95% CI, 2.06–3.13) occurred in the cohort and 40 occurred among the coke-oven workers (SMR, 4.97; 95% CI, 3.55–6.77). The highest risk was observed in workers on top of the oven. [It is not possible to assess the validity of the study from this short report.]

Swaen *et al*. (1991) reported the findings of a cohort study of 5659 male workers who had been employed for at least 6 months at any of three Dutch coke plants at any time between 1945 and 1969; 5740 workers who had been employed at a fertilizer plant during the same period were used as a reference cohort. Information on job histories was

obtained from company records, and study and reference cohorts were followed for mortality up to 1984, using company registers, registers of retired workers or municipal population registers. Although access to causes of death for individuals in the cohort was denied for reasons of confidentiality, numbers of deaths from different causes were obtained from the Central Bureau of Statistics. Mortality in both the study and reference cohort was compared with that of the general male Dutch population by calculation of SMRs, using the person–year method. Of the 5659 coke plant workers, 1374 had died, 127 had emigrated and four were lost to follow-up. The coke plant workers had worked either at the coke ovens or at the by-product plant. There were 520 deaths among the coke-oven workers (SMR, 1.19; [95% CI, 1.09–1.29]) and 854 among the by-product workers (SMR, 0.97; [95% CI, 0.91–1.04]). Among the coke-oven workers, 62 deaths from lung cancer (SMR, 1.29; 95% CI, 0.99–1.65), seven deaths from bladder cancer (SMR, 0.98; 95% CI, 0.39–2.02) and no deaths from skin cancer occurred. The SMR for lung cancer among the coke by-product workers was 1.00 [95% CI, 0.82–1.21] and that among the fertilizer plant workers was 0.87 [95% CI, 0.71–1.05].

Chau *et al*. (1993) investigated mortality among male manual workers who had retired from two coke plants in Lorraine, France, between 1 January 1963 and 31 December 1982. The 536 workers identified were followed for mortality from retirement until 31 December 1987. A report by Bertrand *et al*. (1987) included follow-up of the same cohort until 1982. Underlying causes of death were sought from medical records from hospitals, occupational physicians and general practitioners. Work histories were obtained from company and occupational health records, as well as from foremen. SMRs were calculated by the person–year method using the French male population to obtain expected numbers. Data on tobacco smoking (ever smoker/nonsmoker) were collected from medical records, next of kin or from the individuals themselves and were obtained for 87% of the cohort. By the end of follow-up, 182 deaths had occurred (SMR, 1.41; 95% CI, 1.21–1.63), of which 25 were from lung cancer (SMR, 2.38; 95% CI, 1.54–3.51). A subdivision by work area showed that two lung cancer cases had worked at the ovens (SMR, 175; 95% CI, 21–632) and eight cases had worked near the ovens (SMR, 2.52; 95% CI, 1.09–4.97). Workshop workers had an SMR of 4.33 (95% CI, 1.59–9.42; six cases), by-product workers had an SMR of 2.37 (95% CI, 0.29–8.56; two cases) and non-exposed workers had an SMR of 2.28 (95% CI, 0.84–4.96; six cases). The authors noted that the Lorraine region had a 40% higher rate of death from lung cancer than the national average, on which the expected numbers were based. [The Working Group noted that an indirect adjustment for tobacco smoking habits gave ambiguous results; the proportion of smokers among coke plant workers (74%) was lower than the national average (80% smokers), but adjustment for tobacco smoking habits reduced the SMR for lung cancer to close to unity. It remains unclear whether the findings were confounded by tobacco smoking.]

Franco *et al.* (1993) investigated mortality among 538 male production workers who had been employed for at least 1 year between January 1960 and December 1985 at a coke plant in Carrara, Italy, which first started to operate in 1943 and was closed down in

1989. The cohort was identified from company records and was followed for mortality from January 1960 to December 1990. Vital status and causes of death were traced via municipal registers. SMRs were calculated according to the person–year method, using national, regional (Tuscany) and provincial (Massa Carrara) mortality rates to calculate the expected numbers. Follow-up was complete for 98.1% of the cohort. At the end of follow-up, 118 persons had died (SMR, 1.04; 95% CI, 0.86–1.25) (using regional reference rates), and 19 deaths from lung cancer occurred (SMR, 1.70; 95% CI, 1.02–2.65) (regional rates). Applying reference rates obtained from the local area (Massa Carrara), the SMR was reduced to 1.47 (95% CI, 0.89–2.30). Work histories were complete only for a subset of the cohort, and it was not possible to investigate SMRs by department in the plant. No data on tobacco smoking habits were available.

A cohort study of over 59 000 steel workers from seven plants in Allegheny County, OH (USA) was first reported by Lloyd and Ciocco (1969) and included all steel workers who were employed in 1953. Subdivision by work area showed a high risk for lung cancer among the 2552 coke-oven workers (Lloyd *et al.*, 1970; Lloyd, 1971). An update and extension of the study that focused on coke plant workers was reported by Redmond *et al*. (1972), and included 1356 workers from the two coking facilities of the original cohort and 4661 coke plant workers (all workers who had been employed any time between 1951 and 1955) in 10 plants in the USA and Canada. A further update was published by Redmond (1983). The most recent report (Costantino *et al*., 1995) covered all coke-oven workers from the original study (two coke-oven facilities) as well as those from the new cohort to give a total cohort of 5321 persons. Work histories and vital status were updated through to 1982. Similar procedures were used for cohort identification and follow-up for both cohorts. Company registers were used to identify individuals and work histories and company and federal registers were used to assess vital status. Underlying causes of death were obtained from death certificates. Follow-up for the original cohort of steel workers (in 1966) was complete for all but 61 workers (0.1%), while 40 of 3305 men (1.2%) were lost to follow-up in the new cohort (Redmond *et al*., 1972). Mortality among coke-oven workers was compared with a reference cohort, individually matched (2:1) with regard to race, age, plant and start of hire, that was selected from among non-oven workers at the steel industries involved. The relative risk for death among coke-oven workers versus the reference cohort was estimated by the Mantel-Haenszel procedure. There were 2291 deaths among coke-oven workers (relative risk, 1.08; 95% CI, 1.02–1.14), of whom 255 had died from lung cancer (relative risk, 1.95; 95% CI, 1.59–2.33). Excess mortality was also noted for prostatic cancer (58 deaths; relative risk, 1.57; 95% CI, 1.09–2.30). The earlier report by Redmond *et al*. (1972) regarding the original Allegheny cohort identified that work on top of the ovens was especially hazardous with regard to risk for lung cancer. The extended study that included follow-up through to 1982 showed a positive association between the risk for lung cancer and number of years as a coke-oven worker. The relative risks for lung cancer in categories of increasing duration of employment as a coke-oven worker are shown in Table 2.2 (p for trend <0.001). An even more pronounced trend was noted for duration of

work in top-side jobs: 1.0 (reference), 1.67 (95% CI, 1.41–2.51), 2.58 (95% CI, 1.75–4.23), 4.25 (95% CI, 2.91–7.14), 4.45 (95% CI, 2.79–7.56) and 4.34 (95% CI, 2.89–6.97) for categories of duration of 0 (reference), 1–5, 5–9, 10–14, 15–19 and >20 years (p for trend <0.001). A positive trend in relative risk was also noted for cumulative exposure to coal-tar pitch volatiles (CTPV). An analysis of mortality from lung cancer in relation to the period of follow-up indicated that the high risks noted among the coke-oven workers were greater in the period up to 1965 and lower, but still significantly elevated, for the periods 1966–75 and 1976–82. The relative risk for lung cancer was higher among non-white coke-oven workers (173 deaths; relative risk, 2.22; 95% CI, 1.70–2.84) than among white coke-oven workers (82 deaths; relative risk, 1.62; 95% CI, 1.20–2.17). Further analysis of risk for prostatic cancer was reported only for all coke oven workers by weighted exposure index and indicated no clear exposure–response pattern (p for trend, 0.11).

An analysis of exposure–response within this cohort was published by Mazumdar *et al.* (1975), using follow-up data up to 1966. Data on hygiene measurements were used to classify jobs with regard to exposure to CTPV, and a personal cumulative exposure of CTPV–years was calculated based on work histories. A positive association between cumulative exposure to CTPV and risk for lung cancer was found for non-white, but not for white, coke-oven workers. Similar findings were made when exposure–response was further investigated by Moolgavkar *et al*. (1998) using follow-up data until 1982 and based on more detailed work histories. There was a positive association between cumulative exposure to CTPV and risk for lung cancer among non-whites, both in the Allegheny and non-Allegheny part of the cohort, while no evident exposure–response relationship was found among the whites. However, the risk for lung cancer was clearly elevated amongst both white and non-white coke-oven workers in general in comparison with the steelworker reference cohort. The life-time unit risk associated with an exposure to 1 $\mu g/m^3$ CTPV was estimated to be 1.5×10^{-4} (95 % CI, 1.2×10^{-4}–1.8×10^{-4}).

Bye *et al.* (1998) followed mortality and cancer incidence among 888 male workers employed for >1 year in a Norwegian coke plant in 1962–88 until 1993. Exposure to polycyclic aromatic hydrocarbons (PAHs) was assessed based on individual job histories and time-weighted average exposures using personal measurements. Vital status, causes of death and cancer diagnoses were obtained from national registries and expected numbers were computed based on national statistics. During follow-up, 122 deaths occurred (SMR, 0.87; 95% CI, 0.72–1.04); overall, an excess risk for stomach cancer was observed (nine cases; SIR, 2.22; 95% CI, 1.01–4.21), but not for lung cancer (seven cases; SIR, 0.82; 95% CI, 0.33–1.70). In dose–response analyses, the highest SIRs for cancers of the lung and stomach were observed in categories of high cumulative exposure, and the test for trend was statistically significant for stomach cancer after taking into account a latency period of 20 years.

2.1.3 *Coal-tar distillation* (Table 2.3)

Relatively few studies distinguish tar distillation workers in particular.

An early study by Henry *et al.* (1931) examined 11 429 male deaths from cancer of the urinary bladder and prostate in relation to last recorded occupation (as given on the death certificate) of 13 965 cases that occurred in England and Wales from 1921 to 1928. Expected numbers of deaths were calculated from death rates for cancers of the urinary bladder and prostate in 5-year age groups and were applied to the population of workers in each 5-year age group according to census occupation tables. Among 2665 tar-distillery workers, four deaths from urinary bladder cancer were observed with 1.2 expected, and one death from prostatic cancer with 1.2 expected. [Different sources were used to obtain occupational titles for the numerator and denominator of the occupational death rates, which may have caused bias in the estimated risks.]

Henry (1946) described a large series of epitheliomatous ulcerations or cancers of the skin that were notified as occupational diseases during 1920–43 in England and Wales. The second largest occupational category cited was tar distillers that comprised 767 cases among a total of 3333 notifications. Of these, 451 were on the head and neck, 195 on the hands and arms and 152 on the scrotum. Mortality rates for scrotal cancer were estimated using deaths over the period 1911–38 and the total working population in the relevant job categories taken from the 1921 and 1931 censuses. Tar-distillery workers showed one of the higher rates, with a mortality rate of 213 per million based on 31 cases, compared with a rate in the general population of 4.2 per million. [The Working Group noted that these rates were not age-adjusted, that there may be better case identification and diagnosis in jobs with known tar exposure and that job classification data differed for the numerator and denominator. However, in view of the 50-fold difference in rates, many of these cases can reasonably be attributed to exposure to coal-tar pitch.]

Schunk (1979) reported on the mortality of 76 male blue-collar tar-distillation workers in Gotha, German Democratic Republic. Between 1962 and 1972, on average 38 were employed on an annual basis and, by 1972, a total of 38 had retired. Eight deaths, including seven deaths from cancer (four from lung cancer and two from stomach cancer), were observed. The duration of employment of the deceased workers varied between 7.9 and 15.5 years. In comparison with workers at a local rubber manufacturing plant or with the national reference population, the mortality from cancer and lung cancer was increased approximately threefold. [The Working Group noted that only crude mortality rates were reported.]

Maclaren and Hurley (1987) followed 259 British tar-distillery workers, who represented all those employed at four tar distillation plants on 1 January 1967, until 1983. Occupational histories were extracted from employment records from date of hire to 1975. All but four were successfully traced through the national health service central register, which left 255 for analysis. Comparisons were made with appropriate regional mortality rates to compute SMRs. Twelve lung cancers were observed (7.5 expected; SMR, 1.60 [95% CI, 0.83–2.79]) and three urinary bladder cancers (0.7 expected; SMR,

Table 2.3. Cohort and record linkage studies of coal-tar distillation workers

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Henry *et al.* (1931), England and Wales	11 429 male deaths from cancer of the urinary bladder and prostate that occurred in 1921–28, among whom 2665 had been tar distillery workers	Last recorded occupation as given by the death certificate	Urinary bladder	Tar-distillery workers	4	[3.33 (0.91–8.53)]	Occupational titles for the numerator and denominator came from different sources.
			Prostate		1	[0.83 (0.02–4.64)]	
Henry (1946), England and Wales	1638 male deaths from scrotal cancer that occurred in 1911–38	Last recorded occupation as given by the death certificate	Scrotal cancer			*Crude mortality rates*	Crude mortality rates for the period 1911–38
				General population	1638	4.2/million	
				Tar-distillery workers	31	213/million	
Maclaren & Hurley (1987), England	259 British tar-distillery workers employed at 4 tar distillation plants on 1 January 1967, followed from 1967 to 1983; 4 lost to follow-up		Lung	Tar-distillery workers	12	1.60 [0.83–2.79]	
			Bladder		3	4.29 [0.88–12.5]	

Table 2.3 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Moulin *et al.* (1988), France	963 men employed on or after 1 January 1970 in a tar distillery and who had worked >1 year followed up to 1984; follow-up 100% complete		Lung Larynx Buccal cavity and pharynx	Tar-distillery workers	5 0 10	0.70 (0.23–1.64) (2.4–3.5 expected) 2.94 (1.41–5.41)	Causes of death were not similarly retrieved for people included in the cohort (contact with treating physicians) and for referent rates (death certificates).
Swaen *et al.* (1991), The Netherlands	5659 male workers employed for at least 6 months at any of three plants in 1945–69 followed for mortality up to 1984	Job department (coke plant or by-product plant)	Lung	Tar-distillery workers	NA	1.54 (not significant)	
Swaen & Slangen (1997), The Netherlands	907 male tar-distillery workers employed >6 months between January 1947 and January 1980, identified from pension records; followed up to 1988; 4.2% lost to follow-up for roofers and tar distillers together	Job histories	Lung Urinary bladder Kidney	Tar-distillery workers	48 2 0	1.18 (0.87–1.57) 0.55 (0.06–2.01) (2.4 expected)	No exposure data were reported.

CI, confidence interval; NA, not available; SMR, standardized mortality ratio

4.29 [95% CI, 0.88–12.5]). The SMRs for lung cancer increased with increasing time since hire (p for trend = 0.25). Nested case–control studies were carried out to investigate associations with specific job categories, but these were reported to be non-significant. [The Working Group noted that numbers were small and that the power to subdivide these small case groups was low.]

Moulin *et al.* (1988) studied the mortality of a cohort of 963 men who had worked for at least 1 year in a tar distillery and who had been employed on or after 1 January 1970. The population was followed up to 1984 by contacting the company, physicians, family and registers from the place of birth. Follow-up was 100% successful. Information was sought from next of kin so that treating physicians could be contacted to establish the cause of death. Proportionate mortality ratios (PMRs) and SMRs were computed using national reference rates; SMRs were also computed using local ('département') rates; and a nested case–control study was carried out. Five deaths from lung cancer occurred and expected rates varied from 10.7 in the PMR analysis to 7.1 and 9.4 in the SMR analyses (SMR relative to national rates, 0.70; 95% CI, 0.23–1.64). There were no cases of laryngeal cancer (2.4–3.5 expected in the various analyses), but a significant excess of cancer of the buccal cavity and pharynx was observed (10 deaths; SMR relative to national rates, 2.94; 95% CI, 1.41–5.41). [The Working Group noted that the method of retrieving cause of death for the cohort may have led to some misclassification of deaths relative to the assignment of cause by death certificate for cause-specific reference rates.]

In a study of the mortality of coke plant workers (described in detail in Section 2.1.2), Swaen *et al.* (1991) reported results for a group of tar-distillery workers. An SMR of 154 was reported for lung cancer among the tar-distillery workers; however, this was stated to be non-significant [no observed or expected numbers were given; p-value not stated].

Swaen and Slangen (1997) reported on a cohort 907 tar-distillery workers who were identified from pension records and met the criterion that they had been employed for at least 6 months between January 1947 and January 1980. Women and workers with foreign nationality were excluded. Subjects were traced through municipal registers, with a no-trace rate of 4.2% (for roofers and tar distillers combined). Follow-up was carried out through to 1988. Expected deaths were calculated using Dutch national death rates. Job histories were available for all tar-distillery workers. Forty-eight deaths from lung cancer occurred (SMR, 1.18; 95% CI, 87–157), two deaths from urinary bladder cancer (3.6 expected; SMR, 0.55; 95% CI, 0.06–2.01) and no death from kidney cancer (2.4 expected).

Letzel and Drexler (1998) described an extended case series of skin tumours among German tar-refinery workers. The occupational health records of 606 workers who had been recorded as having had tar dermatitis between 1946 and 1996 were searched for a mention of tumours; 4754 skin tumours had been identified and surgically removed up to the end of 1996, of which 90% (4280) had histological diagnoses. Most (2456) were keratoses that were classified as precancerous lesions. Among the various histologies, 380 squamous-cell carcinomas, 218 basal-cell carcinomas and 182 keratoacanthomas were reported. Some cases had multiple tumours, and one individual was reported to have

had 88 squamous-cell carcinomas over the period of observation. The 598 squamous-cell and basal-cell carcinomas occurred in 207 persons (34.2% of the total). The authors noted that the ratio of squamous- to basal-cell carcinomas was 1.7:1 in contrast to a ratio of 1:10 in the German population. Most of the tumours occurred in areas that had been in contact with the tar or tar fumes, notably the facial area, forearms and hands. In addition, 20 squamous-cell carcinomas of the scrotum were reported. Latency from first exposure to diagnosis ranged up to 69 years with a median latency of 28 years for squamous-cell carcinoma and 35 years for basal-cell carcinoma. [The size of the population within which these 606 individuals with dermatitis were reported was not given. However, the large proportion of subjects with at least one malignant tumour, the high proportion of squamous-cell carcinomas and the occurrence on exposed areas suggest that occupational exposures at this tar refinery represented a risk factor for these tumours.]

2.1.4 *Roofing and paving* (Table 2.4)

Roofing and flooring, and paving of roads have involved the use of bitumen and coal-tar pitch. Coal-tar pitch has been phased out in most countries and, in some areas, bitumen has been used exclusively because of local availability. Some studies of road pavers and roofers include workers who have been only exposed to coal-tar pitch only or to both bitumen and coal-tar pitch and both are considered here. Other studies which are largely or completely restricted to bitumen exposure are not reviewed here and they will be addressed in a later monograph on bitumen (Maizlish *et al*., 1988; Bender *et al*., 1989; Hansen, 1989a,b, 1991; Watkins *et al*., 2002).

Kennaway and Kennaway (1947) analysed mortality from lung and laryngeal cancer in 1921–38 in England and Wales using the occupation recorded on the death certificate and occupational data from the census to calculate expected deaths by occupation. In the category ‘paviours, street masons, concretors, asphalters’, 26 deaths from lung cancer occurred (SMR, 1.64; [95% CI, 1.07–2.40]) and 13 deaths from laryngeal cancer occurred (SMR, 1.40; [95% CI, 0.75–2.39]). [The Working Group noted that this SMR is vulnerable to some numerator/denominator bias. While the proportion of asphalters in this group was unknown, it was believed that, during those years, coal tar would have been used in asphalting tasks.]

A 12-year mortality study was carried out on 5939 members of a roofers’ union in the USA who were alive in 1960 and who had had at least 9 years of union membership; 5788 were traced through to 1971 (Hammond *et al*., 1976). Employment as a roofer in the USA entails the application of hot pitch or hot bitumen. Coal-tar pitch was used more frequently than bitumen in the past but bitumens are now more commonly used. Most of the men were reported to have worked with both substances. Expected numbers of deaths were computed on the basis of US life-tables specific for age and single calendar year. The SMR for all deaths was 1.03 in the first 6 years of the study and 1.10 in the second 6 years. The SMRs for lung cancer generally increased with increasing time since

Table 2.4. Cohort studies of asphalting and roofing workers

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Kennaway & Kennaway (1947), United Kingdom	Register-based national mortality analysis of all deaths in England and Wales, 1921–38	Occupational titles from death certificates	Lung	Paviours, street masons	26	1.64 [1.07–2.40]	
			Larynx	Concretors, asphalters	13	1.40 [0.75–2.39]	
Hammond *et al.* (1976), USA	5939 members of a roofer's union alive in 1960 with >9 years of union membership, among whom 5788 were followed up to 1971		Lung	*Years since joining the union*			No data on tobacco smoking
				9–19	22	0.92 [0.58–1.39]	
				20–29	66	1.52 [1.17–1.93]	
				30–39	21	1.50 [0.93–2.29]	
				≥40	12	2.47 [1.28–4.32]	
			Oral cavity, larynx and oesophagus	≥20 years since joining the union	31	1.95 [1.32–2.76]	
			Stomach	≥20 years since joining the union	24	1.67 (1.07–2.49)	
			Leukemia	≥20 years since joining the union	13	1.68 (0.89–2.87)	
			Urinary bladder	≥20 years since joining the union	13	1.68 (0.90–28.8)	
			Non-melanoma skin cancer	Entire cohort	5	[4.24] [1.38–9.89]	

Table 2.4 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Menck & Henderson (1976), Los Angeles County, USA	3938 white men who had died from or were carrying a lung cancer selected from the county cancer registry for the periods 1968–70 for mortality and 1972–73 for morbidity data	Last recorded occupation and industry of employment from death certificates for mortality data and hospital records for incident cases	Lung	Roofers	6	4.96 [1.82–10.80]	No data on tobacco smoking
Milham (1982), Washington, USA	Proportionate mortality analysis of deaths among white male residents in the State of Washington during 1950–79		Bronchus and lung Larynx	Roofers and slaters	53 4	**PMR** 1.61 [1.21–2.11] 2.70 [0.74–6.91]	No data on tobacco smoking. It is not known if workers in Washington State were likely to use coal tar in these jobs
Engholm *et al.* (1991), Sweden	704 male roofers employed in 1971–79, followed for mortality until 1985 and cancer incidence until 1984	Job titles obtained from the registries of Bygghälsan	Lung	Roofers Road paving asphalt workers	4 8	**SIR** 3.62 [0.99–9.27] 1.24 [0.54–2.44]	

Table 2.4 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Hrubec *et al.* (1991), USA	Cohort assembled from a roster of approximately 300 000 veterans who served in the US Armed Forces some time between 1917 and 1940 and who held active government life insurance policies	Mailed questionnaire that inquired about occupation, industry of employment and tobacco use	Respiratory system	Roofers and slaters	4	3.00 [1.16–7.73]	Relative risk was adjusted for age, calendar time, smoking group and amount of smoking
Pukkala (1995), Finland	Finnish 1970 Population Census file (which consisted of 98% of the inhabitants as of 31 December 1970 who completed a questionnaire on occupation, family structure, living conditions) was linked to the Finnish Cancer Registry and followed for cancer incidence in 1971–85	Job histories	Lung	Asphalt roofers	18	**SIR** 3.25 (1.92–5.13)	Social class; crude SIR was not modified significantly after adjustment for social class

Table 2.4 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Swaen & Slangen (1997), Netherlands	866 male roofers employed >6 months between January 1947 and January 1980, followed up to 1988 (4.2% lost to follow-up for roofers and tar distillers combined)	Job histories	Lung	Roofers	39	1.31 (0.93–1.80)	No exposure data reported
			Urinary bladder		3	1.15 (0.23–3.37)	
			Larynx		1	1.36 (0.02–7.95)	
Stern *et al.* (2000), USA	Proportionate mortality analysis of 11 370 male deaths identified among unionized roofers and waterproofers; 224 were excluded because of missing death certificate or missing date of entry		Lung			**PMR**	
				Entire cohort	1071	1.39 (1.31–1.48)	
				Decade of first membership in the union:			
				<1935		1.41 (1.08–1.80)	
				1935–44		1.70 (1.49–1.93)	
				1945–54		1.39 (1.26–1.53)	
				1955–64		1.42 (1.24–1.62)	
				1965–74		1.53 (1.26–1.85)	
				≥1975		1.69 (1.16–2.39)	
			Larynx	Entire cohort	46	1.45 (1.06–1.93)	
			Urinary bladder	Entire cohort	89	1.38 (1.11–1.70)	

Table 2.4 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Boffetta *et al.* (2003a,b), European study	Cohorts from road paving companies were assembled in Denmark, Finland, France, Germany, Israel, the Netherlands and Norway. In addition, a Swedish cohort drawn from a national surveillance programme for the building industry was included, which was used as a referent population in internal comparisons. Overall, 79 822 workers were included (1 287 209 person–years)	Information on exposure to coal tar was assembled from the published literature, unpublished industrial hygiene measurements and from questionnaires sent to the participating plants used to reconstruct exposure histories	Lung Head and neck	Coal tar	308 104	1.05 (0.93–1.17) 1.11 (0.91–1.34)	Information on workers' smoking habits was not systematically collected

CI, confidence interval; PMR, proportionate mortality ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio

joining the union: 9–19 years: 22 deaths observed; SMR, 0.92; [95% CI, 0.58–1.39]; 20–29 years: 66 deaths observed; SMR, 1.52; [95% CI, 1.17–1.93]; 30–39 years: 21 deaths observed; SMR, 1.50; [95% CI, 0.93–2.29]; and ≥40 years: 12 deaths observed; SMR, 2.47; [95% CI, 1.28–4.32]. In the group with 20 or more years of membership in the union, increases in SMRs were reported for cancer of the oral cavity, pharynx, larynx and oesophagus (31 deaths observed; SMR, 1.95; [95% CI, 1.32–2.76]), cancer of the stomach (24 deaths observed; SMR, 1.67; [95% CI, 1.07–2.49]), leukaemia (13 deaths observed; SMR, 1.68; [95% CI, 0.89–2.87]) and cancer of the urinary bladder (13 deaths observed; SMR, 1.68; [95% CI, 0.90–28.8]). In the total cohort, five deaths from skin cancer other than melanoma occurred (1.18 expected [SMR, 4.24; 95% CI, 1.38–9.89]). [No data on tobacco smoking were available.]

In a study by Menck and Henderson (1976) of occupational differences in lung cancer rates among white men in Los Angeles County, USA, mortality data for 1968–70 and morbidity data from the county cancer registry for 1972–73 were pooled. The 3938 men under study were classified by their last recorded occupation and the industry in which they were employed. This information was obtained from death certificates for mortality and from hospital records for incident cases. Age-adjusted expected numbers of deaths and incident cases were calculated on the basis of a 2% sample of 1970 census records for Los Angeles County classified by occupation and industry. Among roofers, a significantly increased risk for lung cancer was observed (six deaths observed; SMR, 4.96; [95% CI, 1.82–10.80]). [No data on tobacco smoking were available.]

Milham (1982) conducted a proportionate mortality analysis of deaths among white male residents in the State of Washington during 1950–79. Among roofers and slaters, four deaths from laryngeal cancer (PMR, 2.70; [95% CI, 0.74–6.91]) and 53 deaths from cancer of the bronchus and lung (PMR, 1.61; [95% CI, 1.21–2.11]) occurred. [No data on tobacco smoking were available. It is not known whether workers in Washington State were likely to use coal tar in these jobs.]

Engholm *et al.* (1991) followed 704 roofers and 2572 road-paving asphalt workers who were part of the larger Swedish Bygghälsan cohort (the Swedish Construction Industry's Organization for Working Environment, Safety and Health). These men had had at least one annual medical examination during 1971–79 and were followed for mortality and cancer incidence for an average of 11.5 years. The SIR for lung cancer among roofers and asphalt workers was 3.62 ([95% CI, 0.99–9.27]; four cases) and 1.24 ([95% CI, 0.54–2.44]; eight cases), respectively.

Hrubec *et al.* (1992) reported a smoking-adjusted relative risk of 3.00 ([95% CI, 1.16–7.73]; four cases) for respiratory cancer in a cohort of US veterans who had an occupation as 'roofer and slater'. Follow-up for mortality was conducted from 1954 to 1980.

Pukkala (1995) reported a cancer incidence follow-up study from the Finnish 1970 census (which consisted of 98% of inhabitants as at 31 December 1970 who completed a questionnaire on occupation, family structure, living conditions, etc.). Eighteen lung

cancers occurred among asphalt roofers (unadjusted SIR, 3.50; 95% CI, 2.07–5.53; SIR adjusted for social class, 3.25; 95% CI, 1.92–5.13).

Swaen and Slangen (1997) reported a cohort of 866 roofers who had been employed for at least 6 months between 1947 and 1980 in The Netherlands and who were followed up until 1988. They were identified from pension records and traced through municipal registers; the no-trace rate was 4.2% (for roofers and tar distillers combined). Women and workers of foreign nationality were excluded, and no exposure data were reported. During follow-up, 39 deaths from cancer of the lung (SMR, 1.31; 95% CI, 0.93–1.80), three deaths from urinary bladder cancer (SMR, 1.15; 95% CI, 0.23–3.37) and one death from laryngeal cancer (SMR, 1.36; 95% CI, 0.02–7.95) were observed.

Stern *et al.* (2000) carried out a proportionate mortality analysis of unionized roofers and waterproofers in the USA. A total of 11 370 male deaths were identified. Death certificates could not be retrieved for 72 (0.6%) and date of entry into the union was missing for a further 152; consequently, 11 144 men were available for analysis. PMRs were calculated using race-, age- and calendar year (5-year groups)-specific data for US men. The PMR for lung cancer was 1.39 (95% CI, 1.31–1.48; based on 1071 deaths). PMRs for other sites were: laryngeal cancer, 1.45 (95% CI, 1.06–1.93; based on 46 deaths); and urinary bladder cancer, 1.38 (95% CI, 1.11–1.70; based on 89 deaths). Results were subdivided by decade of first membership in the union (up to 1935, 1935–44, 1945–54, 1955–64, 1965–74 and in 1975 and thereafter). The PMRs for lung cancer were 1.41, 1.70, 1.39, 1.42, 1.53 and 1.69, respectively. [The Working Group noted the absence of a reduction in trend over a time when exposure to coal tar relative to that to bitumen was believed to have a downward trend.]

The largest study of exposure to asphalt/bitumen is a European multicentre cohort study of workers engaged in road paving, asphalt mixing and roofing (Boffetta *et al.*, 2003a,b). Cohorts were assembled in Denmark, Finland, France, Germany, Israel, the Netherlands and Norway from road paving and asphalt mixing companies; a further cohort in Sweden was drawn from a national surveillance programme for the building industry. The study was designed to include workers exposed to bitumen and to minimize the inclusion of those with exposure to coal-tar pitch, although some longer-term workers were exposed to both. The cohort included 29 820 workers employed in paving, roofing, waterproofing and asphalt mixing, 32 245 workers employed in building or ground construction work only and other bitumen-exposed jobs, and 17 757 workers who were not classifiable as bitumen workers. The mean follow-up was for 16.7 years which yielded a total of 1 287 209 person–years of observation. The cohort was also analysed in relation to bitumen, coal tar and other exposures. Exposure histories were developed by assembling information from the literature, unpublished industrial hygiene reports and from questionnaires sent to the participating plants. Exposure to the various agents was classified as ever/never. The expected numbers of deaths used to calculate SMR were computed based on national rates for each country and by Poisson regression for internal comparisons. Of the population, 27.5% was classified as having had some exposure to coal tar (334 509 person–years among those exposed and 861 102 person–years among

those not exposed). Exposure to coal tar was assessed from information on the use of coal tar collected from company questionnaires and from expert judgement. The SMR for head and neck cancer (oral cavity, pharynx and larynx) was 1.11 (95% CI, 0.91–1.34), the SMR for lung cancer for those exposed to coal tar was 1.05 (95% CI, 0.93–1.17; based on 308 cases), while the SMR for those who were not exposed to coal tar was 1.08 (95% CI, 0.98–1.19; based on 431 cases).

2.1.5 *Creosote* (Table 2.5)

O'Donovan (1920) reported three cases of skin cancer in men exposed occupationally to creosote. One of them had been applying creosote to timber for 40 years, and warts had appeared on his hands, legs and behind his ears for 7 years. Additional reports of individual cases have also been published (Cookson, 1924; Shimauchi *et al.*, 2000; Carlsten *et al.*, 2005).

Henry (1946) also calculated crude mortality rates for scrotal cancer for some groups that were considered to be occupationally exposed to creosote. The crude mortality rate for scrotal cancer during 1911–38 for brickmakers exposed to 'creosote oil' was 29 per million men, based on nine verified cases compared with a rate of 4.2 per million for the national average in the United Kingdom and rates of one per million or less for groups not exposed to suspected skin carcinogens. In addition, there were several other creosote-exposed groups who had increased rates based on fewer cases.

Henry (1947) reviewed 3753 (3921 sites) cases of cutaneous epitheliomata reported to the British Medical Inspector of Factories from 1920 to 1945 and reported that 35 cases (39 sites), 12 of which were of the scrotum, had been exposed to creosote. Of these 35 cases, 14 (15 sites) occurred among workers who had treated timber with creosote, nine (11 sites) among people who had handled creosote in storage and 10 (11 sites) among people who had used creosote as a releasing agent for brick moulds.

Axelson and Kling (1983) reported a cohort study of 123 Swedish workers who applied creosote to wood between 1950 and 1980. Fifty of these men were exposed to arsenic in addition to creosote. Among the entire cohort, eight workers died from tumours, whereas 6.0 deaths from tumours were expected from national statistics [SMR, 1.33; 95% CI, 0.58–2.63]. In a subgroup of 21 workers who had been exposed to creosote only for 5 years or longer, three deaths from cancer (leukaemia, pancreas and stomach) were observed compared with 0.8 expected deaths [SMR, 3.75; 95% CI, 0.77–10.96]. [Levels of exposure were not reported.]

Tornqvist *et al.* (1986) conducted a cohort study of 3358 power linesmen and 6703 power station operators in Sweden who were identified in the 1960 census and followed up for cancer incidence between 1961 and 1979. SIRs were calculated in relation to the expected number of cancers for all blue-collar workers in the census. The SIRs for power linesmen showed a deficit for lung cancer (SIR, 0.7; 95% CI, 0.4–1.0; based on 17 cases). Some cancer sites showed non-significant excesses: urinary organs

Table 2.5. Cohort and record linkage studies of creosote workers

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Henry (1946), United Kingdom	Brickmakers in the period 1911–38, considered to be exposed to 'creosote oil' occupationally	Job histories	Scrotum			**Crude mortality rate**	Crude mortality rates, calculated from 1911–38, are approximate as there was no adjustment for age distribution or other confounders
				Brickmakers	9	$29/10^6$	
				General population	1631	$4.2/10^6$	
				Workers not exposed to suspected skin carcinogens	Varies by job title	$\leq 1/10^6$	
Axelson & Kling (1983), Sweden	123 workers who applied creosote to wood followed for mortality between 1950 and 1980	Job histories	Any cancer	Entire cohort	8	[1.33] [0.58–2.63]	Levels of exposure not reported. No adjustment for tobacco smoking
				Workers exposed only to creosote >5 years	3	[3.75] [0.77–10.96]	
Tornqvist *et al.* (1986), Sweden	3358 power linesmen and 6703 power station operators identified in the 1960 Swedish census and followed up for cancer incidence between 1961 and 1979 through linkage to the national cancer registry	Job histories				**SIR (90% CI)**	Stratification for age (5-year groups) and county; findings could be due to chance and there may be other relevant exposures. No adjustment for tobacco smoking. The study population overlaps substantially with that included in Steineck *et al.* (1989)
			Lung	Power linesmen	17	0.7 (0.4–1.0)	
			Urinary organs, excl. kidney		18	1.2 (0.8–1.8)	
			Kidney		15	1.3 (0.8–2.0)	
			Non-melanoma skin cancers		8	1.5 (0.7–2.6)	

Table 2.5 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Steineck *et al.* (1989), Sweden	Swedish 1960 census population was linked to national cancer registry and followed up for cancer incidence between 1961 and 1979	Job–exposure matrix	Urinary bladder	Line workers	48	**RR** 1.35 (1.10–1.79)	Age, socioeconomic group, degree of urbanization; non-differential exposure misclassification was probable therefore may have underestimated the magnitude of association. The authors adjusted for socioeconomic group and degree of urbanization as a proxy for smoking. The study population overlaps substantially with that included in Tornqvist *et al.* (1986)
			Renal pelvis		6	2.13 (0.94–4.80)	
Karlehagen *et al.* (1992), Norway and Sweden	All impregnators exposed to creosote employed >1 year in 1950–75 at 13 plants known to have used creosote regularly followed from 1958 to 1985 in Sweden and from 1953 to 1987 in Norway; 992 workers included in analysis		Lung	Entire cohort	13	**SIR** 0.79 (0.42–1.35)	Authors discussed that a joint effect of sunlight and creosote may be relevant to the excess for non-melanoma skin cancer. Information on individual smoking habits could not be obtained
			Urinary bladder		10	1.11 (0.53–2.04)	
			Non-melanoma skin cancer		9	2.37 (1.08–4.50)	

Table 2.5 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Pukkala (1995), Finland	Finnish 1970 Population Census file (which consisted of 98% of inhabitants as of 31 December, 1970 who completed a questionnaire on occupation, family structure, living conditions) was linked to the Finnish Cancer Registry and followed for cancer incidence in 1971–85	Job histories	Non-melanoma skin cancer	Timber workers	5	**SIR** 4.64 (1.51–10.8)	Social class; crude SIR was not modified significantly after adjustment for social class

Table 2.5 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Martin *et al.* (2000), France	Case–control study nested in a cohort of male workers employed >1 year at a gas and electricity company; 310 lung cancer cases occurring between 1978 and 1989 included, 1225 referents selected from the cohort	An industry-specific job–exposure matrix was used. An index of cumulative exposure was developed and used to categorize study subjects in quartiles	Lung	Exposed to creosote	114	**OR** 1.56 (1.08–2.27)	Socioeconomic status and asbestos exposure; socioeconomic status was used as a proxy for tobacco consumption

Table 2.5 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Wong & Harris (2005), USA	2179 individuals employed at some point between 1 January 1979 and 31 December 1999 in 11 plants in the USA that used creosote to treat wood, followed up to December 2001 for mortality (follow-up 100% complete) Two nested case–control studies of cohort members who died of lung cancer and multiple myeloma. Controls were cohort members who died of other causes and matched to cases by age, plant and gender	Detailed employment histories abstracted from employment records; tobacco use ascertained from fellow workers in the case–control studies	Pancreas Lung Larynx Kidney Multiple myeloma Lung	Hourly-paid employees Routine exposure to creosote-treated products	4 34 2 3 6 38	1.18 (0.32–3.02) 1.34 (0.93–1.87) 1.83 (0.22–6.62) 1.88 (0.39–5.49) 4.0 (1.47–8.73) **OR** 1.45 (0.28–7.51)	Results from the nested case–control studies for the different exposure variables were not significant with wide confidence intervals

CI, confidence interval; excl., excluding; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio

excluding kidney (SIR, 1.2; 95% CI; 0.8–1.8; based on 18 cases), kidney (SIR, 1.3; 95% CI, 0.8–2.0; based on 15 cases) and non-melanoma skin cancer (SIR, 1.5; 95% CI, 0.7–2.6, based on eight cases). As power linesmen are exposed to creosote and other chemicals in addition to electrical and magnetic fields, the authors discussed the possible role of exposure to creosote. [The Working Group noted that the findings could be due to chance and that there may be other relevant exposures.]

Steineck *et al.* (1989) applied a job–exposure matrix to the Swedish 1960 census population, which was linked to the national Swedish Cancer Registry to identify incident cases of urothelial cancer during 1961–79. When subjects classified as having been exposed to creosote were compared with men who had no exposure to any industry-related urothelial carcinogen, there was an increased risk for renal pelvic cancer (relative risk, 2.13; 95% CI; 0.94–4.80, based on six cases) and urinary bladder cancer (relative risk, 1.35; 95% CI; 1.10–1.79, based on 48 cases;). Non-differential exposure misclassification was probable and therefore may have underestimated the magnitude of association. [It should be noted that there is substantial overlap in the study populations of Steineck *et al.* (1989) and Tornqvist *et al.* (1986).]

Karlehagen *et al.* (1992) reported on a follow-up of impregnators exposed to creosote at 13 plants in Norway and Sweden that were known to have used creosote regularly. All those who had been employed for at least 1 year between 1950 and 1975 were included; 34 were excluded because of missing information (mainly loss to follow-up) which left 992 eligible subjects. Cancers were identified through linkage to national cancer registries, with follow-up covering 1958–85 in Sweden and 1953–87 in Norway. In the cohort, 129 cancers occurred (SIR, 0.94; 95% CI, 0.78–1.10), of which 13 were lung cancers (SIR, 0.79; 95% CI, 0.42–1.35), 10 were bladder cancers (SIR, 1.11; 95% CI, 0.53–2.04) and nine were non-melanoma skin cancers (SIR, 2.37; 95% CI, 1.08–4.50). The authors discussed the possibility that a joint effect of sunlight and creosote may be relevant to the excess mortality from non-melanoma skin cancer.

Pukkala (1995) analysed the Finnish cancer registry data during 1971–85 in relation to occupational categories in the 1970 census and found a significant excess of non-melanoma skin cancer among timber workers (SIR, 4.64; 95% CI, 1.51–10.8; based on five cases; adjusted for social class). Heikkilä (2001) commented that these job categories include workers exposed to creosote.

Martin *et al.* (2000) (described in detail in Section 2.1.1) estimated the risk for lung cancer for exposures assessed by a job–exposure matrix in a case–control study nested in the French cohort of gas and electricity workers. For creosotes, the odds ratio was 1.56 (95% CI, 1.08–2.27; based on 50 cases; adjusted for socioeconomic status and exposure to asbestos). [The Working Group noted that the published values of case and control numbers have been transposed in the published paper.]

Wong and Harris (2005) reported a cohort study and nested case–control studies of workers in 11 plants in the USA that used creosote to treat wood, particularly railway ties and utility poles. Individuals employed at some point between 1 January 1979 and 31 December 1999 were included and vital status up to December 2001 was established

from company records and linkage to national death indices. Vital status was established for 100% of the cohort and SMRs were computed on the basis of national rates. In the cohort of 2179 individuals, most (92.2%) were male and most were hourly paid employees (87.2%), whose potential exposure to creosote was much higher than that of salaried employees. For hourly paid employees, the SMR for all causes of death was 0.90 (95% CI, 0.80–1.02) based on 260 deaths; 34 deaths were from lung cancer (SMR, 1.34; 95% CI, 0.93–1.87), two deaths were from laryngeal cancer (SMR, 1.83; 95% CI, 0.22–6.62), three deaths were from kidney cancer (SMR, 1.88; 95% CI, 0.39–5.49), four deaths were from pancreatic cancer (SMR, 1.18; 95% CI, 0.32–3.02) and no deaths from urinary bladder cancer occurred. Furthermore, the SMR for lung cancer did not show a trend with latency. There was a non-significant excess of 'cancer of other lymphopoeitic tissue' (primarily non-Hodgkin lymphoma and multiple myeloma) among hourly paid employees (SMR, 1.79; 95% CI, 0.66–3.90; based on six cases); however, all six cases were multiple myeloma, for which the SMR was somewhat higher (SMR, 4.01; 95% CI, 1.47–8.73).

Two case–control studies nested within this cohort were carried out on lung cancer and multiple myeloma. Up to five deceased controls were selected for each case and matched on plant, 5-year age group and gender. Detailed employment histories were abstracted from employment records and tobacco use was ascertained from fellow workers. Exposure to creosote was investigated by classifying jobs in terms of degree and intermittency of routine exposure to creosote directly or indirectly through handling creosote-treated wood. Results from conditional logistic regression in the nested case–control study of lung cancer found no significant results for variables of exposure to creosote, with non-significant and wide confidence intervals for all odds ratios. Routine exposure to creosote preservatives had an odds ratio of 0.58 (95% CI, 0.11–3.03) for lung cancer cancer while routine exposure to creosote-treated products had an odds ratio of 1.45 (95% CI, 0.28–7.51). The nested case–control study of multiple myeloma involved too few numbers to be informative.

2.1.6 *Aluminium production* (Table 2.6)

Konstantinov and Kuz'minykh (1971) compared cancer mortality rates in two aluminium production plants in the former USSR, one of which used the Söderberg process and the other pre-bake anodes. Expected figures were computed from regional rates. Excesses of all cancers and of lung cancer were reported for the Söderberg-process workers over the 10-year period 1956–66; an increase in the incidence of skin cancer was also reported, particularly in young workers. [No detailed figures were given.]

Konstantinov *et al.* (1974) reported an investigation of mortality from cancer among pot-room workers in three aluminium plants in the former USSR, two of which used the Söderberg process and the other pre-bake anodes. Mortality from cancer in the plants was compared with that of the general population of the cities and provinces in which the aluminium plants were located. Elevated ratios were reported for lung cancer in the two

Table 2.6. Epidemiological studies of aluminium production workers

Reference, location	Study description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Wigle (1977), Québec, Canada	163 350 people from the 1971 Chicoutimi census division of Québec followed for mortality during 1969–73	Aluminium production in the area	Urinary bladder		81	1.59 (1.26–1.97)	Hypothesis that this finding was related to the presence of the aluminium production industry that mainly used the Söderberg process in this area
Thériault *et al.* (1981), Québec, Canada	Case–control study; 81 cases identified in 1970–75 in Chicoutimi district; 81 controls identified in case neighbourhood, matched by age and sex		Urinary bladder			**OR**	Tumours classified on the basis of provincial and hospital records
				Aluminium production workers	25	2.83 (1.06–7.54)	
				Non-smoking aluminium Production workers	NA	1.9 (0.51–7.00)	
				Smoking aluminium Production workers	NA	5.7 (2.00–12.30)	

Table 2.6 (contd)

Reference, location	Study description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Gibbs (1985), Canada	5406 men employed on 1 January 1950 in 2 aluminium production plants that used the Söderberg process followed for mortality from 1950 to 1977	Expert assessment of exposure to condensed pitch volatiles ('tar') by occupation	Lung	**Ever exposed**	101	1.43 [1.16–1.74]	
				Years			
				0	30	1.01 [0.68–1.45]	
				1–10	42	0.97 [0.70–1.31]	
				11–20	27	1.72 [1.13–2.50]	
				≥21	32	2.71 [1.85–3.82]	
			Urinary bladder	**Ever exposed**	12	1.60 [0.83–2.79]	
				Years			
				0	1	0.28 [0.01–1.55]	
				1–10	3	0.61 [0.13–1.79]	
				11–20	3	1.88 [0.39–5.48]	
				≥21	6	6.67 [2.45–14.51]	
			Oesophagus and stomach	**Ever exposed**	50	1.52 [1.13–2.01]	
				Years			
				0	17	1.11 [0.65–1.78]	
				1–10	31	1.42 [0.96–2.01]	
				11–20	10	1.43 [0.69–2.63]	
				≥21	9	2.37 [1.08–4.50]	

Table 2.6 (contd)

Reference, location	Study description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Thériault *et al.* (1984); Armstrong *et al.* (1986), Québec, Canada	Case–control study in different regions of Province of Québec where 5 aluminium plants were operating using the Söderberg process; 488 cases identified through the tumour registry and local hospitals during 1970–79, 85 of whom had been employed in the aluminium industry >12 months; three controls matched on age, year of hire in same plant and length of employment		Urinary bladder			**OR**	Similar results after adjustment for smoking
				Söderberg reactor room workers (≥1 year)	45	2.70 (1.64–4.43)	
				Duration (years)			
				<1	40	1.0	
				1–9	12	1.86	
				10–19	12	3.00	
				20–29	18	3.29	
				≥30	3	4.5	
						p for trend <0.05	
				Benzene-soluble material ($mg/m^3 \times years$)			
				0–9	39	1.0	
				10–19	14	2.75 (1.3–5.7)	
				20–29	15	4.81 (2.2–10.6)	
				≥30	17	6.30 (2.8–14.1)	
				Benzo[a]pyrene ($\mu g/m^3 \times years$)			
				0–99	45	1.0	
				100–199	17	5.86 (2.4–14.3)	
				200–299	13	3.78 (1.7–8.4)	
				≥300	10	5.89 (2.2–15.9)	

Table 2.6 (contd)

Reference, location	Study description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Tremblay *et al.* (1995), Québec, Canada	Case–control study in aluminium plant using the Söderberg process; 138 incident cases identified from Québec tumour registry and records of one regional hospital; 3 controls matched to each case on age, year of hire at plant and duration of employment	Job–exposure matrix based on estimated exposure to benzene-soluble matter and benzo[*a*]pyrene	Urinary bladder	*Benzene-soluble matter (mg/m^3–years)*		**OR**	Smoking
				0–0.9	22	1.0	
				1.0–9.9	32	1.67 (0.89–3.16)	
				10.0–19.9	23	3.93 (1.85–8.49)	
				20.0–29.9	35	7.31 (3.56–14.99)	
				≥30.0	26	5.18 (2.47–10.89)	
				Benzo[a]pyrene ($\mu g/m^3$–years)			
				0–9.9	35	1.0	
				10.0–99.9	29	1.97 (1.10–3.51)	
				100.0–199.9	26	6.24 (3.00–12.97)	
				200.0–299.9	30	6.66 (3.42–12.99)	
				≥300	18	4.36 (2.10–9.17)	

Table 2.6 (contd)

Reference, location	Study description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Armstrong *et al.* (1994), Québec, Canada	Case–cohort study of workers employed >1 year in one plant in 1950–79, followed up 1950–98, ~98% complete; 1138 controls selected from the 16 297 aluminium workers eligible for inclusion	Job–exposure matrix based on estimated exposure to benzene-soluble matter and benzo[*a*]pyrene	Lung	*Benzene-soluble matter (mg/m^3–years)*			
				<1	82	1.00	
				1–9	123	1.15 (0.84–1.59)	
				10–19	54	2.25 (1.50–3.38)	
				20–29	42	1.90 (1.22–2.97)	
				≥30	37	2.08 (1.30–3.33)	
				Benzo[a]pyrene (μg/m^3–years)			
				<10	138	1.00	
				10–99	94	1.48 (1.09–2.00)	
				100–199	41	2.23 (1.46–3.39)	
				200–299	46	2.10 (1.40–3.15)	
				≥300	19	1.87 (1.05–3.33)	
Giovanazzi & D'Andrea (1981), Italy	494 workers in an aluminium production plant using the Söderberg process, during 1965–79 followed up to 1979		Lung	Pot-room workers	4	1.74 [0.47–4.46]	

Table 2.6 (contd)

Reference, location	Study description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Rockette & Arena (1983), USA	21 829 workers with >5 years employment in 14 plants between 1946 and 1977 followed up for mortality to 1977	Job histories and process; pre-bake process (2 plants) and Söderberg process (6 plants)	Lung	*Entire cohort*	272	0.96 [0.85–1.06]	Milham (1979) study included; separate analysis of plant 3 which used the pre-bake and the Söderberg process, but job titles did not allow to distinguish between the different processes; plant 11 excluded from analyses by duration of employment because 16% missing data.
				Pre-bake process	161	1.00 [0.82–1.13]	
				Söderberg process	64	0.87 [0.67–1.11]	
				Plant 3 – carbon department >25years of employment	6	3.66 [1.34–7.96]	
				Carbon departments of other pre-bake plants			
			Urinary bladder	*Entire cohort*	19	0.83 [0.50–1.30]	
				Pre-bake process	19	0.78 [0.46–1.18]	
				Söderberg process	11	0.73 [0.35–1.26]	
				>5 years of employment	8	1.62 [0.69–3.15]	
				All workers	6	2.36 (0.46–2.73)	
				White workers	6	4.08 [1.50–8.88]	
			Lymphatic and haemato-poietic system	*Entire cohort*	94	1.09 [0.86–1.30]	
			Lympho-sarcoma and reticulo-sarcoma	*Entire cohort*	22	1.11 [0.68–1.65]	
				1 plant with employment in potroom or carbon department	NA	3.40 (p <0.05)	
			Pancreas	*Entire cohort*	63	1.25 [0.96–1.60]	
				Men employed >15 years			
				Pre-bake process	12	2.22 [1.15–3.88]	
				Söderberg process	17	2.30 [0.92–4.73]	

Table 2.6 (contd)

Reference, location	Study description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Mur *et al.* (1987), France	6455 workers who worked >1 year in one of 11 plants between 1950 and 1976 followed up for mortality to 1976; follow-up 95% complete, cause of deaths known for 71.3%		Lung	*Entire cohort*	37	1.14 (0.85–1.48)	Tobacco smoking for workers still employed in 1976 similar between work areas and length of employment *Process-specific data available for only 31% of pot-room workers
				Söderberg process	4	1.36 (0.39–3.46)*	
				Pre-bake process	0	0 (0–5.27)*	
			Urinary bladder	*Entire cohort*	7	2.09 (0.96–3.68)	
Moulin *et al.* (2000), France	2133 men employed >1 year in 1950–94 followed for mortality 1968–94. The plant used both Söderberg and pre-bake processes, but only pre-bake process since 1982	Ever employment in pot-room and other departments with PAH exposure	Lung	*Entire cohort*	19	0.63 (0.38–0.98)	Extended follow-up of one of the 11 plants studied by Mur *et al.* (1987). Analyses by time since first or duration of employment did not indicate any trend.
				Workers with probable PAH exposure	15	0.69 (0.39–1.15)	
			Urinary bladder	*Entire cohort*	7	1.77 (0.71–3.64)	
				Workers with probable PAH exposure	6	2.15 (0.79–4.68)	

Table 2.6 (contd)

Reference, location	Study description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Spinelli *et al.* (1991), British Columbia, Canada	4213 men who worked >5 years at a Söderberg plant between 1954 and 1985 followed up from 1959 to 1985	Expert assessment of cumulative exposure to CTPV based on benzene-soluble material	Lung			**SIR**	
				Entire cohort	37	0.97 [0.69–1.34]	
				CTPV (Benzene-soluble matter × years)			
				<1	11	0.72 [0.36–1.29]	
				1–4.9	9	1.02 [0.47–1.94]	
				5–9.9	7	1.14 [0.45–2.33]	
				10–19.9	7	1.24 [0.50–2.58]	
				≥20	3	1.43 [0.29–4.17]	
						p for trend >0.05	
			Urinary bladder	**Entire cohort**	16	1.69 [0.97–2.74]	
				CTPV (Benzene-soluble matter × years)			
				<1	4	1.03 [0.28–2.62]	
				1–4.9	1	0.44 [0.01–2.42]	
				5–9.9	2	1.31 [0.16–4.82]	
				≥10	9	5.0 [2.29–9.49]	
						p for trend <0.01	

Table 2.6 (contd)

Reference, location	Study description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Romunstad *et al.* (2000a), Norway	11 103 men employed >3 years between 1953 and 1996 in 6 aluminium plants in Norway followed up 1953–96	Job–exposure matrix to estimate cumulative exposure to PAH and fluorides	Lung	**Entire cohort**	189	**SIR/rate ratio*** 1.0 (0.9–1.2)	Adjustment for tobacco smoking in 5107 workers (3 of 6 plants) produced similar results.
				Cumulative exposure to PAHs (μg/m³–years)			
				0	93	1.0	
				0–499	38	1.4 (0.9–2.0)	*Lagged 20 years; 'weak association' with exposure to fluorides and bladder cancer, possibly due to some correlation with PAH exposures
				500–1999	30	0.9 (0.6–1.3)	
				≥2000	28	1.0 (0.6–1.5)	
						p for trend >0.5	
			Urinary bladder	**Entire cohort**	130	1.3 (1.1–1.5)	
				Cumulative exposure to PAHs (μg/m³–years)			
				0	52	1.0	
				0–499	20	1.3 (0.8–2.1)	
				500–1999	27	1.3 (0.8–1.9)	
				≥2000	31	1.8 (1.1–2.8)	
						p for trend = 0.02	
Carta *et al.* (2004), Italy	1152 men employed for >1 year between 1972 and 1980 in a pre-bake aluminium smelter and followed up to 2001	Job history and PAH measurements by task and department	Lung		11	0.70 (0.39–1.26)	Increased smoking-adjusted risk for pancreatic cancer and employment in anodes factory (4 exposed deaths)
			Urinary bladder		3	0.79 (0.26–2.44)	
			Pancreas		6	2.41 (1.11–5.23)	
			Lymphomas and leukaemias		8	2.03 (1.03–4.00)	

CI, confidence interval; CTPV, coal-tar pitch volatiles; OR, odds ratio; PAHs, polycyclic aromatic hydrocarbons; PMR, proportionate mortality ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio

plants that used the Söderberg process and for skin cancer in one of the two. [The absence of information on both the study population and the reference population precludes evaluation of these results. It was not possible to establish whether any of the factories included in the study had already been surveyed in the earlier report by the same authors.]

A series of overlapping studies assessed cancer risk related to aluminium production in Québec, Canada. In a letter, Wigle (1977) reported a high incidence of bladder cancer in the Chicoutimi census division of Québec, where aluminium is produced. During the 5-year period 1969–73, in a population of 163 350 (1971), 81 newly diagnosed cases of urinary bladder cancer were recorded; 51 were expected on the basis of incidence rates for the Province of Québec [SMR, 1.59; 95% CI, 1.26–1.97]. The hypothesis that this finding was related to the presence in that area of an aluminium production industry which is mainly based on the Söderberg process was tested in a case–control study (Thériault *et al*., 1981). In the Chicoutimi census division, 96 cases of urinary bladder cancer were diagnosed between 1970 and 1975 and were identified from records of the Province Tumor Registry and the Regional Hospital. The case–control study was carried out on the 81 men in the group, who were matched by age and sex with neighbours as controls. There was no difference between cases and controls with regard to previous urinary tract disease (22:19), alcohol intake (45:46) or coffee drinking (61:60). The tobacco smoking-adjusted odds ratio for urinary bladder cancer for men who worked in the aluminium production plant was 2.83 (25 exposed cases; 95% CI, 1.06–7.54).

The mortality of 5881 men employed in three Canadian aluminium production plants in Québec that used the Söderberg process was examined between 1950 and 1977 and compared with the pertinent rates for the Province of Québec (Gibbs & Horowitz 1979; Simonato, 1981; Gibbs, 1983, 1985). Cohort 1 consisted of all 5406 workers employed on 1 January 1950 at plant A or C, and cohort 2 included all 485 men employed on 1 January 1951 at plant B. In cohort 1, workers ever exposed to condensed pitch volatiles ('tar') exhibited significantly increased mortality from all cancers (SMR, 1.23; [95% CI, 110–138]; 304 observed) and from oesophageal and stomach cancer (SMR, 1.52; [95% CI, 1.13–2.01]; 50 observed), lung cancer (SMR, 1.43; [95% CI, 1.16–1.74]; 101 observed) and other malignancies (60 observed, 45.3 expected). Analysis of mortality from lung cancer by increasing years of exposure, tar–years of exposure and years since first exposure to tar revealed a statistically significant, increasing trend. Deaths from cancer of the urinary organs (20 observed; SMR, 1.46; [95% CI, 0.89–2.25]) and urinary bladder (12 observed, 7.5 expected; SMR, 1.60; [95% CI, 0.83–2.79]) were more numerous than expected. When mortality from cancer at each of these sites was analysed according to tar–years of exposure, significantly increasing trends were noted. For cancers of the oesophagus or stomach; SMRs increased with increasing tar–years of exposure. Among workers classified as never exposed to tar, mortality was not elevated above that expected for any cancer site.

The risk for urinary bladder cancer was further investigated in a population-based case–control study based on 488 male cases of bladder cancer that occurred in 1970–79 in different regions of the Province of Québec where five aluminium plants were operating

using the Söderberg production process (Thériault *et al.*, 1984). The aluminium companies identified 96 of these men as being current or former employees. After exclusion of 11 cases who were employed for less than 12 months; 85 remained. For each case, three controls were selected matched on age, year of hire in the same company and length of work. Of the 85 cases, 73 came from one plant in Arvida. A statistically significant odds ratio of 2.70 (95% CI, 1.64–4.43; 45 exposed cases) was found for employment in Söderberg reactor rooms. The risk increased steadily with length of time worked in this department; odds ratios ranged from 1.86 for those who had worked for 1–9 years up to 4.50 for those who had worked in the department for over 30 years, a trend that was statistically significant. The risk also increased steadily with increasing estimated exposure to 'tar' and PAHs and remained almost unchanged after adjustment for cigarette smoking and length of employment. This set of data was later re-analysed in an attempt to quantify better the noted exposure–response relationship (Armstrong *et al.*, 1986). More refined quantitative estimates of historical workplace exposure and more complete information on tobacco smoking habits were used. Estimates of risk for urinary bladder cancer were statistically significantly related to three exposure indices: years spent in the Söderberg pot-room, cumulative exposure to benzene-soluble material, an indicator of overall exposure to tar volatiles, and cumulative exposure to benzo[*a*]pyrene, an indicator of exposure to PAHs. It was estimated that an aluminium smelter worker who had been exposed to 0.2 mg/m^3 benzene-soluble material for 40 years had a likelihood of developing urinary bladder cancer that was approximately 2.5-fold that of an unexposed person. Workers who had been exposed to 5 μg/m^3 benzo[*a*]pyrene for 40 years had a likelihood of developing urinary bladder cancer that was approximately fivefold that of an unexposed person. Tobacco smoking did not confound the relationship. Tremblay *et al.* (1995) expanded the previous study and included 138 cases of bladder cancer, 66 cases of the previous study, 69 cases diagnosed between 1980 to 1988 and three additional cases diagnosed before 1980. Three matched controls were taken from the previous studies or selected from a subcohort of 1138 men enumerated by Armstrong *et al.* (1994, see below) drawn mainly from the same subcohort. The smoking adjusted odds ratios increased with years of employment in Södberg rooms and with estimated exposure to benzo[*a*]pyrene and benzene-soluble matter.

Mortality from lung cancer up to 1988 was analysed for exposure–response relationships using a case–cohort design (Armstrong *et al.*, 1994) in a population of men who had worked for at least 1 year between 1950 and 1979 at one plant in Québec, Canada. Cases were identified from the Québec tumour registry, from records of the single local hospital and from the study by Gibbs (1985). A total of 338 deaths from lung cancer (including 131 from the previous study) were observed and were compared with a random sample (subcohort) of 1138 men drawn from the 16 297 aluminium workers eligible for inclusion. Exposure to benzo[*a*]pyrene and total PAHs measured as benzene-soluble material was estimated and relative risks by cumulative exposure were computed. The smoking-adjusted relative risks for lung cancer rose with increasing duration of

employment in Söderberg rooms: rate ratios were 1.0, 1.32, 1.37 and 2.00 for <1, 1–9, 10–19 and 20–41 years of employment, respectively.

Giovanazzi and D'Andrea (1981) examined the mortality of 494 workers in a primary aluminium production plant in Trentino, Italy, that mainly used the Söderberg process during the period 1965–79. Among 212 pot-room workers, 40 deaths (2115 person–years) occurred and, among 282 workers in other departments, 13 deaths (3191 person–years) occurred. Expected figures were computed on the basis of national mortality data and municipal data. In pot-room workers, more deaths than expected were observed for all tumours (14 deaths; SMR, 1.75; [95% CI, 0.96–2.94]) and for liver cirrhosis (seven deaths; SMR, 3.89; [95% CI, 1.56–8.01]); a statistically non-significant excess of lung cancer (four deaths; SMR, 1.74; [95% CI, 0.47–4.46]) was also observed.

Milham (1976) noted an elevated PMR in aluminium workers in Washington State, USA, during the period 1950–71 for all neoplasms and for cancer of the pancreas (PMR, 204) and lymphoma (PMR, 250) among pot-room workers. Mortality was subsequently investigated in a cohort of 2103 men who had worked for at least 3 years, and at least for 1 year between 1946 and 1962, at a pre-bake aluminium plant in Washington State (Milham, 1979). The cohort was followed up for 30 years from 1946 to 1976. Expected figures were computed on the basis of national rates. The SMR for respiratory cancer was 1.17 ([95% CI, 0.82–1.63]; 35 cases). An excess was noted for lymphosarcoma and reticulosarcoma (SMR, 3.16; [95% CI, 1.27–6.51]; 17 cases) and for pancreatic cancer (SMR, 1.80; [95% CI, 82–342]; nine cases). The cohort was divided into exposed and unexposed workers: exposure was defined as those incurred in carbon plants, rodding, pot-lining, pot-rooms and quality control; 'unexposed' workers were defined as mechanics, maintenance workers, electrical workers, yard workers, metal product workers, guards, janitors, storeroom workers, south plant workers, exempt workers, welders, carpenters, pipe-shop workers and masons. The SMR for respiratory cancer was 1.29 ([95% CI, 0.74–2.10]; 16 cases) for exposed and 1.09 ([95% CI, 0.66–1.71]; 19 cases) for non-exposed workers. No cases of urinary bladder cancer were observed (1.0 expected in exposed, 1.5 expected in unexposed). The SMR for lymphosarcoma/reticulosarcoma was 6.43 ([95% CI, 2.36–14.0]; six cases) among 'exposed' workers. [There were no data on tobacco smoking.]

Rockette and Arena (1983) reported a cohort of 21 829 workers who had had 5 or more years of employment in 14 aluminium production plants in the USA between 1946 and 1977, and who were followed up to 1977. The plant studied by Milham (1979) was included (plant 11). The earliest date when production started was 1903. Three types of process were used in the plants: pre-bake (seven plants), vertical-stud Söderberg (one plant) and horizontal-stud Söderberg (five plants). In addition to studying overall patterns of mortality for selected causes of death, a more detailed analysis was made for individual processes in relation to years of cumulative employment. SMRs were used to compare cause-specific mortality of the workers with that of the US male population. Data from plant 3 were analysed separately, since all three processes were used in this plant but, in most cases, no indication was given in the job history of the process in which an

employee worked. Overall, the SMR for lung cancer was 0.96 ([95% CI, 0.83–1.06]; 272 deaths;); among workers in plants using the Söderberg process, 64 deaths from lung cancer occurred (SMR, 0.87; [95% CI, 0.67–1.11]); among workers in plants using the pre-bake process, 161 deaths from lung cancer occurred (SMR, 1.0; [95% CI, 0.82–1.13]); and among the remainder, 47 deaths from lung cancer occurred (SMR, 0.99; [95% CI, 0.72–1.30]). Analyses by plant, work area and cumulative duration of employment were carried out and the authors noted that the only significant excess of lung cancer was for plant 3 in the carbon department for workers with ≥25 years of employment (1.64 expected; SMR, 3.66; [95% CI, 1.34–7.96]; six deaths). The excess was concentrated in the pre-bake process which is reported to have one of the highest exposures to CTPV. However, the SMR for lung cancer for the same area in the remainder of the plants was 0.83 [95% CI, 0.50–1.30], based on 19 observed deaths. For men employed in the pot-room or carbon department of the Söderberg plants for 5 or more years, the SMR for urinary bladder cancer was found to be 2.36 (95% CI, 0.46–2.73; six deaths). This excess occurred in whites, for whom the SMR was 4.08 ([95% CI, 1.50–8.88]; six deaths). Among the 94 deaths from haematolymphopoietic cancers, 22 were from lymphosarcoma and reticulosarcoma; 13 of these occurred in plants 1 and 11 (pre-bake) for which the SMRs were 1.77 and 2.82, respectively, but were not statistically significant. For men in plant 11 who had been employed in the pot-room or carbon department, the SMR was 3.40 (p <0.05). The largest SMR in the haematolymphopoietic category was for leukaemia and aleukaemia (1.28 [95% CI, 0.90–1.68]; 43 deaths). For men who had less than 15 years of cumulative employment in the pot-room or carbon department in plants using the Söderberg process, there was a statistically significant excess (SMR, 2.75; [95% CI, 1.32–5.05]; 10 deaths). Although it was not statistically significant, there was a more than 20% excess of stomach cancer in white workers in both the pre-bake and Söderberg processes. Of the 55 deaths observed in the cohort, 22 occurred in plant 1 (pre-bake) (SMR, 1.74; p <0.05). This excess occurred in men with exposure in the pot-room and time since first employment of at least 30 years (SMR, 2.96; p <0.01). Examination of the work histories revealed no common factor that might explain the excess. Men employed for 15 or more years in the pre-bake and horizontal-stud Söderberg process and in plant 3 had an increased risk for pancreatic cancer (SMR, 2.22; p <0.05; 2.71; p <0.05; and 1.68, respectively). Because an estimated 16% of the cohort from plant 11 (pre-bake) was lost to follow-up, it was not included in the analysis that was based on duration of employment. However, an excess of pancreatic cancer was also seen in the pot-rooms in this plant (SMR, 1.97), as noted by Milham (1979) in a different cohort from the same plant.

Mur *et al.* (1987) reported mortality in a cohort of 6455 aluminium smelter workers who had worked for at least 1 year in one of 11 plants in France between 1950 and 1976, during which time they were also followed up for mortality, giving a total of 113 671 person–years. The earliest date of exposure was 1907, and several of the plants used both pre-bake and Söderberg processes. The majority of workers (about two-thirds) had been employed for more than 10 years and one-third for over 20 years. Vital status was

established for about 95% of the cohort by consulting registry offices at cohort members' birthplaces (for French-born workers) and consulates for foreign workers. Cause of death was ascertained by contacting attending physicians or consulting hospital records. Cause was established for only 71.3% of deaths. Cause-specific deaths were 'corrected' by the ratio of the total number to deaths with a known cause. Expected deaths were based on national rates. Confidence intervals were calculated on the basis of these corrected observed deaths, rounded to nearest integer. [The Working Group noted that the use of different sources of cause of death other than death certificates may lead to misclassification. This may be compounded by the method of compensating for missing information on cause of death.] Tobacco smoking habits were surveyed in workers who were still employed in 1976. The overall SMR for all causes was 0.85, based on 996 deaths, with 37 deaths from lung cancer (SMR, 1.14; 95% CI, 0.85–1.48) and seven from urinary bladder cancer (SMR, 2.09; 95% CI, 0.96–3.68).

In one of the French plants, Moulin *et al.* (2000) updated the study of Mur *et al.* (1987) to cover mortality among 2133 male workers who had been employed in the plant for at least 1 year between 1950 and 1994. The cohort was followed up for mortality for an average of 16.5 years from 1968 to 1994, giving a total of 35 145 person–years. Cause of death was obtained by matching with the national file of all causes of death given on French death certificates. Risks for lung and urinary bladder cancer were reported by time since first employment and duration of exposure and were based on comparison with regional rates. Both pre-bake and Söderberg anodes were used in this plant, although only pre-bake had been used since 1982. Overall, 335 deaths occurred (SMR, 0.81), with 19 deaths from lung cancer (SMR, 0.63; 95% CI, 0.38–0.98) and seven from urinary bladder cancer (SMR, 1.77; 95% CI, 0.71–3.64). Among a subset of workers in workshops where exposure to PAHs was judged to be probable, six urinary bladder cancers occurred (SMR, 2.15; 95% CI, 0.79–4.68). Analyses by time since first employment and duration of employment did not indicate any trend.

Spinelli *et al.* (1991) reported morbidity risks for both lung and urinary bladder cancer by cumulative exposure to CTPV (measured as benzene-soluble material) in a cohort of 4213 men who had worked for at least 5 years at a Söderberg aluminium plant in British Columbia, Canada, between 1954 and 1985. A total of 60 590 person–years were observed, with 2.9% accounted for by 204 men with more than 20 benzene-soluble material–years of exposure. Risks were compared with regional rates, with a 3-year lag period and follow-up from 1959 to 1985 for mortality and from 1970 to 1985 for cancer incidence. Overall, the SMR for all causes was 0.77 (based on 337 deaths), with 32 deaths from lung cancer (SMR, 0.93; [95% CI, 0.64–1.31]) and 37 incident cases (SIR, 0.97; [95% CI, 0.69–1.34]). For bladder cancer, three deaths (SMR, 1.37; [95% CI, 0.28–4.00]) and 16 incident cases (SIR, 1.69; [95% CI, 0.97–2.74]) occurred. There was a significant increasing trend in the incidence of urinary bladder cancer with cumulative exposure to CTPV ($p < 0.01$), and the SIR rose to 5.0 based on nine cases with ≥10 benzene-soluble material–years of exposure. No significant trend was observed for lung cancer, although there was some suggestion of an increase with increasing cumulative exposure; the

highest SMRs of 1.24 (seven cases) and 1.43 (three cases) were found for the highest categories of 10–19.9 and ≥ 20 benzene-soluble material–years. When a lag of 10 years was applied, the corresponding SIRs were 1.53 (seven cases) and 2.23 (two cases). This study was updated and results were available as an abstract (Friesen *et al.*, 2005). Among 6444 men employed at least 3 years between 1954 and 2000, patterns of the incidence of lung cancer and urinary bladder cancer were reported to be more consistently, monotonically increased with cumulative exposure than in the earlier reports, with a significant trend for both cancer outcomes with or without a 20-year lag. There was a twofold risk for lung and bladder in the highest versus lowest category of exposure expressed as CTPV or benzo[*a*]pyrene.

Romundstad *et al.* (2000a) updated the results from previous cohort studies of workers in six aluminium plants in Norway (Andersen *et al.*, 1982; Rønneberg & Andersen, 1995; Rønneberg *et al.*, 1999; Romundstad *et al.*, 2000b,c). Cancer incidence was investigated among 11 103 men who had been employed for more than 3 years between 1953 and 1996, during which time they were also followed up to provide 272 554 person–years. The earliest date at which the plants started production was 1914. A job–exposure matrix was constructed to estimate cumulative exposure to PAHs and fluorides. Information on smoking habits was available for 5107 workers from three of the six plants. No increase in the risk for lung cancer was observed (SIR, 1.0; 95% CI, 0.9–1.2; 189 cases) though an increased risk for bladder cancer was observed (SIR, 1.3; 95% CI, 1.1–1.5; 130 cases). Poisson regression analysis in relation to estimated cumulative exposure to PAHs showed evidence of an increasing trend for cancer of the urinary bladder but not of the lung. The rate ratio for bladder cancer increased with increasing dose (1.0, 1.3, 1.3 and 1.6; p for trend = 0.05) and with 30 years of latency (1.0, 1.0, 1.3 and 2.0; p for trend = 0.03). Results were similar after adjustment for smoking. Further analyses were conducted using a cumulative fluoride measurement and only a 'weak association' with urinary bladder cancer was reported for lag times of <20 years, possibly due to some correlation with exposures to PAHs. [Fluoride has been shown to be associated with urinary bladder cancer in a Danish cryolite mill (Grandjean & Olsen, 2004); however, the evidence for a higher risk in pot-room areas where exposure to PAHs but not necessarily to fluoride is higher points to PAHs as the causal factor rather than fluoride.] Positive exposure–response associations were also reported for cumulative exposure to PAHs and pancreatic and kidney cancer.

Carta *et al.* (2004) followed mortality from cancer up to 2001 in a population of 1152 men who had been employed at a pre-bake aluminium smelter in Sardinia, Italy, for at least 1 year between 1972 and 1980. Results were presented for various sites including the lung (SMR, 0.70; 95% CI, 0.39–1.26; 11 deaths), urinary bladder (SMR, 0.79; 95% CI, 0.26–2.44; three deaths), lymphoma and leukaemia (SMR, 2.03; 95% CI, 1.03–4.00; eight deaths) and pancreas (SMR, 2.41; 95% CI, 1.11–5.23; six deaths). Analyses by increasing rank of exposure to PAHs showed an increasing trend only for pancreatic cancer among these four sites. In a small nested case–control study, employment in the

anodes factory was associated with an increased risk for pancreatic cancer (four exposed cases) after adjustment for smoking.

2.1.7 *Carbon electrode manufacture* (Table 2.7)

Teta *et al*. (1987) reported the findings of a mortality surveillance system at the carbon product department of the Union Carbide Corporation; 2219 white men who were employed at the beginning of 1974 and who had a prior service of ≥10 years were followed for mortality from 1974 to 1983; six of these men were lost to follow up. To assess the potential impact of differences in socioeconomic status and job exposures on the healthy worker effect, three exposure groups were formed based on job tasks: supervisory, office and research (A), crafts (B) and operations, labour and service (C). Vital status was ascertained annually from payroll registers, the company's benefits department and from the Social Security Administration. Underlying causes of deaths were obtained from death certificates. SMRs were calculated according to the person–year method, using death rates among US white men to calculate the expected numbers. In all, 223 of the cohort members had died at the end of follow-up (SMR, 0.67; 95% CI, 0.55–0.72). The number of deaths was small for all types of cancer (SMR, 0.93; 95% CI, 0.74–1.17; 78 deaths) and for respiratory cancer (SMR, 0.85; 95% CI, 0.57–1.21; 29 deaths). An internal analysis of mortality by job category showed that mortality from respiratory cancer was lowest among the low-exposed workers (group A; three deaths; 40% of the average risk in the cohort), highest among the craftsmen (group B; six deaths; 1.3 times the average risk in the entire group) and intermediate among labourers (group C; 20 deaths, 1.2 times the average risk); SMRs were not calculated. There was a non-significant trend of increasing mortality with increasing time since entry into employment. High mortality from respiratory cancer was noted in a particular location (SMR, 3.36; significant at the 5% level; five deaths) where asbestos had been used and where use of coal-tar pitch had been abandoned in 1928. [The Working Group noted a strong healthy worker effect in the cohort.] These five men who had died from respiratory cancers had smoked cigarettes, had been hired after 1934 and had worked at that location for at least 25 years; however, these data are insufficient to confirm that exposure to asbestos and tobacco were involved in the etiology of their death.

Moulin *et al*. (1989) reported the findings of an epidemiological study of two carbon electrode manufacturing plants in France. In plant A (which produced graphite electrodes), all male workers employed at the beginning of 1975 were followed for cancer incidence in 1975–85. In plant B, all workers employed at the beginning of 1957 were followed for mortality in 1957–84. Cohort definitions and outcome (mortality or incidence) were chosen depending on the availability of data. Causes of death were obtained from attending physicians. SIRs for plant A were computed by the person–year method. Local cancer rates were not available, and cancer rates for the population from an adjacent district were used, after verification that cancer mortality did not differ substantially between the two districts. SMRs for plant B were computed using national

Table 2.7. Cohort studies of carbon electrode manufacturing workers

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Teta *et al.* (1987), USA	2213 white men employed at a carbon product department in 1974 and who had a prior service of at least 10 years followed for mortality from 1974 to 1983	Job task (three groups) and job location (11 locations)	Respiratory system	Entire cohort	29	0.85 (0.57–1.21)	Strong healthy worker effect expected with current study design; no data on tobacco smoking
Moulin *et al.* (1989), France	Two carbon electrode plants: plant A: 1302 male workers in employment on 1 January 1975 followed for cancer incidence 1975–85; plant B: 1115 workers in employment on 1 January 1957 followed for mortality 1957–84	Contact with PAH (yes/no) based on job tasks				**SIR**	Stratification by job type and age at hire; an internal analysis taking exposure status and tobacco smoking into account gave low numbers, wide CI and was uninformative
			Lung	Plant A	7	0.79 (0.32–1.63)	
			Urinary bladder		0	0 (0–1.92)	
			Kidney	Plant B	2	1.71 (0.21–6.17)	
			Lung		13	1.18 (0.63–2.01)	
			Urinary bladder		3	1.94 (0.40–5.66)	
			Kidney		0	Not calculated	

Table 2.7 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Gustavsson *et al.* (1995), Sweden	901 blue- and white-collar workers from a graphite electrode manufacturing plant employed >3 months from 1968 to 1988 followed for mortality 1969–89 and for cancer incidence 1969–88	Cumulative exposure to BaP ($\mu g/m^3$ BaP × years) calculated from job histories and hygiene investigations; tobacco smoking habits investigated by means of a questionnaire given to workers employed in 1990	Lung Larynx	Entire cohort	2 deaths 2 cases 2 cases	1.68 (0.20–6.07) **SIR** 1.80 (0.22–6.51) 10 (0.25–55.64)	Local death and cancer rates were used. Survey of smoking habits indicated lower level of smoking than in the general population in the area
Liu *et al.* (1997), China	6635 male carbon electrode workers from six carbon electrode manufacturing companies and one aluminum smelter employed for more than 15 years since January 1971 followed for mortality up to 1985	Degree of contact with carbon compounds was coded from occupational histories and smoking habits were obtained from a questionnaire	Lung	**Entire cohort** *Contact with carbon compounds* None Low Moderate High	50 13 6 5 26	2.16 [1.61–2.85] 1.49 [0.79–2.54] 1.20 [0.44–2.60] 1.52 [0.49–3.54] 4.30 [2.81–6.30]	This study included some aluminium reduction plant workers in addition to carbon electrode manufacturing workers

Table 2.7 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Donato *et al.* (2000), Umbria, Italy	1006 male graphite electrode manufacturing workers employed ≥1 year in 1945–71 followed for mortality in 1955–96	Duration of employment was used as a proxy for cumulative PAH exposure	Lung Larynx Urinary bladder Skin		34 4 7 3	0.77 (0.53–1.08) 0.79 (0.21–2.02) 2.29 (0.47–6.69) 1.04 (0.42–2.14)	Local death rates showed slightly higher SMRs. Detailed data on job titles and smoking habits were not available. Smoking survey in subgroup indicated a somewhat lower proportion of smokers in the cohort than in the population in central Italy.
Mori (2002), Japan	332 male blue-collar workers employed for ≥5 years in 1951–74 at a Japanese graphite electrode manufacturing plant were followed for mortality in 1951–88.	Department and duration of employment	Lung Multiple myeloma	Entire cohort	9 2	2.62 (1.20–4.98) 13.4 (1.62–48.3)	Analysis by time period, department, time since first exposure or duration of employment gave no further information.

Table 2.7 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Merlo *et al.* (2004), Brescia, Italy	1291 male blue-collar workers employed ≥1 year at a graphite electrode plant in 1950–89 and followed for mortality in 1950–97	Duration of employment	Lung		32	0.97 (0.67–1.37)	Very large number of deaths from silicosis was found (79 observed versus 1.19 expected). Information on smoking and drinking habits was not available
			Urinary bladder		5	1.08 (0.35–2.53)	
			Larynx		5	1.32 (0.43–3.07)	
			Lip, mouth, pharynx		8	2.10 (0.91–4.14)	
			Oesophagus		5	2.19 (0.80–4.77)	
			Liver		24	4.19 (2.68–6.23)	
			Lung	1–10 years	2	2.37 (0.29–8.57)	
				10–19 years	5	1.35 (0.44–3.14)	
				>19 years	25	0.88 (0.57–1.3)	

BaP, benzo[*a*]pyrene; CI, confidence interval; PAH, polycyclic aromatic hydrocarbon; SIR, standardized incidence ratio; SMR, standardized mortality ratio

mortality rates, stratified by cause, sex, 5-year groups and calender year. In plant A, 1302 workers were identified and 11.8% were lost to follow-up. In plant, B 1115 workers were identified and 13.5% were lost to follow-up. Those lost to follow-up were assumed to be alive. [The Working Group noted that this procedure would lead to an underestimation of the risk.] Tobacco smoking habits for plant A were obtained from the personnel office. In plant A, 38 cases of cancer were observed during follow-up (SIR, 0.87; 95% CI, 0.61–1.19), seven cases of lung cancer (SIR, 0.79; 95% CI, 0.32–1.63), no case of urinary bladder cancer and two cases of kidney cancer occurred (ICD-8 189; SIR, 1.71; 95% CI, 0.21–6.17). In plant B, 164 deaths were observed (SMR, 0.82; 95% CI, 0.70–0.96); 13 deaths from lung cancer (SMR, 1.18; 95% CI, 0.63–2.01) and three deaths from urinary bladder cancer (SMR, 1.94; 95% CI, 0.40–5.66) occurred, but none from kidney cancer. Nested case–control studies of lung cancer and cancer of the pharynx, larynx and buccal cavity were performed for both plants in relation to occupational exposure to PAHs; however, the numbers of cases were too small and the confidence intervals were too wide to allow for meaningful interpretation.

Gustavsson *et al*. (1995) reported the mortality from and incidence of cancer among 901 employees at a Swedish graphite electrode manufacturing company. The plant started operations in 1968 and was closed down in 1990. All employees who had been employed for at least 3 months between 1968 and 1988 were included in the study, regardless of age, gender or work task; 914 individuals were identified, but 13 could not be traced so the analysis was based on the remaining 901. Follow-up was carried out via national population registers: underlying causes of death were obtained from death certificates and cancer incidence was obtained from the national cancer registry. The cohort was followed from 1969 to 1989 for mortality and from 1969 to 1988 for cancer incidence. SMRs and SIRs were calculated by the person–year method, using national death and cancer incidence rates (standardized for age, gender, calendar time and county) to calculate the expected numbers. Aggregate personal historical exposure to benzo[*a*]pyrene was calculated from assessments of job-specific exposure, based on current and previous hygiene measurements and personal work histories obtained from company records. The number of benzo[*a*]pyrene–years ($\mu g/m^3$ benzo[*a*]pyrene × years) was computed by multiplying the task-specific level of benzo[*a*]pyrene and the duration of exposure, aggregated over the entire work history. At the end of follow-up, 15% of the cohort members had no exposure to benzo[*a*]pyrene, 48% had >0–5 benzo[*a*]pyrene–years, 15% had 5–10 benzo[*a*]pyrene–years and 22% had >10 benzo[*a*]pyrene–years of exposure. Tobacco smoking habits were investigated by means of a questionnaire given to workers who were employed in 1990. Forty-two deaths occurred in the cohort (SMR, 1.30; 95% CI, 0.94–1.76), and 14 incident cases of cancer were observed (SIR, 1.13; 95% CI, 0.62–1.90). Two cases of lung cancer (SIR, 1.80; 95% CI, 0.22–6.51) and one case of laryngeal cancer (SIR, 10; 95% CI, 25–55.64) were observed. The investigation of tobacco smoking habits among those in employment in 1990 showed that graphite electrode manufacturing workers smoked slightly less than the general population in the same region.

Liu *et al.* (1997) reported the mortality among 6635 male workers from various carbon plants in the People's Republic of China. The cohort included workers from six carbon plants that mainly manufactured carbon electrodes and a carbon department and pot-room in an aluminium reduction plant. All workers who had been employed for more than 15 years since January 1971 were followed for mortality up to 1985. Information on occupational history and tobacco smoking habits were obtained from a questionnaire that was completed by the individuals themselves or by next-of-kin for deceased subjects. SMRs were calculated by the person–year method, using the mortality in a cohort of 11 470 Chinese steel workers to calculate the expected numbers of deaths. The level of exposure to 'carbon compounds' was coded from the occupational title of the job in which the employees had worked the longest. In the cohort, 390 deaths occurred (SMR, 1.10; [95% CI, 1.00–1.22]) and 50 persons had died from lung cancer (SMR, 2.16; [95% CI, 1.61–2.85]). There was a positive trend in SMR with increasing contact with carbon compounds (see Table 2.7). An elevated risk for lung cancer remained in the exposed and highly exposed workers when the study was limited to nonsmokers. [The Working Group noted that this study included an unspecified number of aluminum reduction plant workers in addition to carbon electrode manufacturing workers.]

Donato *et al*. (2000) studied the mortality of workers at a plant manufacturing carbon (graphite) electrodes in Umbria, Italy, that had started to operate in 1901. A cohort of 1006 male workers who had been employed for ≥ 1 year in 1945–71 was identified from company registers and followed up for mortality in 1955–96. Vital status was assessed from municipal registers, and 44 (4.4%) of the cohort members were lost to follow-up. SMRs were calculated by the person–year method, using both national and local death rates to compute expected numbers. Poisson regression was used to study the effect of duration of employment and time since first exposure. During follow-up, 424 deaths occurred, giving an SMR of 0.85 (95% CI, 0.77–0.93), and 125 deaths from cancer gave an SMR of 0.84 (95% CI, 0.70–1.00). Thirty-four deaths were from lung cancer (SMR, 0.77; 95% CI, 0.53–1.08), four deaths were from laryngeal cancer (SMR, 0.79; 95% CI, 0.21–2.02), three deaths were from skin cancer (including melanoma) (SMR, 2.29; 95% CI, 0.47–6.69) and seven deaths were from urinary bladder cancer (SMR, 1.04; 95% CI, 0.42–2.14); SMRs were based on national death rates because the Umbria region has slightly lower death rates than Italy as a whole. However, use of the regional reference rates did not change the results substantially. Analysis by duration of employment showed no trend for lung cancer or urinary bladder cancer, but an increased risk for gastric cancer was observed among those who had been employed for >20 years compared with those who had been employed for 1–9 years (based on seven deaths; relative risk, 7.06; 95% CI, 1.27–39.3; *p* value for trend, 0.03). Analysis by time since first exposure showed a positive trend for mortality from all causes and cancer of the lung (10–19 years since first employment: relative risk, 1.38; 95% CI, 0.39–4.80; >20 years since first employment: relative risk, 2.06; 95% CI, 0.49–8.72).

Mori (2002) reported the findings of a cohort mortality study at a graphite electrode manufacturing plant in Japan, which had started to operate in 1934 and was relocated in

1974. All male workers who had been employed for ≥5 years from 1951 to 1974 in the manufacturing, transportation and maintenance divisions of the plant were identified from its labour union registers; 336 workers were identified and four were excluded due to incomplete identification data; 21 of the remaining 332 were lost to follow-up but were assumed to be alive at the end follow-up. The cohort was followed for mortality from 1951 to 1988 via population registers. Underlying causes of death were obtained from death certificates, the attending physician, the families of the deceased or from the municipal cancer register. SMRs were calculated by the person–year method, using Japanese national death rates as well as approximate local rates to compute expected numbers. During follow-up, 52 deaths occurred in the cohort (SMR, 0.68; 95% CI, 0.51–0.89), 22 of which were from cancer (SMR, 1.01; 95% CI, 0.63–1.53) and nine from lung cancer (SMR, 2.62; 95% CI, 1.20–4.98). Analyses by department, time period, time since first exposure and duration of employment gave little additional information due to the small number of workers in these subgroups. A survey of smoking habits in a subset of the cohort, based on 65 skilled workers, was reported. [However, the Working Group questioned the representativity of this survey and noted the possibility that incomplete ascertainment of individuals in the cohort for the early years may have contributed to the low overall SMR.]

Merlo *et al*. (2004) investigated mortality among 1291 male workers at a graphite electrode manufacturing plant in Brescia, Italy, which had started to operate in 1929 and was closed down in 1994. All male blue-collar workers who had been employed for >1 year from 1950 to 1989 were identified from company registers and followed up for mortality in the period 1950–97 through municipal and local health unit registers. SMRs were calculated by the person–year method. Expected numbers were calculated from national death rates, supplemented by analyses based on local death rates for selected causes which were only available for 1970–97. At the end of follow-up, 747 (57.9%) members of the cohort were still alive, 541 (41.9%) had died and three (0.2%) people were lost to follow-up. The 541 deaths gave an SMR for all causes of 1.44 (95% CI, 1.32–1.56); 141 of the deaths were from cancer (SMR, 1.27; 95% CI, 1.07–1.50). There was a marked excess of cancers of the liver (24 deaths; SMR, 4.19; 95% CI, 2.68–6.23). It was noted that numbers of observed deaths were greater than those expected for cancers of the lip, mouth and pharynx as well as oesophagus, but SMRs for these sites were not significantly increased. Thirty-two deaths from lung cancer gave an SMR of 0.97 (95% CI, 0.67–1.37). Five deaths were from urinary bladder cancer (SMR, 1.08; 95% CI, 0.35–2.53) and five were from laryngeal cancer (SMR, 1.32; 95% CI, 0.43–3.07). A very large number of deaths from silicosis occurred (79 observed versus 1.19 expected; SMR, 66.39; 95% CI, 52.56–82.74). Silicosis was mentioned as a contributing cause of death on another 21 death certificates. The use of local death rates to calculate expected numbers generally produced lower SMRs, but these were still significantly elevated for mortality from all causes and from liver cancer. No clear exposure–response pattern was observed for lung cancer. [The Working Group noted that several potential causes of liver cancer, including viral infections (the rates of which are known to be high in the area),

alcohol consumption and other occupational exposures may have contributed to the excess mortality from liver cancer.]

2.1.8 *Calcium carbide production*

Kjuus *et al.* (1986) reported on the incidence of cancer in a cohort of 790 male Norwegian calcium carbide production workers. All workers who had been employed for at least 18 months between 1953 and 1970 were followed for cancer incidence and mortality until 1983. SMRs and SIRs were calculated by the person–year method and expected numbers were calculated from national statistics. Söderberg electrodes were used in the plant, but PAHs were not considered to be a main occupational hazard by the authors. The workers were exposed to calcium carbide and asbestos among other substances. In the cohort, 234 deaths occurred (SMR, 0.93; 95% CI, 0.81–1.06). Excesses of prostatic cancer (25 cases; SIR, 1.78; 95% CI, 1.16-2.63) and colon cancer (12 cases; SIR, 2.09; 95% CI, 1.08–3.66) were observed and 10 lung cancers occurred (SIR, 1.15; 95% CI, 0.55–2.11). No significant excesses were noted at other sites. A subdivision by department showed that the excess of prostatic cancer was mostly found among furnace workers. A subdivision by duration of employment showed that the excess of prostatic and colonic cancer occurred in workers who had been employed for ≥25 years. [The Working Group noted that there were few cases of either tumour who had less than 25 years of employment.]

2.1.9 *Chimney sweeps and other exposures to soot* (Table 2.8)

As early as 1775, Sir Percival Pott documented the occurrence of scrotal cancer among chimney sweeps in London (Pott, 1775). Several subsequent cases of skin or scrotal cancer among chimney sweeps have been reported (e.g. Earle, 1808; Butlin, 1892; Henry & Irvine, 1936). A report to the Registrar General for England and Wales (Henry, 1937) indicated a clear excess of skin cancer among chimney sweeps.

Kennaway and Kennaway (1947) reported mortality among chimney sweeps in England and Wales; 21 deaths from lung cancer occurred compared with 17.6 expected (SMR, 1.19; [95% CI, 0.74–1.82]). [Different sources were used to obtain occupational titles for the numerator and denominator of the occupational death rates, which may have caused bias in the estimated risks.] (see IARC (1985) for further details)

Kupetz (1966) reported analyses of mortality and morbidity among chimney sweeps in Berlin, Germany. Age-adjusted expected numbers of deaths were calculated using 5-year age groups and the male population of Berlin as the reference. Among an average of 255 chimney sweeps, 31 died (33.8 expected) between 1954 and 1963. Among the nine deaths from cancer, seven were histologically confirmed lung cancers (2.0 expected; [SMR, 3.50; 95% CI, 1.41–7.21]); the average duration of exposure was 49 years. The incidence rate for respiratory cancer among chimney sweeps in former East Germany between 1956 and 1958 was 13.7/10 000 (eight observed, 6.7/10 000 expected).

Table 2.8. Cohort studies of chimney sweeps and other exposures to soot

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders/Comments
Hansen *et al.* (1982), Copenhagen, Denmark	106 chimney sweeps active any time between 1958 and 1977 followed for mortality up to 1977	–	Cancer		11	1.77 [0.88–3.16]	No
Hansen (1983), Denmark	713 chimney sweeps active in 1970 followed for mortality 1970–75	–	Cancer		12	[2.27 (1.17–3.97)]	No
Evanoff *et al.* (1993), Sweden	5313 chimney sweeps active any time between 1917 and 1980 followed for mortality up to 1990 and cancer incidence up to 1987	Employment duration	Incidence			**SIR**	An analysis of asbestos exposure levels and dose–response calculations showed that asbestos could contribute to only a minor part of the lung cancer excess. A survey of tobacco smoking habits in 1972 was used to calculate adjusted SIRs. SIRs for lung and urinary bladder cancer were still significantly elevated after adjusting for smoking.
			Lung	*All*	50	2.09 (1.55–2.76)	
				1–9 years of employment	4	0.89 [0.24–2.28]	
				10–19 years of employment	16	2.16 [1.24–3.51]	
				20–29 years of employment	15	2.68 [1.50–4.42]	
				>30 years of employment	15	2.34 [1.31–3.87]	
			Oesophagus	All	11	3.87 (1.93–6.93)	
			Urinary bladder	All	37	2.53 (1.78–3.49)	
			Skin (non-melanoma)	All	4	0.61 (0.17–1.57)	
			Haemato-lymphatic	All	36	1.51 (1.06–2.09)	

Table 2.8 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	SIR (95% CI)	Adjustment for potential confounders/Comments
Pukkala (1995), Finland	The Finnish 1970 Census file was linked to the national cancer registry to follow men for cancer incidence in 1971–85	Occupational titles	Lung		23	1.35 (0.86–2.03)	Age, time period, social class
Haldorsen *et al.* (2004), Norway	All men aged 25–64 years in the Norwegian census 1970 followed for cancer incidence 1971–91	Occupational titles	Lung	Chimney sweeps	14	1.19 (0.7–2.0)	Adjusted for tobacco smoking habits at the group level by indirect method

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

Hansen *et al*. (1982) investigated mortality from cancer and non-cancerous diseases among all male chimney sweeps in Copenhagen, Denmark, who were also members of the Copenhagen Chimney Sweeps' Pension Fund from 1958 to 1977. Membership in the pension fund was mandatory both for employed and self-employed chimney sweeps. A total of 106 chimney sweeps were identified and followed for mortality until 1977. Follow-up was complete and underlying causes of death were obtained from death certificates. A life-table survival analysis was performed, which compared mortality from cancer and non-cancerous diseases among chimney sweeps with that of the male population of Copenhagen, adjusted for age and calendar period. The ratio of observed to expected number of deaths was calculated; 33 deaths occurred in the cohort (SMR, 1.32; [95% CI, 0.91–1.86]), of which 11 were from cancer (SMR, 1.77; [95% CI, 0.88–3.16]). Of these, four deaths were from lung cancer but the expected number was not given.

Cadez (1983) reported a study on all chimney sweeps in Slovenia. Tar concentrations were reported to exceed the maximum accepted concentration (0.2 mg/m^3) by 30–96-fold. Of 479 chimney sweeps employed in 1969, 54 died between 1969 and 1981, 23% of whom died from cancer — 11 from lung cancer, eight from laryngeal cancer and four from stomach cancer but none from cancer of the scrotum. [The Working Group noted that only crude numbers of deaths were reported.]

Hansen (1983) investigated mortality among all male Danish chimney sweeps identified from the national census in 1970, and 713 were followed for mortality in 1970–75 by linkage with national population registries. Expected numbers of deaths were calculated by the person–year method, based on the death rates among all employed Danish men. The study group partly overlapped with a previous study (Hansen *et al*., 1982). During follow-up, 38 deaths were observed [SMR, 2.08; 95% CI, 1.47–2.85], 12 of which were from cancer [SMR, 2.27; 95% CI, 1.17–3.97].

Evanoff *et al*. (1993) investigated mortality and cancer incidence among a cohort of 5313 Swedish chimney sweeps from previous studies (Hogstedt *et al*., 1982; Gustavsson *et al*., 1988). All male members of the Swedish chimney sweeps' trade union from 1918 to 1980 and who were still alive in the beginning of 1951 were included. This trade union represented approximately 95% of all Swedish chimney sweeps. The cohort was followed for mortality from 1951 to 1990 (restricted to persons aged <80 years at death) and for cancer incidence from 1958 to 1987. Underlying causes of death were obtained from death certificates and cancer diagnoses from the national cancer register. SMRs were calculated by the person–year method, using national mortality and cancer rates to calculate expected numbers of deaths. Tobacco smoking habits were available for 1040 chimney sweeps employed in 1972 and were used to additionally calculate smoking-adjusted SIRs and SMRs. Of the cohort members, 919 had died at the end of follow-up, which was complete for 98.2%. The SMR for all causes of death was 1.35 (95% CI, 1.27–1.44) and was 1.46 for all cancers (95% CI, 1.27–1.67). Three hundred and thirty-five incident cases of cancer were observed (SIR, 1.43; 95% CI, 1.28–1.59). Significant excess risks were noted for lung cancer (SIR, 2.09; 95% CI, 1.55–2.76; based on 50 cases), urinary bladder cancer (SIR, 2.53; 95% CI, 1.78–3.49; based on 37 cases),

oesophageal cancer (SIR, 3.87; 95% CI, 1.93–6.93; based on 11 cases) and haematolymphatic malignancies (SIR, 1.51; 95% CI, 1.06–2.09; based on 36 cases). Three pleural mesotheliomas were observed versus 0.6 expected (SIR, 4.69; 95% CI, 0.94–13.70). No excess incidence of skin cancer was noted. Analysis of cancer incidence by duration of employment (categories 1–9, 10–19, 20–29 and ≥ 30 years) showed statistically significant positive trends for all cancer and for lung cancer. The recalculated effect estimates adjusted for smoking habits in 1972 showed somewhat higher expected numbers of lung (SMR) and urinary bladder (SIR) cancers, but the SMRs and SIRs still remained significantly elevated. Three cases of pleural mesothelioma indicated that the cohort had been exposed to asbestos. [The ratio of the excess number of lung cancers to the number of mesotheliomas (27:3) does not suggest that asbestos was an important confounder for lung cancer.]

A study in Finland (Pukkala, 1995) linked the occupations of individuals in the 1970 census with cancer incidence during 1971–85, as ascertained through the Finnish Cancer Registry. SIRs were calculated and adjusted for age, time period and social class. The entire national economically active population was used as the reference population. The SIR for lung cancer was 1.35 (95% CI, 0.86–2.03; based on 23 incident cases) for male chimney sweeps.

Haldorsen *et al.* (2004) investigated the incidence of lung cancer among all Norwegian men aged 25–64 years included in the census of 1970, who were followed from 1971 to 1991 and for whom occupational titles were obtained from censuses. Deaths and cancer cases were identified from national registers. Adjustment was made for tobacco smoking habits at the group level by an indirect method. Fourteen lung cancers occurred among chimney sweeps (SIR, 1.19; 95% CI, 0.7–2.0; adjusted for smoking).

2.2 Case–control studies by cancer site

2.2.1 *Lung cancer* (Table 2.9)

Blot *et al*. (1983) conducted a case–control study in Pennsylvania, USA, of all deaths from primary lung cancer among white men aged 30–79 years resident in Lehigh and Northampton counties during 1976–77 and in Carbon county during 1974–77. These counties had a substantial population that was employed in the steel industry. A total of 360 cases were identified at the files of the Pennsylvania Division of Vital Statistics. Three hundred and sixty deceased controls matched to cases on sex, race, age, county of residence and year of death were selected at random from among deaths from causes other than respiratory cancer, chronic respiratory disease or suicide: the majority of the controls had acute heart conditions or non-respiratory cancer as the cause of death. Personal interviews were conducted by trained interviewers, blinded to case/control status, to obtain information from the next of kin on residential, occupational and smoking histories and demographic data. Usual industry, adapted partly from the Standard Industrial Classification system, and usual job title were defined as those in which largest

Table 2.9. Case–control and case–cohort studies of lung cancer and exposure to polycyclic aromatic hydrocarbons (PAHs)

Reference, location	Effective no. of subjects	Job/exposure category	Lung cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Blot *et al*. (1983), Pennsylvania, USA	335 white male cases (deceased), 332 matched white male population-based controls (deceased)	Coke worker in the steel industry as longest held job	Any	2	1.2 (0.2–6.9)	Odds ratios adjusted for sex, race, age, county and year of death, relative to men never employed in the steel industry, based on two cases among coke-oven workers. Odds ratios were not adjusted for tobacco smoking
Schoenberg *et al.* (1987), New Jersey, USA	763 white male cases identified in 1980–81, 900 population-based controls	Roofer or slater	Any	13	1.7 (0.68–4.40)	Adjusted for tobacco smoking
Zahm *et al.* (1989), Missouri, USA	4431 white male cases 1980–85, 11 326 white male cancer controls	Roofer	Any Adenocarcinoma Squamous-cell Other/mixed	6 1 3 2	2.1 (0.6–8.2) 1.5 (0.1–13.3) 2.6 (0.5–12.7) 2.9 (0.4–18.0)	Adjusted for tobacco smoking and age; latest job available for 52% of cases and 45% of controls
Morabia *et al.* (1992), USA	1793 male cases and 3228 male cancer and non-cancer hospital-based controls identified from 24 US hospitals in 1980–89	Roofer and slater	Any	7	2.1 (0.7–6.2)	Adjusted for race, age, geographical location, version of questionnaire and tobacco smoking

Table 2.9 (contd)

Reference, location	Effective no. of subjects	Job/exposure category	Lung cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Partanen & Boffetta (1994)	Meta-analysis of Schoenberg *et al*. (1987), Zahm *et al.* (1989), Morabia *et al.* (1992)	Roofer and slater	Any	26	1.88 (1.23–2.76)	Adjustments as in the original studies: age, gender, geographical area, questionnaire version and cigarette/tobacco smoking
Bovenzi *et al*. (1993), Trieste, Italy	756 male cases (deceased), 756 male matched population-based controls (deceased) identified from local registries	Gas workers Asphalt workers	Any Any	7 7	1.43 (0.45–4.47) 2.27 (0.50–10.3)	Adjusted for tobacco smoking
Wu-Williams *et al*. (1993), People's Republic of China	965 female incident cases identified from local cancer registries between 1985–87; 959 randomly selected age-matched, female population-based controls	**Coke-oven emissions** *Years of exposure* 1–10 years 11–20 years ≥21 years *p* trend	Any	51	1.5 (0.9–2.5) 1.2 1.4 3.0 0.04	Adjusted for tobacco smoking, study area, age and education

Table 2.9 (contd)

Reference, location	Effective no. of subjects	Job/exposure category	Lung cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Nadon *et al*. (1995), Montréal, Canada	857 male cases rapidly ascertained from all major Montréal hospitals, 2056 male population controls (identified from electoral lists and RDD) and cancer controls identified from the same hospitals as cases	*Total PAHs*	Any			All analyses adjusted for age, ethnic group, family income, cumulative tobacco smoking index and exposure to asbestos, silica and chromium, nickel and arsenic compounds
		Low		418	1.0 (0.8–1.3)	
		High		209	1.0 (0.8–1.3)	
		BaP				
		Low		160	0.9 (0.7–1.2)	
		High		75	1.0 (0.7–1.4)	
		Total PAHs	Small-cell (oat-cell)			
		Low		78	1.0 (0.6–1.5)	
		High		40	1.0 (0.6–1.7)	
		BaP				
		Low		28	0.8 (0.5–1.3)	
		High		14	0.6 (0.3–1.3)	
		Total PAHs	Squamous-cell			
		Low		184	1.2 (0.9–1.7)	
		High		93	1.2 (0.8–1.7)	
		BaP				
		Low		75	1.0 (0.8–1.5)	
		High		33	1.0 (0.7–1.7)	
		Total PAHs	Adenocarcinoma			
		Low		85	1.1 (0.7–1.7)	
		High		37	1.0 (0.6–1.7)	
		BaP				
		Low		29	0.9 (0.6–1.4)	
		High		10	0.5 (0.3–1.2)	

Table 2.9 (contd)

Reference, location	Effective no. of subjects	Job/exposure category	Lung cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Nadon *et al*. (1995) (contd)		**<800 cigarettes–years**	All			For all analyses stratified by smoking status, the reference category was the unexposed among light smokers.
		Total PAHs				
		Unexposed		41	1.0 (ref)	
		Low		80	1.4 (0.9–2.1)	
		High		31	1.8 (1.1–3.0)	
		BaP				
		Unexposed		112	1.0 (ref)	
		Low		24	1.1 (0.7–1.7)	
		High		16	2.4 (1.3–4.4)	
		≥800 cigarettes–years	All			
		Total PAHs				
		Unexposed		189	6.7 (4.6–9.8)	
		Low		341	6.1 (4.2–8.7)	
		High		175	6.0 (4.1–8.9)	
		BaP				
		Unexposed		510	5.2 (4.1–6.6)	
		Low		142	5.3 (3.9–7.2)	
		High		53	3.9 (2.6–5.8)	
van Loon *et al*. (1997), Netherlands	524 male cases identified through national registries; cohort subsample of 1688 men used to calculate person–years at risk	*Cumulative occupational exposure to PAHs*	All		**Rate ratio**	Adjusted for age, other occupational exposures, tobacco smoking, dietary intake of vitamin C, β-carotene and retinol; response rate to baseline questionnaire was low (36%).
		Ever versus never		34	0.53 (0.26–1.07)	
		I tertile		10	0.53 (0.13–2.14)	
		II tertile		12	0.83 (0.32–2.20)	
		III tertile		12	0.28 (0.09–0.89)	
					p for trend <0.01	

Table 2.9 (contd)

Reference, location	Effective no. of subjects	Job/exposure category	Lung cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Grimsrud *et al*. (1998), Rana, Norway	86 male cases identified from the national cancer registry, 196 male population controls matched by year of birth and selected from the national registry	Exposed to PAHs at steel, iron and coke plant only	All	13	1.9 (0.8–4.6)	Adjusted for tobacco smoking
		Any occupational exposure to PAHs (see text for details)		18	2.9 (1.2–6.7)	Adjusted for tobacco smoking
Droste *et al*. (1999), Belgium	478 male cases and 536 male hospital controls identified during 1995–97 from hospitals that served the entire Antwerp area	Self-reported exposure to PAHs	All	77	1.1 (0.7–1.7)	A lag time of 10 years was applied to all exposure variables to allow for an induction latency period before diagnosis of disease. [The job–exposure for PAHs included several occupations in which exposure to PAHs is questionable]. All odds ratios were adjusted for age, smoking history, marital and socioeconomic status
		Matrix-based exposure to PAHs		235	1.2 (0.9–1.6)	

Table 2.9 (contd)

Reference, location	Effective no. of subjects	Job/exposure category	Lung cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Brüske-Hohlfeld *et al*. (2000), Germany	2 pooled case–control studies; 4184 male cases, 4253 male controls	*Occupational PAH exposure*	All			Adjusted for smoking and exposure to asbestos
		Ever versus never		181	1.53 (1.14–2.04)	
		Up to 20 BaP–years		80	1.15 (0.77–1.71)	
		>20 BaP–years		101	2.09 (1.36–3.22)	
Gustavsson *et al*. (2000), Sweden	1042 male cases, 2364 male population controls matched by 5-year age group and year of inclusion (1985–90)	**Combustion products**	All	824	1.00 (ref)	All odds ratios adjusted for age, year of inclusion, tobacco smoking, residential radon level and environmental exposure to nitrogen dioxide
		Unexposed				
		μg/m^3 BaP				
		0.05–0.4 (>1 year)		46	1.07 (0.72–1.60)	
		0.5–4.9 (>1 year)		48	1.33 (0.89–2.00)	
		≥5 (>1 year)		35	2.10 (1.25–3.53)	
		μg/m^3–years of BaP				
		>0–2.9		47	1.20 (0.80–1.80)	
		3.0–6.6		51	1.05 (0.71–1.57)	
		6.7–23.8		47	1.05 (0.69–1.59)	Additionally adjusted for diesel exhaust and exposure to asbestos
		≥23.9		73	1.60 (1.09–2.34)	
		Duration (years)				
		>0–9		Not stated	1.42 (0.96–2.10)	
		10–29			1.37 (1.01–1.85)	
		≥30			1.37 (0.98–1.91)	

BaP, benzo[*a*]pyrene; CI, confidence interval; RDD, random digit dialling

number of years were spent. After exclusions, most of whom were non-respondents (response rate, 96% in cases and 94% in controls), the effective numbers of cases and controls were 335 and 332, respectively. The odds ratio (adjusted for the matching variables) for coke-oven worker in the steel industry as the longest job held was 1.2 (95% CI, 0.2–6.9; based on two cases and two controls in that job).

Schoenberg *et al*. (1987) conducted a case–control study among 763 white male cases of lung cancer who were identified in 1980–81 in New Jersey (USA) municipalities that have high mortality from lung cancer and 900 population controls matched to cases by race, age, area of residence and closest date of death (for deceased persons). Occupational histories were obtained from the subjects or their next of kin. The odds ratio for roofers and slaters, adjusted for tobacco smoking, was 1.7 (95% CI, 0.68–4.40; based on 13 exposed cases).

Zahm *et al*. (1989) conducted a case–control study of 4431 male residents in Missouri (USA) who were identified as lung cancer cases in 1980–85 at the Missouri Cancer Registry. Controls were selected from this Registry during the same period and comprised 11 326 white male Missouri residents who did not have cancer of the lip, oral cavity, oesophagus, lung, urinary bladder, ill-defined sites or unknown sites. Occupation at the time of cancer diagnosis was abstracted and coded from the Cancer Registry records; this information was available for only 52% of the cases of 45% of the controls. Data on tobacco smoking were coded into seven categories, including 'unknown smoking history'. The odds ratio for roofers, adjusted for age and tobacco smoking, was 2.1 (95% CI, 0.6–8.2; based on six exposed cases).

Morabia *et al*. (1992) conducted a case–control study of 1793 male cases of lung cancer who were identified in 24 hospitals in the USA and 3228 cancer and non-cancer hospital controls matched to cases on race, age, hospital and cigarette smoking history. All subjects were identified between 1980 and 1989. Data on usual occupation, tobacco smoking and other potential confounders were obtained by interviews of the subjects. Job titles were coded according to the standard of the United States Bureau of Census codes. The odds ratio for roofers and slaters, adjusted for race, age, geographical location, version of the questionnaire (I and II) and tobacco smoking, was 2.1 (95% CI, 0.7–6.2; based on seven exposed cases). [The Working Group noted that the control group included some cancer sites that are possibly related to exposure to PAHs, and thereby the odds ratio is potentially understimated.]

Partanen and Boffetta (1994) conducted a meta-analysis of the results of Schoenberg *et al*. (1987), Zahm *et al*. (1989) and Morabia *et al*. (1992) for roofers and slaters. The overall relative risk was 1.88 (95% CI, 1.23–2.76; based on 26 exposed cases).

Bovenzi *et al*. (1993) conducted a case–control study of 756 cases among 938 male deaths from primary lung cancer who were identified at the records of the cancer registry of the province of Trieste, Italy, during 1979–81 and 1985–86, and for whom next of kin could be located and interviewed. For each case, one male control of similar age, who had died within the same 6-month period, was randomly selected at the registry of the Department of Pathology that holds the autopsy records of 70% of all deaths of the

province. The controls represented causes of death other than chronic lung diseases or cancers of the upper aerodigestive tract, urinary tract, pancreas, liver or gastrointestinal system; the majority died from circulatory or gastrointestinal disease. Telephone interviews were conducted with the next of kin of the subjects at least 1 year after their death to obtain information on residential, occupational (jobs, industries, places of work, employers and durations of employment in each job) and tobacco smoking histories and demographic data. The principal source of occupational histories was the subjects' employment cards which were carefully kept by the families for social security purposes. No next of kin refused the interview. The industries/occupations were classified into two lists by an occupational physician: those that were considered to be causally associated with lung cancer and those suspected of being related to an increased risk for lung cancer. Of the single occupational titles, gas workers had a smoking-adjusted odds ratio of 1.43 (95% CI, 0.45–4.47; seven cases) for risk for lung cancer and asphalt workers had an odds ratio of 2.27 (95% CI, 0.50–10.3; based on seven cases) compared with subjects who had presumably not been exposed to occupational lung carcinogens. [It was unclear whether 'gas workers' referred to coal gasification and whether coal tar was used in the asphalt mix of asphalt workers.].

In a case–control study in the People's Republic of China (Wu-Williams *et al*., 1993), 965 confirmed cases of primary incident lung cancer among women aged 29–70 years in the general population of Shenyang and Harbin (the major industrial cities of northern China) were identified, located and interviewed during 1985–87 through the cancer registries of the two cities. The refusal rate among cases was 0.3%. The 959 control women were randomly selected from the general populations of the two cities, frequency matched to the cases by 5-year age group and interviewed. Subjects were interviewed at the hospital, at home or at work with a structured questionnaire that addressed occupational histories and exposures, tobacco smoking histories, indoor and outdoor sources of pollution, medical and dietary histories and demographic data. The odds ratio for self-reported exposure to coke-oven emissions, adjusted by unconditional logistic regression for tobacco smoking, study area, age and education, was 1.5 (95% CI, 0.9–2.5; based on 51 exposed cases). An increase in trend for mortality from lung cancer (p=0.04) was found for increasing years of exposure to coke-oven emissions (odds ratios, 1.2, 1.4 and 3.0 for 1–10, 11–20 and >20 years of exposure, respectively). The point estimates of the odds ratios were similar when analyses were restricted to nonsmokers only.

A population-based case–control study of occupational cancer in Montréal, Canada (Nadon *et al*. 1995), included 857 histologically confirmed male cases of lung cancer, aged 35–70 years, who were newly diagnosed between 1979 and 1986 and ascertained in all large hospitals that serve Montréal, as well as 533 population controls and 1523 non-lung cancer controls. The two control series were pooled for the analyses because parallel analyses showed little difference between results based on each control group used separately as the referent. The cases included 159 small-cell (oat-cell) cancers, 359 squamous-cell cancers and 162 adenocarcinomas. Cases were rapidly ascertained and personally interviewed to obtain information on each job held during their lifetime and on

potential confounders. The interviewers were trained to probe for as much information as the subjects could supply on the employer's or company's activities, the raw materials used, the type of room or building in which he had worked, the activities of workmates, the presence of gases, fumes or dusts and other pertinent data. The exposure of each subject to approximately 300 occupational agents was assessed by a group of hygienists and chemists on the basis of job descriptions and lung cancer cases were compared with the rest of the study population, after adjustment for age, ethnic group, family income, cumulative tobacco smoking index and exposure to asbestos, silica and chromium, nickel and arsenic compounds. Occupational exposure was defined as levels that exceeded general environmental levels; 68% of all subjects were classified as ever having been exposed to PAHs from any source, 24% were thought to have been exposed to benzo[*a*]pyrene and 9% had been exposed to PAHs from coal. Cumulative exposures at low, medium or high levels were also computed, based on the sum product of duration, frequency and concentration of exposure. Table 2.9 summarizes the odds ratios and confidence intervals for exposure to total PAHs, benzo[*a*]pyrene and coal-derived PAHs for all lung cancers and small-cell (oat-cell) and squamous-cell lung cancers and lung adenocarcinomas. None of the associations with type of PAH were significant and the odds ratios were generally close to unity. However, effect modification was observed between tobacco smoking and exposure to PAHs. Among heavy smokers (800 cigarette–years or more), there was no effect on the risk for lung cancer with different levels of exposure to PAHs. However, among 'light smokers and nonsmokers' (<800 cigarette–years), there was evidence of an increasing risk for lung cancer with increasing exposure to total PAHs and benzo[*a*]pyrene. The odds ratio for exposure to high levels of total PAH was 1.8 (95% CI, 1.1–3.0; based on 31 exposed cases) for 'light smokers and nonsmokers' and 6.0 (95% CI, 4.1–8.9; based on 175 exposed cases) for heavy smokers compared with those not exposed to total PAHs. For high-level exposure to benzo[*a*]pyrene, the odds ratio was 2.4 (95% CI, 1.3–4.4; based on 16 exposed cases) for 'light smokers and nonsmokers' and 3.9 (95% CI, 2.6–5.8; based on 53 exposed cases) for heavy smokers compared with those not exposed to benzo[*a*]pyrene.

In 1986, the Netherlands Cohort Study was initiated as a prospective follow-up for cancer incidence in relation to lifestyle factors within a cohort of 340 439 men and women aged 55–69 years selected from the general population of the Netherlands (van Loon *et al*., 1997). Prevalent cases of cancer were excluded. A self-administered questionnaire was sent to all cohort members regarding job history, diet, lifestyle and other sociodemographic factors. Only 36% of the cohort responded and after comparing several variables between the cohort and Dutch population, it was considered that the remaining members of the cohort were still representative of the Dutch population. A case–cohort study of lung cancer was designed in the remaining cohort of 58 279 men, and 677 cases of incident lung cancer were determined between September 1986 and December 1990 through the national pathology register and the regional cancer registers. Person–years at risk were estimated from a subsample of 1630 men who were followed up biennially for vital status. A self-administered baseline questionnaire enquired about

lifetime job history with job titles, type of company, periods and duration of employment as well as the company's products up to September 1986. Exposure assessment was conducted with no knowledge of health outcomes. Experts classified the job histories for probabilities of exposure to asbestos, paint dust, PAHs and welding fumes into four categories: no exposure, possible exposure (probability of exposure <30%), probable exposure (30–90% probability) and nearly certain exposure (>90% probability). Cumulative exposure to each agent was calculated as the product of the midpoint of the probability in each of the four exposure categories (scored as 0, 0.15, 0.6 and 0.95, respectively) and the duration of exposure. Distributions of cumulative probability were then compared between the cases and the subcohort. Case–cohort analyses were completed by calculating rate ratios for each occupational cumulative probability, adjusted for age, other occupational exposures, tobacco smoking and dietary intake of vitamin C, β-carotene and retinol. The adjusted rate ratio for ever versus never exposure to PAHs was 0.53 (95% CI, 0.26–1.07; based on 34 exposed cases); thus, exposure to PAHs was inversely associated with the risk for lung cancer. The adjusted rate ratios for the non-zero tertiles of cumulative probability of exposure to PAHs were all below unity: the highest tertile was associated with a risk ratio of 0.28 (95% CI, 0.09–0.89; based on 12 cases) and the *p* value associated with this negative trend was <0.01. The odds ratios were considerably higher (but not significantly so) when adjusted for age and other occupational exposures or age only.

Another population-based case–control study was conducted in Norway (Grimsrud *et al*., 1998); the national cancer registry was used for the ascertainment of 88 incident cases of lung cancer registered among male residents of the municipality of Rana during 1980–92. Rana is located in northern Norway and had had an iron and steel plant (since 1955) and a separate coke plant (since 1964) that were in operation until the late 1980s. Three male population controls were selected for each case, were matched on year of birth, were free of lung cancer and lived in the municipality at the time of diagnosis of the case. Occupational histories (period of employment, department, details on section and job) were gathered from personnel files of the iron, steel and coke plants and by personal interviews with subjects or their next of kin. All interviews were performed by one interviewer who addressed occupational and tobacco smoking histories, dietary habits, education and residential history. After refusals, exclusions because of insufficient data and replacement of controls, 86 cases and 196 controls remained for data analysis. Subjects exposed to PAHs only at the iron, steel and coke plants had a smoking-adjusted odds ratio of 1.9 (95% CI, 0.8–4.6; 13 exposed cases).

Droste *et al*. (1999) conducted a hospital-based case–control study of lung cancer and exposure to occupational carcinogens in the Antwerp region of Belgium. A total of 478 histologically confirmed male cases and 536 male controls without cancer or primary lung disease (mainly admitted from cardiovascular surgery wards) were identified and interviewed personally in 10 hospitals during 1995–97. The catchment area of the participating hospitals had to include the total Antwerp area so that there would be no selection bias for socioeconomic status, occupational conditions or potential exposures.

The interviews covered information on occupation (job tasks, industries and duration of employment), exposure to 16 potential carcinogens, hobbies and tobacco smoking histories. Job titles were coded into a standard classification, and exposures were assessed by self-reporting and through an exposure matrix that converted data on jobs and tasks into selected exposures. Exposure data were reviewed by occupational hygienists. Odds ratios were calculated with logistic regression models, adjusting for age, tobacco smoking history, marital status and socioeconomic status. The time lag between the onset of exposure and diagnosis of disease was set at 10 years; the same time lag was also used for other covariates that may have acted as confounders. Relative to no exposure, the odds ratio for self-reported exposure to PAHs was 1.1 (95% CI, 0.7–1.7; 77 exposed cases). For exposure matrix-based exposure to PAHs, the odds ratio was 1.2 (95% CI, 0.9–1.6; 235 exposed cases). [The Working Group noted that the job–exposure matrix for PAHs included several occupations in which exposure to PAHs is questionable.]

Data from two German case–control studies of lung cancer were pooled for joint analysis (Brüske-Hohlfeld *et al*., 2000). One study was carried out by the Bremen Institute for Prevention Research and Social Medicine in Bremen, the area surrounding Bremen and the Frankfurt/Main area to determine the association between lung cancer and occupational risk factors among 1004 cases and 1004 population controls randomly selected from mandatory community registries and matched on age, sex and region of residence in 1988–93. The other study was carried out to determine the risk for lung cancer from exposure to indoor radon in West and East Germany (covering the regions of Nordrhein-Westfalen, Rheinland-Pfalz, Bayern, Saarland, Thüringen and Sachsen) among 3180 cases and 3249 controls matched by sex, age and region in 1990–94. A standardized questionnaire was administered by trained interviewers in both studies to collect data on occupational exposure, residential history, tobacco smoking and other risk factors. The response rates were 69% for cases and 68% for controls (in the Bremen BIPS study) and 77% for cases and 41% for controls (in the 'indoor radon study'). The final pooled analyses were restricted to 3541 male controls and 3498 male cases that were cytologically and/or histologically verified, excluding metastases secondary to other primary tumours. Using 'never exposed' as the reference category, odds ratios were calculated for workers who had been 'ever exposed', for duration of exposure and for cumulative exposures through a job–exposure matrix. The 'ever' category of exposure to PAHs was associated with an odds ratio of 1.53 (95% CI, 1.04–3.95), adjusted for tobacco smoking and exposure to asbestos. Duration of exposure to PAHs did not show a clear trend, while job–exposure matrix-based cumulative exposure to benzo[*a*]pyrene did, yielding risk ratios of 1.15 (95% CI, 0.77–1.71) for 0–20 benzo[*a*]pyrene–years and 2.09 (95% CI, 1.36–3.22) for 20 or more benzo[*a*]pyrene–years. The risk was highest for workers in coking plants; no increased risk was seen for chimney sweeps or those working in smelters, after adjustment for tobacco smoking and exposure to asbestos. [TheWorking Group noted the low response rate among controls of the indoor radon study.]

Gustavsson *et al*. (2000) conducted a study among male residents of Stockholm County, Sweden, aged 40–75 years: 1042 lung cancer cases and 2364 population controls, matched on age and year of inclusion (1985–90). Questionnaires were mailed to the subjects or their next of kin on detailed lifetime occupational history, residential history, tobacco smoking habits and other potential risk factors for lung cancer. Response rates were 87% in cases and 85% in controls. Intensity, probability and duration of exposure were assessed for seven specific occupational exposures for each work period by an occupational hygienist who was blinded to case/control status. For combustion products, odds ratios were elevated for the highest categories of exposure intensity, assessed as ≥5 μg/m^3 benzo[*a*]pyrene (odds ratio, 2.10; 95% CI, 1.25–3.53; based on 35 exposed cases), cumulative exposure of ≥23.9 μg/m^3–years benzo[*a*]pyrene (odds ratio, 1.60; 95% CI, 1.09–2.34; based on 73 exposed cases; adjusted additionally for exposure to diesel exhaust and asbestos) and duration of exposure of 10–29 years (odds ratio, 1.37; 95% CI, 1.01–1.85) and ≥30 years (odds ratio, 1.37; 95% CI, 0.98–1.91). The odds ratios were adjusted for age, year of inclusion, tobacco smoking, residential radon level and environmental exposure to nitrogen oxide.

2.2.2 *Cancer at sites other than the lung*

(a) Renal-cell carcinoma (Table 2.10)

A population-based case–control study was conducted in the seven-county Minneapolis–St Paul Standard Metropolitan Statistical Area (USA): eligible cases were white residents of the area who were diagnosed with renal-cell carcinoma (International Classification of Diseases (ICD) 8, 189.00) in 1974–79 (McLaughlin *et al*., 1984). A total of 506 cases, aged 30–85 years, were ascertained; 495 interviews were conducted, more than half of which were with the next of kin because 237 (47%) cases were deceased and 14 were too ill to be interviewed. A group of 714 population controls was identified, who were an age- and sex-stratified random sample of white residents of the area. Those who were 30–64 years of age were chosen at random from a complete listing of telephone subscribers that included 98% of the households in this area; those over 65 years of age were chosen at random from a health care financial administrative list that included 95% of US residents in this age group. A total of 697 controls were interviewed. To account for the possible influence of interviews with next of kin, a second control group of 495 of subjects who had died from causes other than urinary tract cancer during the period 1974–79 was constituted from death certificates and were frequency-matched to deceased cases on the age and year of death and gender. For this group, 493 next of kin answered the questionnaire, which included a category on occupation, although occupational exposures were not reported in detail and exposure to specific PAHs was not described. A very high response rate was observed (approximately 95% in the different groups of cases and controls). Statistical models were systematically adjusted for age, and separate odds ratios were estimated to take into account the type of respondent (index subject or next of kin). A final model included all different exposures studied in the analysis to adjust simultaneously

Table 2.10. Case–control studies of kidney cancer and exposure to polycyclic aromatic hydrocarbons (PAHs)

Reference, location	Effective no. of subjects	Job/exposure category	Kidney cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
McLaughlin *et al.* (1984), Minneapolis, USA	495 cases (1974–79), 1190 population controls (697 alive and directly interviewed, 493 deceased) matched by age and sex	Petroleum, tar, pitch Exposure ≥20 years	Renal-cell carcinoma	36 Not given	1.7 (1.0–2.9) 2.6 (1.2–5.7)	Occupational history was not described in detail; the number of controls used in odds ratio estimations was not clear (total 1190 controls or 697 alive controls); the results were adjusted for tobacco smoking
Sharpe *et al.* (1989), Canada	164 cases (1982–87), 161 hospital controls matched by age, sex and urologist	Coke Tar or pitch	Renal-cell carcinoma	6 9	2.00 (0.49–8.14) 9.29 (1.16–74.20)	Detailed occupational history not described; no description of the exposure evaluation: the exposures studied were derived from job titles; adjusted for matching variables but not for smoking; a statistically significant trend (p <0.025) of increasing odds ratios was seen with increasing intensity of exposure to burning coal
Partanen *et al.* (1991), Finland	408 cases (1977–78), 819 population controls matched by year of birth, sex and vital status	PAH (men and women) PAH (men only) Blue-collar workers (men and women) Male blue-collar workers	Renal-cell carcinoma	7 NA NA	1.1 (0.4–3.1) 1.2 (0.4–3.4) 4.4 (0.4–43.1) 5.5 (0.5–58.9)	Whole occupational history for the period 1920–68; adjusted for smoking, coffee consumption and obesity; the number of women was not given, therefore could not evaluated the number of male exposed cases. Increase in association after exclusion of white-collar workers

Table 2.10 (contd)

Reference, location	Effective no. of subjects	Job/exposure category	Kidney cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Mandel *et al.* (1995), Australia, Denmark, Germany, Sweden and USA	1732 cases (1989–91), 2309 population controls	Blast furnace/coke-oven industries	Renal-cell carcinoma	57	1.7 (1.1–2.7)	Information on specific occupations and industries of interest and whole occupational history reported in Germany; these results were for men only.
Nadon *et al.* (1995), Canada	181 male cases (1979–85), 2196 male population and cancer controls	*PAHs derived from coal* Low High	Renal-cell carcinoma	 11 4	 1.0 (0.5–1.9) 0.9 (0.3–2.6)	Lifetime occupational history evaluated on a case-by-case basis; adjusted for smoking, age, socioeconomic status and ethnic group; diagnoses of lung and urinary bladder cancers were excluded from the control group.
Pesch *et al.* (2000), Germany	935 cases (1991–95), 4298 population controls	**Tar, pitch, mineral oil** *Men* Medium High Substantial *Women* Medium High Substantial	Renal-cell carcinoma	 86 96 34 15 16 10	 1.1 (0.9–1.5) 1.2 (0.9–1.6) 1.4 (0.9–2.1) 1.0 (0.6–1.7) 1.2 (0.7–2.0) 2.1 (1.0–4.5)	Whole occupational history using English job–exposure matrix; adjusted for tobacco smoking; exposure categories were defined by the 30th, 60th and 90th percentiles of the distribution of the exposure among controls; adjusted for age, centre and smoking.

Table 2.10 (contd)

Reference, location	Effective no. of subjects	Job/exposure category	Kidney cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Pesch *et al.* (2000) (contd)		**PAH**				
		Men				
		Medium		71	0.9 (0.7–1.2)	
		High		96	1.3 (1.0–1.6)	
		Substantial		32	1.2 (0.8–1.9)	
		Women				
		Medium		17	1.1 (0.6–1.8)	
		High		21	1.5 (0.9–2.4)	
		Substantial		6	1.3 (0.5–3.3)	
		Men				Job–task–exposure matrix
		Medium		80	0.9 (0.7–1.2)	
		High		67	0.8 (0.6–1.0)	
		Substantial		26	0.9 (0.6–1.4)	

CI, confidence interval; NA, not applied

for age, tobacco smoking, body mass index, use of phenacetin, kidney infection, kidney stones, nationality of the parents, consumption of tea, beer and meat and exposure to petroleum, tar and pitch. Few results concerned occupational exposure to PAHs. The results were presented according to the industry in which the index subject worked the greatest number of years but did not include sectors that are of interest to this monograph. The authors studied some occupational exposures that included the group petroleum, tar and pitch and found a significant relationship with renal-cell carcinoma (odds ratio, 1.7; 95% CI, 1.0–2.9; based on 36 exposed cases). This relationship was reinforced when persons who had been exposed for 20 years or more (odds ratio, 2.6; 95% CI, 1.2–5.7) were compared with those who had been exposed for less than 20 years (odds ratio, 1.1; 95% CI, 0.5–2.5). No other estimation was made (i.e. level or latency). In the final model that included all items studied, the odds ratio for renal-cell carcinoma in relation to petroleum, tar and pitch was 1.6 (95% CI, 0.9–2.7) for men and 4.6 (95% CI, 0.4–51) for women.

In a hospital-based case–control study in Canada, cases who were diagnosed between 1982 and 1987 were determined retrospectively from the medical records of nine hospitals in the Montréal area (Sharpe *et al*., 1989). Eligible cases were alive at the time of the review and had a histologically confirmed diagnosis (ICD-8, 189.00). Of the 403 cases identified, only 168 were able to participate; 163 had died, 43 could not be traced, the physician refused to participate for 25 and four were too ill to participate. Controls were patients who attended the same hospital departments for haematuria during the same 5-year interval as the cases, and for whom a non-neoplastic diagnosis had been given. One control per case was selected and matched for sex, 5-year age group and urologist. A total of 164 cases and 161 controls completed a mailed questionnaire (97% overall response rate); a telephone interview was conducted to clarify and complete missing information. No information was given on the content of the questionnaire, particularly on the occupational section. The authors highlighted that information on exposure to hydrocarbons was requested for regular and repeated exposure (at least once a week). Statistical analysis was carried out using unconditional logistic regression. All models were adjusted for the matching variables and the other exposures studied; however, it is unclear which variables were included in the final models. Although tobacco smoking was studied, the authors did not consider it to be a significant confounder and therefore excluded it from the final models. Exposure to coke was associated with a non-significant increase in risk for renal-cell carcinoma (odds ratio, 2.00; 95% CI, 0.49–8.14; based on six exposed cases and three exposed controls). Those considered to be occupationally exposed to coke were persons who had been exposed to burning fuels (e.g. janitors, foundry workers, locomotive engineers, forced labourers, sailors and those involved in heating buildings). Exposure to tar or pitch was related to a large increase in risk for renal-cell carcinoma (odds ratio, 9.29; 95% CI, 1.16–74.20; based on nine exposed cases (three in roofing, three in the construction industry, one laboratory worker, one petrochemical salesman and one prisoner of war) and one control

exposed through road paving). A statistically significant trend ($p < 0.025$) of increasing odds ratios was seen with increasing intensity of exposure to burning coal.

A population-based case–control study carried out in Finland included men and women aged 20 years or above who were diagnosed in 1977–78 as having renal adenocarcinoma (ICD-7, 189.0) registered with the Finnish Cancer Registry (Partanen *et al*., 1991). Two controls per case were identified at random from the Population Register Centre, and matched by year of birth, gender and vital status. A total of 672 cases and 1344 controls were thus identified. Information was collected by questionnaire sent to the index person for live subjects or to a next of kin for deceased subjects. Response rates were almost identical between cases and controls, and were slightly higher for subjects who were alive (78%) than for those who were deceased (66%). After exclusion of subjects without employment, the study included 408 cases (98 alive and 310 deceased) and 819 controls (195 alive and 624 deceased). Information included in the questionnaire concerned the whole occupational history (jobs, time period, employers) as well as information on tobacco smoking history, coffee consumption and obesity. Occupational histories from the period 1920–68 were reconstructed on an annual basis to examine occupational exposure to PAHs and eight other agents. An industrial hygienist scored each annual exposure into three classes: background (<0.01 μg/m^3 benzo[*a*]pyrene), low level (0.01–1 μg/m^3 benzo[*a*]pyrene if exposed for more than 30% of the normal annual worktime) and high level (>1 μg/m^3 benzo[*a*]pyrene if exposed for more than 30% of the normal annual worktime). Statistical analysis was carried out using a dichotomous exposure indicator: 0 (background exposure) and 1 (≥5 years at a low or high level or ≥1 year at a high level). Odds ratios were estimated by conditional logistic regression, adjusted for tobacco smoking (never/ever), coffee consumption (no/medium/heavy) and obesity (five classes) as potential confounders. Odds ratios were estimated for selected industries, job titles and the nine occupational exposures. Very few subjects were classified as having been exposed to PAHs (seven cases). The estimated odds ratio for the whole population was 1.10 (95% CI, 0.39–3.09). Exclusion of women did not modify the result (odds ratio, 1.21; 95% CI, 0.43–3.45; based on seven exposed cases). Restriction to blue-collar workers increased the association (for men and women combined: odds ratio, 4.4; 95% CI, 0.4–43; for men only: odds ratio, 5.5; 95% CI, 0.5–58.9).

An international population-based case–control study was carried out in Australia, Denmark, Germany, Sweden and the USA using a similar protocol in the participating centres (Mandel *et al*., 1995). Cases were patients with incident renal-cell carcinoma [ICD-9, 189.0], histologically confirmed and diagnosed between 1989 and 1991. Cancer registries were the main source of ascertainment of cases, except in Germany, where cases were identified through active surveillance. Controls were chosen at random from different population sources (registries, electoral rolls, residential lists) and frequency-matched to cases on sex and age. Personal interviews were conducted at home for most centres except Germany, where subjects were interviewed at the hospital. Most centres requested information on selected occupations or industries of interest to the study (German centres collected complete occupational histories) in addition to information on

demographics, personal and family medical history, lifestyle factors, and use of tobacco, alcohol and medication. All centres coded occupations and industries according to standard occupational and industrial classification codes. The response rates were 72% for cases and 75% for controls, resulting in 1732 cases and 2309 controls available for analysis. Statistical analysis was carried out using logistic regression separately for men and women, adjusted for age, smoking status, body mass index, education and study centre. A minimum of 1 year in a specific job or exposure was considered as being exposed. Working at least 1 year in the 'blast furnace and coke ovens' industry was associated with an increased risk for renal-cell carcinoma (odds ratio, 1.7; 95% CI, 1.1–2.7; based on 57 exposed male cases). The exposures incurred in other industries were not relevant to the topic of this monograph. Duration of exposure in the blast furnace industry was studied, but no dose–response was seen (odds ratio for 1–2 years of exposure: 1.9; 95% CI, 0.9–4.0; 21 exposed cases; 3–7 years: 1.6; 95% CI, 0.7–3.3; 18 exposed cases; 8–41 years: 1.6; 95% CI, 0.7–3.4); 14 exposed cases.

A large population-based case–control study was carried out in Canada (Nadon *et al*., 1995) as part of a larger study (described in detail in Section 2.2.1). A total of 181 male renal-cell carcinoma patients [ICD, 189.0] were selected from the database of all cancer patients registered during 1979–85. and 2196 male population and cancer controls were selected after exclusion of those with lung and urinary bladder cancer. Odds ratios derived from unconditional logistic regression were adjusted for age, family income, ethnicity and cumulative tobacco smoking index. Results related to PAHs derived from coal did not show any association with renal-cell carcinoma.

A population-based case–control study was carried out in five regions of Germany (two in East Germany and three in West Germany) (Pesch *et al*., 2000). Cases were male and female patients at large German hospitals and of German nationality, with no restriction on age, who had had histologically confirmed renal-cell carcinoma diagnosed between 1991 and 1995. Local residency registries provided controls, who were frequency-matched by region, sex and age. A total of 935 incident cases of renal-cell carcinoma (570 men and 365 women) and 4298 controls (2650 men and 1648 women) were included in the study. The response rate was 88% for cases and 71% for controls. Cases and controls were interviewed personally using a questionnaire to obtain full occupational histories, as well as supplemental information on job tasks with suspected exposure to different agents. Job titles were coded according to the International Standard Classification of Occupations (ISCO) code. Retrospective evaluation of exposure was made using a job–exposure matrix (English or German). In addition, German experts created a job–task–exposure matrix that accounted for the probability and intensity of exposure to a specific agent. To assess the effect of occupational exposures, the ISCO code (three-digit) of the longest job held was used for statistical analysis. The total number of years worked in a job title represented a subject's lifetime exposure, whereas the quantification of exposures in job tasks involved summing of the number of years worked, weighted by the percentage of time spent at the specific task ('duration'). The results according to duration were given for job groups that represented an aggregate of

job titles or job tasks with similar exposure circumstances. The job groups constituted were not relevant to the topic of this monograph. The job–exposure matrix (English or German) or the job–task–exposure matrix allowed the construction of an index that corresponded to the product of the duration × intensity × probability of exposure. This exposure index was divided into four categories according to the 30th, 60th and 90th percentiles. All odds ratios were adjusted for age, region and sex. Results given for the job title (three-digit ISCO code) included only those with a significant odds ratio. The English job–exposure matrix included a category entitled 'tar, pitch and mineral oil' that showed a non-significant association that increased with the level of the exposure index (odds ratio: medium, 1.1; 95% CI, 0.9–1.5; based on 86 exposed cases; high, 1.2; 95% CI, 0.9–1.6; based on 96 exposed cases; substantial, 1.4; 95% CI, 0.9–2.1; based on 34 exposed cases). The same trend was observed for women and was of borderline significance with 'substantial' exposure (odds ratio: medium, 1.0; 95% CI, 0.6–1.7; based on 15 exposed cases; high, 1.2; 95% CI, 0.7–2.0; based on 16 exposed cases; substantial, 2.1; 95% CI, 1.0–4.5; based on 10 exposed cases). Similar estimates could not be made with the German job–exposure matrix. The English job–exposure matrix also considered exposure to PAHs. The results were similar to those for 'tar, pitch and mineral oil'. Results for PAHs using the German job–task matrix were available only for men and did not show any increased risk (odds ratio, 0.9; 95% CI, 0.7–1.2; 0.8; 95% CI, 0.6–1.0; 0.9; 95% CI, 0.6–1.4 for medium, high and substantial exposure; based on 80, 67 and 26 exposed cases, respectively).

(b) Urinary bladder cancer (Table 2.11)

Baxter and McDowall (1986) conducted a case–control study in London, United Kingdom, based on death certificates. Cases were all deaths from urinary bladder cancer (ICD-8, 188) from 1968 to 1978 among male residents of six London boroughs. Two controls per case were selected, one from among male deaths from all other cancers and one from among all deaths including cancer, and matched on borough, age and year of death. A total of 1080 cases were included [the number of controls was not given but was assumed to be 2160, given two per case]. Occupational information was abstracted from death certificates by one of the authors. The occupation of 'gas worker' had odds ratios of 0.8 and 1.4 using the control groups of deaths from all other cancers and deaths from all other causes including cancer, respectively [confidence intervals were not given and the results were not statistically significant].

A hospital-based case–control study was carried out in 27 hospitals in the Copenhagen area, Denmark (Jensen *et al*., 1988). Cases were 97 incident cancers of the renal pelvis and ureter diagnosed between 1979 and 1982. The authors estimated that their case population represented approximately 80% of all Danish incident cases. Three hospital controls per case were matched for hospital, sex and age. Patients with urinary tract or tobacco smoking-related diseases were excluded from the controls, leaving 288 controls enrolled. Trained interviewers used a detailed questionnaire to obtain information on tobacco smoking, consumption of beverages, use of analgesics and occupational

Table 2.11. Case–control studies of urinary tract cancers and exposure to polycyclic aromatic hydrocarbons (PAHs)

Reference, location	Effective no. of subjects	Job/exposure category	Urinary cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Baxter & McDowall (1986), United Kingdom	1080 deceased male cases (1968–78), 2160 deceased male population controls	Gas workers	Bladder	11	0.8 [not given] 1.4 [not given]	Controls: deaths from all other cancers Controls: included deaths from all other causes, including cancer Job category extracted from death certificates; data of too poor quality to be considered; number of exposed deaths (cases + controls)
Jensen *et al.* (1988), Denmark	97 cases (1979–82), 288 hospital controls	Coke, coal Asphalt, tar	Renal pelvis, ureter	8 9	4.0 (1.2–13.6) 5.5 (1.6–19.6)	Only men were employed in these occupations and occupational history was not described in detail; adjusted for tobacco smoking
Risch *et al.* (1988), Canada	835 cases (1979–82), 792 population controls	*Aluminium smelting* Ever/never 8–28 years before diagnosis *Tar, asphalt* Ever/never 8–28 years before diagnosis	Bladder, including tumours of borderline malignancy	14 46 	1.91 (0.64–6.43) 2.61 (0.70–12.5) 1.44 (0.78–2.74) 3.11 (1.19–9.68)	From a list of industries/occupations and specific agents; only men were exposed to these occupations/agents; adjusted for smoking
Bonassi *et al.* (1989), Italy	144 male cases (1972–82), 405 male population controls	*Road menders* Definite exposure to PAHs Possible exposure to PAHs	Bladder, including papillomas	2 25 74	1.40 (0.27–7.28) 2.14 (0.82–5.60) 1.05 (0.45–2.44)	Job–exposure matrix for >1 year of exposure developed; adjusted for tobacco smoking and aromatic amines

Table 2.11 (contd)

Reference, location	Effective no. of subjects	Job/exposure category	Urinary cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Schumacher *et al.* (1989), Utah, USA	417 cases (1977–83), 877 population controls	**Coal tar, pitch**	Bladder			A job–exposure matrix was applied to code the complete lifetime occupational history collected; adjusted for tobacco smoking, age, religion, and education
		Men		92		
		Ever/never			1.08 (0.78–1.49)	
		<10 years/never			1.10 (0.76–1.60)	
		≥10 years/never			1.04 (0.64–1.68)	
		Women				
		Ever/never		3	2.30 (0.30–17.5)	
Clavel *et al.* (1994), France	658 male cases (1984–87), 658 male hospital controls	*Exposure to PAHs*	Bladder			Exposure assessed on case-by-case basis; adjusted for matching variables, tobacco smoking and coffee consumption; excluding subjects possibly exposed to aromatic amines; results unchanged after inclusion of subjects with possible exposure to aromatic amines
		Ever/never		231	1.3 (1.0–1.7)	
		Maximum intensity of exposure to PAHs				
		Low			1.2 (0.9–1.7)	
		Medium			1.3 (0.9–2.1)	
		High			1.8 (0.8–3.3)	
					p for trend <0.05	
Nadon *et al.* (1995), Canada	486 male cases, 2196 male population and cancer controls	*PAHs derived from coal*	Bladder			Case-by-case evaluation of lifelong occupational history; adjusted for tobacco smoking, age, socioeconomic status, ethnic group, proxy respondent and aromatic amines
		Low		154	0.8 (0.6–1.3)	
		High		67	0.6 (0.3–1.2)	

Table 2.11 (contd)

Reference, location	Effective no. of subjects	Job/exposure category	Urinary cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Grimsrud *et al.* (1998), Norway	52 male cases (1980–92), 156 male population controls	ISCP >1 year and exposed to PAHs	Bladder	3	0.5 (0.1–1.9)	Exposure was obtained from personnel files at the ISCP; no interview of the subjects, no data available for work outside these plants or for tobacco smoking; considered exposed to PAHs if worked in pig iron smelter department or >1 year in coke plant, according to an industrial hygienist
		ISCP >1 year without exposure to PAHs		20	1.4 (0.7–2.9)	

CI, confidence interval; ISCP, iron, steel and coke plants

and related exposures; 99% of cases and 100% of controls were enrolled and most (94%) of these subjects were interviewed at the hospital. Results were listed by occupation; however, no details were given on which jobs were concerned [i.e. the longest job held, the job held at the time of diagnosis]. Significant associations were obtained for occupational exposure to: coke and coal (odds ratio, 4.0; 95% CI, 1.2–13.6; based on eight exposed cases and seven exposed controls) and asphalt and tar (odds ratio, 5.5; 95% CI, 1.6–19.6; based on nine exposed cases and six exposed controls); only male subjects worked in these industries. All of the results were adjusted for lifetime tobacco consumption. [This study is qualified by the authors as an "explorative study with regard to occupational exposure". Neither temporal associations (duration, latency) nor the effect of the level of exposure was tested.]

Risch *et al*. (1988) conducted a population-based case–control study in Canada. Incident cases of urinary bladder cancer, diagnosed between 1979 and 1982 and aged 35–79 years, were included. Identification of the cases differed according to their residential region (registry, active review of medical records in main hospitals). A total of 1251 cases were identified, and a response rate of 67% resulted in a group of 835 cases. Controls were randomly selected through population listings, matched for year of birth, sex and area of residence; 1483 controls were selected and 792 accepted to participate (53% response rate). Questionnaires were completed at the subjects' home by trained interviewers. The occupational component included a list of 26 specific industries/occupations selected *a priori* by the authors, and subjects were asked whether they had ever worked in such industries. In the case of a positive answer, duration of employment was also requested. In addition, a list of substances was proposed to the subjects. Data were analysed in terms of ever versus never and duration of exposure, for which the authors defined a window of exposure from 8 to 28 years [the Working Group queried the choice of the time window] before case diagnosis in which they investigated an association with industries/occupations and with occupational exposure to agents. Statistical analysis was performed using conditional logistic regression models that systematically included tobacco smoking history. Among the industries/occupations studied, the odds ratio for ever working in aluminium smelting was 1.91 (95% CI, 0.64–6.43; based on 14 exposed cases). Interestingly, this association was reinforced when exposure occurring between 8 and 28 years before diagnosis was considered (odds ratio, 2.61; 95% CI, 0.70–12.50) as well as the trend with duration of exposure (odds ratio, 5.92; 95% CI, 1.07–3.20; for a unit of 10 years of duration). With regard to occupational exposure to substances, the odds ratio for urinary bladder cancer for the group 'tar asphalt' was 1.44 (95% CI, 0.78–2.74; based on 46 exposed cases) for subjects ever exposed versus never exposed, 3.11 (95% CI, 1.19–9.68) for subjects exposed 8 to 28 years before diagnosis and 2.02 (95% CI, 1.08–4.97) for a trend with a 10-year duration of exposure. [Some (n = 64) of the total (n = 826) cases that were included in the analysis were of borderline malignancy. However, exclusion of these cases and their matched controls did not modify the results.]

Bonassi *et al*. (1989) carried out a population-based case–control study in the Bormida valley (Italy) that focused on urinary bladder cancer and occupational exposure to PAHs. Cases were 150 histologically confirmed bladder cancers that were identified through hospital admission discharges and diagnosed between 1972 and 1982; 52% of cases were deceased at the time of interview. Population controls were randomly selected from the demographic registries of the region at the time of the diagnosis of the case, and were matched to cases on sex and age; 5% of the controls were deceased. The response rate among subjects (or the next of kin for the deceased) was 96% among cases and 90% among controls. A questionnaire was administered in 1983. Women were finally excluded from the analysis because of their small number and absence of exposure to PAHs, which left 144 male cases and 405 matched controls for the analysis. An a-priori list of 11 occupational categories of interest for bladder cancer was devised based on previous literature. A subject was classified as exposed if he had worked for more than 1 year in one of these categories (none of the subjects had worked in more than one category). In addition, a job–exposure matrix was constructed specifically for this study. According to the literature, some occupations were classified as having definite exposure to PAHs: coke worker, mechanic, railroad worker, glass worker, road mender, stoker (in a distillery), welder, coalman and mason (in a kiln). Imprecise occupational exposure to PAHs was classified as possible exposure. Odds ratios were adjusted for tobacco smoking using unconditional logistic regression. Among the list of the nine occupational categories, the odds ratio for road menders was 1.40 (95% CI, 0.27–7.28; based on two exposed cases and six exposed controls). Analysis for definite exposure to PAHs showed a non-significant increase in the risk for bladder cancer (odds ratio, 2.14; 95% CI, 0.82–5.60; based on 25 exposed cases and 48 exposed controls; also adjusted for exposure to aromatic amines). This increase in risk was not observed for subjects with possible exposure to PAHs (odds ratio, 1.05; 95% CI, 0.45–2.44; based on 74 exposed cases and 199 exposed controls; also adjusted for exposure to aromatic amines). In addition, an analysis stratified for exposure to aromatic amines showed that the odds ratio related to definite exposure to PAHs among subjects not exposed to aromatic amines was 2.53 (95% CI, 0.56–11.50; based on three exposed cases and five exposed controls). [The 'possible' category included jobs with imprecise occupational histories that are very heterogeneous with regard to exposure to PAHs (craftsman, carpenter, blacksmith) and therefore suffered from non-differential exposure misclassification, biasing the odds ratios towards the null value.]

A population-based case–control study was conducted in Utah, USA (Schumacher *et al*., 1989). Eligible cases were Utah residents, aged 21–84 years, who had had a urinary bladder cancer diagnosed between 1977 and 1983, and were identified through the Utah Cancer Registry. Controls, matched to cases by sex and age, were identified through random-digit dialling (for those aged 21–64 years) or through the Health Care Financial Administrative list (for those aged 65–84 years). The response rate was 76% for cases and 79% for controls, leading to a final sample of 417 cases and 877 controls after exclusion of subjects who did not have any occupation listed. Interviews were conducted at home

and provided information on several items including tobacco smoking, coffee consumption and complete lifetime occupational history (with the time period worked for each job). Occupations were coded using the 1970 US Bureau of Census Alphabetic Index of Industries and Occupations and a job–exposure matrix was applied (Hoar *et al*, 1980). Duration of exposure was classified as ever/never exposed or less than 10 or more than 10 years. Odds ratios and confidence intervals were generated using logistic regression models that were stratified by sex, smoking status and/or age. Men that had been ever exposed to coal tar and pitch did not have a significantly increased risk for bladder cancer (odds ratio, 1.08; 95% CI, 0.78–1.49; based on 92 exposed cases and 160 exposed controls). Taking duration of exposure into account did not modify the results (odds ratio, 1.10; 95% CI, 0.78–1.49; and 1.04; 95% CI, 0.64–1.68, respectively, for the categories <10 years and ≥10 years). These associations were adjusted for age, tobacco smoking, religion and education. Very few women were assessed as ever having been exposed to coal tar and pitch (odds ratio, 2.30; 95% CI, 0.30–17.5; based on three exposed cases and three exposed controls).

Clavel *et al*. (1994) conducted a multicentre, hospital-based case–control study in France to investigate occupational risk factors and urinary bladder cancer. A total of 765 histologically confirmed bladder cancers, diagnosed between 1984–1987 and aged <80 years, were identified as well as 765 controls who had been admitted to the same hospitals for different diseases, excluding cancer, haematuria and work accidents. The controls were matched to cases on sex, age, hospital, place of residence and ethnicity. Analysis was restricted to men (658 cases and 658 controls), since few women had been exposed to PAHs. A questionnaire was developed specifically for occupational history in which each job held by the subject was described. Job titles were further coded with the International Labour Office code and the French code of industrial sectors. Occupational exposure was assessed on a case-by-case basis by a hygienist team following the procedure developed by Gérin *et al*. (1985). Exposure to PAHs was considered in three categories (<10 ng/m^3, 10–999 ng/m^3 and ≥1000 ng/m^3), in terms of maximum dose, average or cumulative exposure to PAHs and according to time-related variables (total duration, age at start, time since starting, time since cessation of exposure). Statistical analysis was performed using unconditional logistic regression models adjusted for the matching variables, tobacco smoking and/or coffee consumption. Associations were also re-estimated after exclusion of subjects who had possibly been exposed to aromatic amines. When all job titles with exposure to PAHs were considered, regardless of the level, an odds ratio of 1.3 (95% CI, 1.0–1.7; adjusted for the matching variables, cumulative smoking and coffee consumption; excluding subjects possibly exposed to aromatic amines) was observed. A more restrictive definition of exposure to PAHs (>30% of workers exposed to the medium or high level) resulted in an association of 1.6 (95% CI, 1.0–2.5; based on 64 exposed cases; adjusted for matching variables and smoking status). Significant dose–response relationships (p-value for trend <0.05) were observed with average and maximum exposure to PAHs (odds ratio for categories of maximum exposure to PAHs compared to unexposed: low exposure, 1.2; 95% CI, 0.9–1.7; medium

exposure, 1.3; 95% CI, 0.9–2.1; high exposure, 1.8; 95% CI, 0.9–3.6). The dose–response relationship with cumulative exposure was more heterogeneous and therefore the test for trend was not significant (odds ratio: <100 ng/m^3, 1.7; 95% CI, 1.2–2.4; 100–499 ng/m^3, 0.8; 95% CI, 0.5–1.3; 500–14 999 ng/m^3, 1.3; 95% CI, 0.8–2.0; ≥ 15 000 ng/m^3, 1.8; 95% CI, 0.8–3.9; adjusted for matching variables, cumulative smoking, coffee consumption; excluding subjects possibly exposed to aromatic amines). No significant trend was seen with total duration of exposure or time since start or cessation of the exposure. Taking latency into account, the highest association was observed for the category 20–29 years since start of exposure (odds ratio, 1.8; 95% CI, 0.9–3.5; adjusted for matching variables, cumulative smoking, coffee consumption; excluding subjects possibly exposed to aromatic amines).

The study by Nadon *et al*. (1995) (described in detail in Section 2.2.2(*a*)) also reported results for urinary bladder cancer among 486 male cases and 2196 male population and cancer controls (excluding cancers of the lung and kidney). Overall, there were no significant associations between bladder cancer and exposure to different types of PAHs; however, high exposure to benzo(*a*)pyrene was associated with a significantly reduced risk for bladder cancer (odds ratio, 0.5; 95% CI, 0.3–0.8; based on 176 exposed cases). The odds ratios for low and high exposure to coal were 0.8 (95% CI, 0.6–1.3; based on 154 cases) and 0.6 (95% CI, 0.3–1.2; based on 67 exposed cases), respectively. There was no interaction between exposure to PAHs and smoking status in the risk for bladder cancer.

A population-based case–control study was carried out in the municipality of Rana, a town in Norway where iron, steel and coke plants are located (Grimsrud *et al*., 1998), and was aimed at determining why the incidences of lung and urinary bladder cancer in this area increased steadily during 1980–92 whereas the national incidence rates stabilized during the late 1980s. Lung cancer was the main end-point studied, although bladder cancer was included in the protocol. Fifty-two incident cases of bladder cancer diagnosed among male residents of Rana in 1980–92 and registered at the cancer registry constituted the case group. A group of 156 controls (three per case), matched to cases on sex and year of birth, was identified from the national registrar and selected from among residents living in Rana on January 1993 and deceased persons who had Rana as their last place of residence. Information on job titles and work area were taken from personnel files of the plants studied. Evaluation of exposure to PAHs was based on measurements in the job–exposure matrix used for lung cancer. Positive exposure was assigned for those who had worked for more than 1 year in the pig iron department of the iron or steel plants or those who had worked at the coke plants and had been exposed to PAHs according to environmental measurements made previously by industrial hygienists. Odds ratios and confidence intervals for urinary bladder cancer were derived from unadjusted conditional logistic regression models. Information on smoking habits and occupations outside the industry was not available. There was no increased risk for bladder cancer related to employment in the iron, steel and coke plants: the odds ratio for exposure to PAHs was 0.5 (95% CI, 0.1–1.9; based on three exposed cases and 19 exposed controls), and was

1.4 (95% CI, 0.7–2.9; based on 20 exposed cases and 45 exposed controls) for non-exposed workers at the same plants. The authors mentioned that the highest level of exposure to PAHs for top-side coke-oven workers was <300 μg/m^3 in the late 1970s, which was less than reported levels from American coke plants. The PAH level in the pig iron department of the iron and steel foundries was 25 μg/m^3, which was less than the national occupational exposure limit.

(c) Skin cancer (Table 2.12)

Kubasiewicz *et al*. (1989, 1991) conducted a population-based case–control study among men in Poland which also included a hospital-based control group. A total of 534 incident cases of skin cancer were identified from a hospital registry during 1983–88 and 376 of these were enrolled. Two age-matched (2:1) control groups comprised 752 subjects each, one from the general population and one from hospital clinics in the same area, which included dermatological outpatients who were treated for conditions other than skin cancer. A personal interview was conducted in the subjects' homes, in which detailed lifetime occupational history was collected using a questionnaire. Substances that contain PAHs were extracted from the occupational history (grease, tar, pitch, soot, mineral oil, creosote oil, anthracene oil, coke, petrol, paraffin, gasoline, paraffine oil, soft asphalt, mazout, bituminous mass, petroleum and asphalt). Only significant confidence intervals were reported. The frequency of exposure among cases, population controls and hospital controls was 57%, 54% and 57%, respectively. The association between exposure to PAHs and skin cancer was non-significant, regardless of the control group used (odds ratios, 1.15 and 1.14 for population and hospital controls, respectively; based on 216 exposed cases). There was also no significant association with duration of exposure. The study of each PAH considered separately, ignoring potential concomitant exposure to other PAHs, showed a statistically significant relation only for mineral oils (odds ratio, 1.46; 95% CI, 1.06–2.05; based on 99 exposed cases). This association was significant with the population control group but not with the hospital controls and was confirmed when a latency of 30 years or more was considered (1.60; 95% CI, 0.98–2.63; based on 36 exposed cases; odds ratio). [The Working Group noted that the description of the population was poor for both the cases and the controls. The histology of the skin cancer was not described and was not confirmed (except for the fact that they were selected from the registry). The assessment of exposure was not well described, and statistical analysis was also poor. Confounding factors were not taken into account, and confidence intervals were not given, except when significant. Therefore, the results of this study should be considered with caution.]

Gallagher *et al*. (1996) conducted a population-based case–control study among men in Canada. Eligible cases were men aged 20–79 years who had been diagnosed with a first primary basal-cell carcinoma (*n*=314) or a first primary squamous-cell carcinoma (*n*=225) and who were selected through the cancer registry. The group with basal-cell cancer included every fourth man registered with a head and neck basal-cell cancer and all men with a basal-cell cancer at any other anatomical site. Response rates were slightly

Table 2.12. Case–control studies of skin cancers and exposure to polycylic aromatic hydrocarbons (PAHs)

Reference, location	Effective no. of subjects	Job/exposure category	Skin cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Kubasiewicz *et al.* (1991), Poland	374 cases (1983–88), 752 population and 752 hospital controls	*Exposure to PAHs* Tar Pitch Soot Coke	Any	216 28 15 29 32	1.15 [NA, p >0.05] 1.09 [NA, p >0.05] 0.93 [NA, p >0.05] 1.22 [NA, p >0.05] 1.29 [NA, p >0.05]	Lifetime occupational history. [poor description of study population; the results should be interpreted with caution].
Gallagher *et al.* (1996), Canada	226 BCC cases and 180 SCC cases (1983–84), 406 population controls	Pitch tar and tar products Coal dust	BCC SCC BCC SCC	32 27 67 69	1.2 (0.7–2.1) 0.9 (0.5–1.7) 1.4 (0.9–2.1) 1.6 (1.0–2.4)	Lifetime occupational history; adjusted for skin and hair colour and mother's ethnicity

BCC, basal-cell carcinoma; CI, confidence interval; NA, not applied; SCC, squamous-cell carcinoma

higher for the group with squamous-cell carcinoma (80%) than for the basal-cell cancer patients (72%). A total of 226 basal-cell and 180 squamous-cell carcinomas were finally included. Eligible controls were 573 age-matched subjects randomly selected from the files of Alberta Health care insurance plan subscribers, who had had no prior basal-cell cancer or squamous-cell carcinoma. A 71% response rate resulted in 406 enrolled subjects. Subjects were interviewed at home by trained interviewers who were unaware of the objectives of the study and were blinded to case–control status. The questionnaire included questions on phenotype and pigmentation factors, factors related to the medical history, smoking history and detailed lifetime occupational history (job titles, periods). Detailed information on exposure assessment was not given. A list of specific substances to which subjects might have been exposed was created that included 'coal dust' and 'pitch tar and tar products'. To test for a dose–response effect, a 'duration' variable was constructed from the duration of the jobs held weighted with the source of exposure (direct job, job environment, hobby, home) and intensity of exposure (<1 h/week, 1–4 h/week, 5–19 h/week, ≥20 h/week). Subjects were dichotomized to compare exposed with unexposed subjects. The same control group was used for comparisons between the two case groups (basal-cell cancer and squamous-cell carcinoma). Statistical analysis was carried out using conditional logistic regression models adjusted for age, skin and hair colour, mother's ethnic origin and exposure to sunlight as potential confounding factors. No association was noted with pitch tar and tar products (odds ratio, 1.2; 95% CI, 0.7–2.1; 32 exposed cases of basal-cell cancer; odds ratio, 0.9; 95% CI, 0.5–1.7; 27 exposed cases of squamous-cell carcinoma), but an association of borderline significance was noted with exposure to coal dust (odds ratio, 1.4; 95% CI, 0.9–2.1; 67 exposed basal-cell cancer cases; odds ratio, 1.6; 95% CI, 1.0–2.4; 69 exposed squamous-cell carcinoma cases). All the results were adjusted for age, mother's ethnicity, and skin and hair colour. [The frequency of exposure was 16% for pitch tar and 43% for coal dust. Job titles that were considered to entail exposure to these substances were not specified. The duration–effect relationship with squamous-cell carcinoma, observed for exposure to petroleum products and coal dust, increased the credibility of the association.]

(d) Laryngeal cancer (Table 2.13)

Ahrens *et al*. (1991) conducted a hospital-based case–control study in a main general hospital of the Bremen region, Germany. Cases included in the study were 55 incident male patients who were diagnosed with histologically confirmed laryngeal cancer in 1986 and 30 prevalent male cases diagnosed during 1984–85. Age, localization of the tumours and region of last residence were distributed equally between the two groups of cases, and all but one were squamous-cell carcinomas. Controls were selected from among the admission list of the same hospital, excluding neoplastic diseases and tobacco smoking-related diseases. Patients were interviewed with a standardized questionnaire that included questions on smoking and drinking habits as well as lifetime occupational history (industry, job titles, period). Industries and job titles were coded blinded to case–control status using standard German codes. Analysis was performed by grouping industries and

Table 2.13. Case–control studies of laryngeal cancer and exposure to polycyclic aromatic hydrocarbons (PAHs)

Reference, location	Effective no. of subjects	Job/exposure category	Head and neck cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Gustavsson *et al.* (1998), Sweden	157 cases (1988–91), 641 population controls	*Exposure to PAHs*	Larynx			Lifetime occupational history; adjusted for region, age group and tobacco and alcohol consumption
		Low		26	0.77 (0.46–1.28)	
		High		53	1.47 (0.96–2.24)	
Elci *et al.* (2003), Turkey	940 cases (1979–84), (227 glottic cancer, 438 supraglottic cancer, 275 subglottic or unspecified cancer), 1519 hospital controls	Exposure to PAHs	All larynx	376	1.3 (1.1–1.6)	Lifetime occupational history; adjusted for age, tobacco smoking and alcohol consumption; no participation rates given
			Supraglottis	174	1.3 (1.1–1.7)	
			Glottis	94	1.4 (1.0–1.9)	
			Other sites	108	1.3 (0.9–1.7)	
		Intensity of exposure to PAHs	All larynx			
		Low		189	1.4 (1.1–1.7)	
		Medium		138	1.3 (1.0–1.6)	
		High		49	1.5 (1.0–2.2)	
Becher *et al.* (2005), Germany	257 cases (1998–2000), 769 population controls	**Road construction worker**	Larynx	22	6.4 (2.4–17.3)	Lifetime occupational history; adjusted for cigarette smoking and alcohol consumption
		Exposure to PAHs				
		Based on supplementary job questionnaire		19	2.3 (1.15–5.2)	
		Based on exposure checklist		25	1.6 (0.9–3.1)	

CI, confidence interval

job titles into 31 occupations and 21 branches of industry. In addition, the subjects declared at the end of the occupational history if they had been exposed to any substance on a list of 19 occupational exposures. Statistical analysis was performed using unconditional logistic regression, adjusting for age, tobacco smoking and alcohol drinking as potential confounders. With regard to self-reported occupational exposures, there was no association with coal tar/bitumen (odds ratio, 0.6; 95% CI, 0.2–1.9 [the number of exposed subjects was not given]). The coal tar/bitumen group included subjects who had been employed in the following industries: manufacture of machinery and transport equipment, general construction and interior construction; and for the following occupations: bricklayers and reinforced concreters, stone masons, road and other construction workers, stationery engine, crane and hoist operators, earth-moving machine operators, managers and accountants. [The Working Group considered that the category coal tar/bitumen was too wide to be considered in the scope of this monograph.]

Gustavsson *et al.* (1998) conducted a population-based case–control study of oral cancer in Sweden. Incident male cases of oral cancer (oral cavity, oropharynx, hypopharynx, oesophagus and larynx; ICD-9: 141, 143, 144, 145, 146, 148, 150 and 161), aged 40–79 years, who were registered in the cancer registry as being from Stockholm or living in the southern health care region and who were diagnosed between 1988 and 1991 were included. Controls were selected from population registers, and were frequency-matched to cases for region and age group. The response rates were 90% in cases and 85% in controls. A total of 157 cases of laryngeal cancer and 641 controls were included in the analysis. A standardized questionnaire included questions on lifestyle, tobacco and alcohol consumption as well as lifetime occupational history. Occupational history was reviewed blinded to the case–control status by an occupational hygienist who coded job titles according to a standard Swedish classification as well as the intensity and probability of exposure to 17 specific occupational exposure factors, including PAHs. Intensity of exposure to PAHs was assessed on a four-level scale, using benzo[*a*]pyrene as an indicator of exposure; level 3 represented exposures that were greater than one-fifth of the threshold limit value (TLV) for benzo[*a*]pyrene. The ratio between levels 1, 2 and 3 was 1, 10 and 100 for PAHs. Probability of exposure was also assessed on three levels: >70%, 33–70% and <33%. Cumulative exposure was calculated as the product of intensity, probability and duration of exposure; the contribution over the entire work history was also added. Statistical analysis was performed using unconditional logistic regression, adjusted for region, age group, tobacco smoking (current/former/never) and alcohol consumption (average level of alcohol intake in the past 5 years in grams of ethanol per week). Exposure to PAHs was first dichotomized in two classes (low, high), using the median of the cumulative index for the exposed controls as the cut-off point. Low exposure was not significantly related to laryngeal cancer (odds ratio, 0.77; 95% CI, 0.46–1.28; 26 exposed cases). For high exposure to PAHs, the odds ratio increased to 1.47 (95% CI, 0.96–2.24; 53 exposed cases). Among controls, the authors assessed the level of exposure to PAHs to be high for 1 year of employment as a coke or gas worker or 10 years as a steel or foundry worker and to be low for car repairers, garage workers and

iron miners because they would never accumulate enough exposure to be included in the high-exposure group.

Elci *et al*. (2003) carried out a hospital-based case–control study among men in Turkey. A total of 940 laryngeal cancer patients (ICD 161.0, 161.1, 161.2 and 161.9), diagnosed between 1979 and 1984 in the oncology treatment centre, and a control group of 1308 other cancer patients and 211 non-cancer subjects were analysed. During a personal interview, subjects were asked about tobacco smoking, alcohol drinking and lifetime occupational history. Each job held was coded for industry and occupation according to standard US codes by an industrial hygienist who created a job–exposure matrix that allowed assessment of exposure to several agents including PAHs and diesel exhaust. Exposure was assessed in terms of probability (lower than 25%, 25–75% and >75%) and intensity (<TLV, between TLV and 2 TLV and >2 TLV). Probability and intensity were then combined to achieve a final score that was categorized into unexposed, and low, medium and high exposure. Statistical analysis was performed using unconditional logistic regression, adjusted for age, tobacco smoking and alcohol drinking. Data on tobacco smoking and alcohol drinking were included in the models as ever/never exposure. Results were given only according to the occupational exposure assigned by the job–exposure matrix. The most prevalent exposure among cases was to PAHs (40%) followed by diesel exhaust (32%). The association between exposure to PAHs and all laryngeal cancers was significant (odds ratio, 1.3; 95% CI, 1.1–1.6; 376 exposed cases and 486 exposed controls), and was similar for the individual subsites (supraglottic, glottic and others). However, these results were mainly influenced by exposure to diesel exhaust since all subjects exposed to diesel exhaust were also exposed to PAHs. After exclusion of the subjects exposed to diesel exhaust, the association with PAHs was no longer significant (odds ratio, 0.8; 95% CI, 0.6–1.1). The association was further explored by intensity and probability of exposure. For intensity, no dose–response relationship was observed with exposure to PAHs in general (odds ratio: low, 1.4; 95% CI, 1.1–1.7; medium, 1.3; 95% CI, 1.0–1.6; high, 1.5; 95% CI, 1.0–2.2), although a dose–response was observed for supraglottic cancers only (odds ratio: low, 1.2; 95% CI, 0.9–1.6; medium, 1.4; 95% CI, 1.0–1.9; high, 1.7; 95% CI, 1.1–2.8). [The Working Group noted the poor adjustment for tobacco smoking and alcohol consumption, which are strong risk factors for laryngeal cancer. In addition, consideration of exposure to these factors with a covariable 'ever use' may lead to an underadjustment. The analysis clearly shows that the association with PAHs is actually governed by exposure to diesel exhaust, which is outside of the scope of this monograph.]

Becher *et al*. (2005) conducted a population-based case–control study in Germany among citizens aged up to 80 years. Cases were selected from the clinics of the different cities, and had been diagnosed with a histologically confirmed laryngeal tumour during 1998–2000. Local practitioners were also contacted to verify complete case ascertainment. Controls were randomly selected from population registries, and were frequency matched to cases (1:3) on age and gender. Personal interviews were carried out on 257 cases (89% response rate) and 769 controls (62% response rate). Occupational

exposure was assigned using three sources of the questionnaire: a detailed lifetime occupational history, an exposure checklist and supplementary job questionnaires. Industries and occupations were coded using standard German and International Labour Organization codes. Job titles were grouped into broader categories, which were analysed for their association with laryngeal cancer. Exposure to PAHs was assessed from selected jobs known to entail such exposures: roofer and installer of house siding, insulation installer, and workers in road construction, civil engineering, building construction, agriculture and forestry. In addition, the following substances were also listed in the questionnaire: coal tar, pitch, carbolineum and coal or graphite electrodes. Odds ratios were obtained using conditional logistic regression, adjusting for tobacco smoking and alcohol consumption and stratifying by age and gender. The category of road construction worker (on an 'ever held job' basis) was strongly associated with laryngeal cancer (odds ratio, 6.4; 95% CI, 2.4–17.3; based on 22 exposed cases and nine exposed controls). [It was not clear to the Working Group the type of exposures that were covered by the definition of road construction.] Exposure to PAHs assessed by the supplementary job questionnaire was statistically related to laryngeal cancer (odds ratio, 2.3; 95% CI, 1.1–5.2; based on 19 exposed cases and 15 exposed controls), although the relation diminished when assessment was based on the checklist of the questionnaire (odds ratio, 1.6; 95% CI, 0.9–3.1; based on 25 exposed cases and 29 exposed controls). Duration of exposure was explored in three categories, and the relation was significant only for the highest class (odds ratio, 3.8; 95% CI, 1.3–11.1; corresponding to >1300 h of exposure; 15 exposed cases and seven exposed controls). The odds ratio for the intermediate class (>0–1300 h) was 1.06 (95% CI, 0.3–4.0; four exposed cases and eight exposed controls).

(e) Pancreatic cancer (Table 2.14)

Kauppinen *et al.* (1995) conducted a population-based case–control study in Finland, on 1419 deceased cases of pancreatic cancer (ICD-9, 157), aged 40–74 years, who were identified from the Finnish Cancer Register files during 1984–87. Controls comprised 3150 subjects who had died from cancer at other sites (stomach, colon, rectum), at the same age and time period as the cases. Lifetime occupational histories were collected by a postal questionnaire sent to the next of kin, for which the response rates were 47% and 50% for cases and controls, respectively. After exclusions, mainly non-respondents (n=2497), the study included 595 cases and 1622 controls. Occupational histories were reviewed by industrial hygienists. Statistical analysis was performed using unconditional logistic regression models, adjusted for age, gender, history of diabetes mellitus, and smoking and alcohol use in the 1960s. The odds ratio for exposure to PAHs, based on industrial hygienist expertise of work histories, was 1.33 (95% CI, 0.69–2.57; based on 14 exposed cases).

Alguacil *et al*. (2000) conducted a hospital-based case–control study in Spain. Cases were incident pancreatic cancer patients who were diagnosed in one of the five hospitals included in the study. A total of 185 cases were identified, and 164 (96 men and 68 women) were included in the analysis (participation rate, 89%). Hospital controls were

Table 2.14. Case–control studies of pancreatic cancer and exposure to polycyclic aromatic hydrocarbons (PAHs)

Reference, location	Effective no. of subjects	Job/exposure category	Pancreatic cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Kauppinen *et al.* (1995), Finland	595 deceased cases (1984–87), 1622 hospital controls	PAH exposure as assessed by an industrial hygienist	Any	14	1.33 (0.69–2.57)	Adjusted for age, gender, history of diabetes, smoking and alcohol use
Alguacil *et al.* (2000), Spain	164 cases (1992–95), 238 hospital controls	**Exposure to PAHs** *Intensity (for duration >10 years, lag of 10 years before diagnosis)*	Any	13	0.81 (0.37–1.76)	List of 10 activities, and jobs held for more than 6 years; lifetime occupational history obtained; Finnish job–exposure matrix used
		Low		8	1.08 (0.39–3.00)	
		High		2	1.73 (0.22–13.8)	
		>35μg/m^3 PAH		2	0.78 (0.12–5.18)	
Nadon *et al.* (1995), Canada	117 cases, 2741 population and hospital controls	*PAHs derived from coal*	Any			Other cancers among controls were lymphoma, periampullary cancer, and cancers of the lung, stomach, colon, liver, small intestine and oesophagus
		Low		7	1.1 (0.5–1.5)	
		High		5	2.1 (0.8–5.4)	

CI, confidence interval

selected from the same hospital as the case, and were free of pancreatic cancer, but an initial diagnosis was suspicious of pancreatic cancer, biliary cancer or chronic pancreatitis. Controls were diagnosed with acute or chronic pancreatitis, benign biliary pathology as well as lymphoma, periampullary neoplasms, abdominal digestive neoplasms of unspecified origin, metastasis and cancers of the colon, lung, liver, small intestine and oesophagus. Of the 264 eligible controls, 238 patients (167 men and 71 women) accepted to participate (90%). A panel of experts reviewed the diagnoses of all patients. Interviews took place during hospitalization by trained monitors who recorded occupation and lifestyle histories. A list of 10 work-related activities, defined *a priori* as being potentially related to pancreatic cancer, was proposed to the subjects. Subjects were also asked to describe jobs held for more than 6 years. Two industrial hygienists assessed exposure to 22 substances and classified them by level of exposure (exposed, unexposed or unknown) as well as by intensity of exposure (low, medium, high or unknown). In addition, the Finnish job–exposure matrix was used to assess exposure to 21 substances (unexposed, low, substantial). The cut-off point between low and substantial was at the 75th percentile of the distribution of the product of probability × intensity. Statistical analysis was performed by unconditional logistic regression, adjusted for age, gender, tobacco smoking and alcohol use. An assessment of exposure to PAHs by industrial hygienists was associated with an odds ratio of 0.81 (95% CI, 0.37–1.76; 13 exposed cases (8%) and 34 exposed controls (13%)). Although the results were non-significant, the relation increased when intensity, duration and latency were accounted for: low exposure for at least 10 years, 10 years before diagnosis (odds ratio, 1.08; 95% CI, 0.39–3.00; eight cases (5%) and 17 controls (7%)) and high exposure for at least 10 years, 10 years before diagnosis (odds ratio, 1.73; 95% CI, 0.22–13.8; two cases (1%) and two controls (<1%)). The association between exposure to PAHs (>0.35 μg/m^3) and pancreatic tumours using the Finnish job–exposure matrix as a method of assessment was not significant (odds ratio, 0.78; 95% CI, 0.12–5.18; two cases (1%) and three controls (2%) exposed for at least 10 years, 10 years before the diagnosis).

In the case–control study conducted by Nadon *et al*. (1995) in Canada (described in detail in Section 2.2.2*(a)*), 117 pancreatic cancer patients were included, and 2741 population and cancer controls were enrolled after exclusion of lung cancers. No significant association was observed between pancreatic cancer and exposure to PAHs.

A meta-analysis on occupational exposures and pancreatic cancer (Ojajärvi *et al.*, 2000) identified four informative studies of occupational exposures to PAH compounds (Cammarano *et al.*, 1986; Moulin *et al.*, 1989; Siemiatycki, 1991; Kauppinen *et al.*, 1995). The meta-risk ratio for pancreatic cancer associated with exposure to PAHs was 1.5 (95% CI, 0.9–2.5).

(f) Stomach cancer (Table 2.15)

In the case–control study conducted by Nadon *et al*. (1995) in Canada (described in detail in Section 2.2.2*(a)*), 250 stomach cancers were included, together with a total of

Table 2.15. Case–control studies of stomach cancer and exposure to polycyclic aromatic hydrocarbons (PAHs)

Reference, location	Effective no. of subjects	Job/exposure category	Stomach cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Nadon *et al.* (1995), Canada	250 male cases (1979–86), 2514 male population and cancer controls	*PAHs derived from coal*	Any			Lifetime occupational history; case-by-case evaluation; adjusted for tobacco smoking, age, socioeconomic status and ethnicity; cancers of the lung and oesophagus were excluded from the control group
		Low		17	1.1 (0.7–1.9)	
		High		9	1.5 (0.8–3.1)	
Cocco *et al.* (2005), USA	41 957 cases (1984–94), 83 914 population controls	*Intensity of exposure to PAHs (white men)*	Any			Study subjects were obtained from death certificates. Occupation and industry reported on the death certificate; crude occupational data; results are given in terms of number of exposed subjects.
		Low		4047	1.00 (0.95–1.04)	
		Medium		1983	1.08 (1.02–1.15)	
		High		616	1.00 (0.90–1.10)	
		Probability of exposure to PAHs (white men)				
		Low		1356	1.04 (0.97–1.12)	
		Medium		1896	1.06 (1.00–1.13)	
		High		3394	0.99 (0.95–1.05)	

CI, confidence interval

2514 population and cancer control patients (excluding cancers of the lung and oesophagus). Results are presented in Table 2.15 but no significant results were observed.

Cocco *et al*. (2005) carried out a case–control study in 24 states of the USA based on death certificates. The authors obtained deaths from stomach cancer for the period 1984–96 among persons aged ≥25 years for 20 878 white men, 14 125 white women, 4215 African–American men and 2739 African–American women. Controls were deaths from non-malignant disease, matched (2:1) on region, gender, age and race. Occupation and industry, coded routinely since 1984 according to the 1980 US census occupation and industry codes, were extracted from the certificates. A job–exposure matrix was developed by two of the authors, which assessed a probability of exposure and an intensity level for each three-digit occupation and industry code. A probability and intensity score was then built. This score was based on the product of the subject's probability (and intensity) score attributed to the occupation with that of industry, if industry was the main contributor to exposure assessment. If the information on exposure came from occupation irrespective of the industry (i.e. plumber, welder), the score was based on the square of the occupational score. Odds ratios derived from logistic regression models included the following covariables: age, ethnic origin, marital status, urban/non-urban residence and socioeconomic status (based on Green's standardized score for specific occupation). Among white men, there was no association with exposure to PAHs, regardless of the intensity of exposure: low (odds ratio, 1.0; 95% CI, 0.95–1.04; 4047 exposed cases), medium (odds ratio, 1.08; 95% CI, 1.02–1.15; 1983 exposed cases) or high (odds ratio, 1.0; 95% CI, 0.90–1.10; 616 exposed cases). A weak association among white women was found at the low (odds ratio, 1.29; 95% CI, 1.06–1.59; 159 exposed cases) and medium levels of intensity (odds ratio, 1.39; 95% CI, 1.13–1.70; 158 exposed cases) but not at the high intensity level of exposure (odds ratio, 0.89; 95% CI, 0.67–1.18; 72 exposed cases). There were no significant associations with different exposure intensities observed among the African–American men and women. Probability of exposure gave similar results in white men for low (odds ratio, 1.04; 95% CI, 0.97–1.12; 1356 exposed cases), medium (odds ratio, 1.06; 95% CI, 1.00–1.13; 1896 exposed cases) and high probability (odds ratio, 0.99; 95% CI, 0.95–1.05; 3394 exposed cases).

(g) Oesophageal cancer (Table 2.16)

Gustavsson *et al.* (1998) (described in detail in Section 2.2.2(*d*)), included 122 cases of oesophageal cancer and 641 age- and region-matched population controls. Results for exposure to PAHs showed a significant relation at both low levels (odds ratio, 2.01; 95% CI, 1.16–3.48; based on 32 exposed cases) and high levels (odds ratio, 1.87; 95% CI, 1.11–3.16; based on 37 exposed cases) of exposure. However, no increase in the effect was observed with increasing exposure.

Parent *et al*. (2000) studied male oesophageal cancer patients (63 squamous-cell, 23 adenocarcinoma and 13 of uncertain morphology) aged 35–70 years, selected from a database of all cancer patients registered during 1979–85, who were included in a large

Table 2.16. Case–control studies of oesophageal cancer and exposure to polycyclic aromatic hydrocarbons (PAHs)

Reference and country	Effective no. of subjects	Job/exposure category	Oesophageal cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Gustavsson *et al.* (1998), Sweden	122 cases (1988–91), 641 controls	*Exposure to PAHs*	Any			Lifetime occupational history
		Low		32	2.01 (1.16–3.48)	
		High		37	1.87 (1.11–3.16)	
Parent *et al.* (2000), Canada	99 cases (1979–85) (63 squamous-cell, 23 adenocarcinoma, 13 uncertain origin), 1066 population and cancer controls	*PAHs from coal*	Any			Lifetime occupational history; case-by-case exposure assessment
		Ever/never		10	1.2 (0.6–2.5)	
		Non-substantial		4	0.7 (0.2–2.1)	
		Substantial		6	2.0 (0.8–5.3)	
		Benzo[a]pyrene				
		Ever/never		24	1.1 (0.7–1.9)	
		Non-substantial		19	1.0 (0.5–1.7)	
		Substantial		5	2.3 (0.8–6.5)	

CI, confidence interval

Canadian case–control study. Controls were selected from electoral lists by random digit dialling. The response rates were 82% for cases and 75% for controls, which resulted in a final sample size of 99 cases and 1066 age-matched controls (533 population controls and 533 cancer controls) for analysis. Odds ratios were estimated by unconditional logistic regression, adjusted for age, birthplace, education, respondent (self or proxy), tobacco smoking, alcohol consumption and β-carotene intake. Branches of occupation and industry were coded using standard classification systems and were analysed by duration of employment, excluding the 5 years preceding diagnosis or enrolment into the study. The odds ratio for exposure to PAHs from coal in the ever-exposed category for all histological types was 1.2 (95% CI, 0.6–2.5; 10 exposed cases) and that for a substantial level of exposure was 2.0 (95% CI, 0.8–5.3; six exposed cases). Results were also non-significant for exposure to benzo[*a*]pyrene. When squamous-cell carcinoma was considered separately, the results were not significantly modified. When other potential exposures to carcinogens (sulfuric acid, toluene, chrysotyle asbestos, other paints and varnishes, iron compounds) were taken into account, the results remained similar for exposure to carbon black (odds ratio, 2.1; 95% CI, 0.8–5.3; nine exposed cases). [No industrial branches or occupations for which odds ratios were estimated were within the scope of this monograph.]

(h) Prostatic cancer (Table 2.17)

Aronson *et al*. (1996) studied occupational risk factors for prostatic cancer within a large Canadian case–control study (Gérin *et al*, 1985). Male patients with histologically confirmed prostatic cancer were selected from a database of all cancer patients registered in Montréal during 1979–85 (557 eligible patients) and 449 were interviewed (response rate, 81%). The statistical analysis was carried out with a pooled control group of 533 population-based (response rate, 72%) and 1550 other cancer controls for 17 occupations, 11 industries and 27 substances using unconditional logistic regression, adjusted for age, family income, ethnicity, Quetelet (body mass) index and respondent status. Each occupation, industry or substance was included in separate models. Exposure to the substances was assessed as non-substantial/substantial according to an index that combined confidence of assessment, latency, duration and the product of the concentration of and frequency of exposure to the substance (both scored as low, medium and high). Results by industry or occupation were reported according to duration (dichotomized into greater or less than 10 years of employment). Results for the assessment of exposure to PAHs from any sources showed no relation with either non-substantial or substantial exposure (odds ratio for non-substantial, 0.84; 95% CI, 0.63–1.12; odds ratio for substantial, 1.21; 95% CI, 0.68–2.17). With regard to exposure to PAHs from coal, a significant relation was observed at the non-substantial level (odds ratio, 1.99; 95% CI, 1.24–3.20) which was not confirmed at the substantial level (odds ratio, 1.08; 95% CI, 0.40–2.95). The relationship between prostatic cancer and exposure to PAHs from coal was further explored according to confidence of assessment,

Table 2.17. Case–control studies of prostatic cancer and exposure to polycyclic aromatic hydrocarbons (PAHs)

Reference, location	Effective no. of subjects	Job/exposure category	Prostatic cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Aronson *et al.* (1996), Canada	449 cases (1979–85), 2083 population and hospital controls	**PAH from any source**	Any			Lifetime occupational history; case-by-case expertise; categories were based on an index of cumulative exposure.
		By level of exposure				
		Non-substantial		238	0.84 (0.63–1.12)	
		Substantial		62	1.21 (0.68–2.17)	
		PAH from coal				
		By level of exposure				
		Non-substantial		40	1.99 (1.24–3.20)	
		Substantial		20	1.08 (0.40–2.95)	
		By confidence				
		Probable		13	1.3 (0.7–2.5)	
		Definite		47	1.6 (1.1–2.3)	
		By concentration				
		Low		21	2.0 (1.2–3.5)	
		Medium-high		39	1.3 (0.9–2.0)	
		By frequency				
		Low-medium		35	1.4 (0.9–2.1)	
		High		25	1.7 (1.0–2.7)	
		By duration				
		<10 years		31	1.6 (1.0–2.4)	
		>10 years		29	1.4 (0.9–2.3)	
Krstev *et al.* (1998), USA	981 incident cases (1986–89), 1315 population controls	**Power plant operators**	Any			Lifetime occupational history
		By ethnicity				
		African–American		9	3.96 (1.05–14.90)	
		White		7	1.68 (0.55–5.08)	
		By duration of employment				
		<5 years		7	1.51 (0.50–4.55)	
		5–19 years		6	3.68 (0.74–18.40)	
		≥20 years		3	4.04 (0.41–39.8)	
		p for trend			0.03	

CI, confidence interval

concentration of exposure and duration. Results are included in Table 2.17 and are of moderate magnitude (range, 1.3–2.0) and mostly of borderline significance.

Krstev *et al.* (1998) conducted a population-based case–control study in the USA that included 981 incident cases of prostatic cancer (479 African–American and 502 white men) diagnosed between 1986–89 and 1315 controls (594 African–American and 721 white men category matched by age and race), aged 40–79 years, who resided in Atlanta, Detroit and 10 counties in New Jersey that were covered by population-based cancer registries. Lifetime occupational history was obtained from the subjects and job titles were coded according to standard occupational codes. The odds ratio for power plant operators adjusted for age, study site and race was 2.28 (95% CI, 1.00–5.21; based on 16 exposed cases). When stratified by race, the odds ratio was 3.96 (95% CI, 1.05–14.90; based on nine exposed cases) among African–Americans and 1.68 (95% CI, 0.55–5.08) among whites. A trend (p = 0.03) was observed for duration of exposure (odds ratios, 1.51, 3.68 and 4.04 for <5, 5–19 and ≥20 years of exposure, respectively).

2.3 Meta-analyses of studies of workers exposed to PAHs

Partanen and Boffetta (1994) reviewed 20 studies of asphalt workers and roofers that included 11 cohort and nine case–control studies of exposure to asphalt/bitumen or coal tar. All of the cohort studies addressed lung cancer and some provided data on additional sites. The case–control studies addressed cancers of the lung, urinary bladder and stomach, leukaemia and non-melanoma skin cancer. The meta-analysis excluded some studies that specified occupational categories poorly. Pooled relative risks were presented for the cohort and case–control studies separately, as well as for all cohort and case–control studies combined; the results were presented together with a test for heterogeneity between individual studies. Results were presented for the whole population and separately for three categories of occupational exposure: pavers and highway maintenance workers, roofers and miscellaneous or unspecified workers. For roofers, the overall pooled relative risk was 1.76 (95% CI, 1.46–2.11; based on 118 cases) for lung cancer in four cohort studies and 1.88 (95% CI, 1.23–2.76; based on 26 cases) in three case–control studies. The pooled relative risk across both designs was 1.78 (95% CI, 1.50–2.10; based on 144 cases; p-value for heterogeneity, 0.03). For pavers and highway maintenance workers, the overall pooled relative risk for lung cancer in three cohort studies was 0.87 (95% CI, 0.74–1.01; based on 167 cases). For stomach cancer, the pooled relative risks in three cohort studies were 1.33 (95% CI, 1.05–1.66; based on 77 cases) for all asphalt workers, 1.71 (95% CI, 1.12–2.51; based on 26 cases) for roofers and 1.14 (95% CI, 0.83–1.53; based on 44 cases) for pavers and highway maintenance workers. [The potential separate contributions of exposure to coal tar and bitumen to the observed excess risks could not be distinguished. The potential for exposure to coal tar was probably higher for roofers than for pavers.] For urinary bladder cancer, the pooled relative risks in cohort studies were 1.38 (95% CI, 1.06–1.78; based on 60 cases) for all asphalt workers, 1.68 (95% CI, 0.90–2.88; based on 13 cases in one study) for roofers and

1.20 (95% CI, 0.74–1.83; based on 21 cases in two studies) for pavers and highway maintenance workers. Only cohort studies investigated non-melanoma skin cancer and the pooled relative risks were 1.74 (95% CI, 1.07–2.65; based on 21 cases in four studies) for all asphalt workers, 4.0 (95% CI, 0.83–11.7; based on three cases in one study) for roofers and 1.20 (95% CI, 1.19–3.66; based on 14 cases in one study) for pavers and highway maintenance workers. Only cohort studies investigated leukaemia and the pooled relative risks were 1.41 (95% CI, 1.05–1.85; based on 51 cases in six studies) for all asphalt workers, 1.73 (95% CI, 0.94–2.90; based on 14 cases in two studies) for roofers and 1.31 (95% CI, 0.92–1.81; based on 36 cases in three studies) for pavers and highway maintenance workers.

Armstrong *et al.* (2002, 2004) performed a meta-analysis of published cohort studies in which PAHs were judged to be the predominant carcinogens implicated in lung (Armstrong *et al*., 2004) or urinary bladder (Armstrong *et al.*, 2002) cancer; 39 cohorts met these criteria. For each study, a unit relative risk for lung cancer was calculated in relation to cumulative exposure to benzo[*a*]pyrene. Eleven studies provided measurements of exposure to PAHs indexed as benzo[*a*]pyrene, five provided measurements of exposure to PAHs that were converted to benzo[*a*]pyrene from benzene-soluble matter, total PAHs or carbon black and, in 20 studies, benzo[*a*]pyrene was estimated by industrial hygienists from published measurements in comparable workplaces (Armstrong *et al.*, 2002). These latter estimations were carried out blind to the relative risks in the studies to which they were applied. To calculate cumulative exposure (as benzo[*a*]pyrene concentration–years), duration of employment was taken from the studies or, for those studies that did not provide duration of employment, a default value of 20 years was chosen, which was close to the average duration reported in other studies. Unit relative risks for each study were calculated by Poisson regression, assuming a log-linear relative risk model, and these were presented with 95% confidence intervals for the risk per 100 μg/m^3 benzo[*a*]pyrene–years of cumulative exposure. In studies that provided more than one contrast, internal comparisons were used rather than external comparisons, and higher contrasts in estimated exposure were used rather than lower ones. For all the studies combined and for groupings of results by industrial sector, heterogeneity of unit relative risk was estimated, and pooled unit relative risk values were estimated by meta-regression, using a log-linear random effects model with restricted maximum likelihood. Twenty-eight (72%) of the unit relative risks were >1, with the lower confidence limit >1 (p <0.05) in 14 of these. The pooled unit relative risk estimates were 1.17 (95% CI, 1.12–1.22; based on 10 studies) for coke ovens, 1.15 (95% CI, 1.11–1.20; based on four studies) for gas distillation and 1.16 (95% CI, 1.05–1.28; based on eight studies) for aluminium reduction. The test for heterogeneity between the three latter estimates was not significant (p >0.2). Higher values were found for other sectors: the pooled unit relative risk was 17.50 (95% CI, 4.21–72.78; based on three studies) for asphalt workers, 12.28 (95% CI, 0.48–314.4; based on three studies) for tar distillers, 16.24 (95% CI, 1.64–160.7; based on two studies) for chimney sweeps and 4.30 (95% CI, 0.81–22.79; based on four studies) for carbon electrode manufacturers. In addition, estimates were made for workers

in thermoelectric power plants that resulted in a very high but unstable unit relative risk (>1000; lower CI, 0; based on three studies) and in carbon black plants that gave a unit relative risk of 0 (upper CI, >1000; based on two studies). [The latter two industries had very low estimated levels of of benzo[*a*]pyrene and, as they do not use or process coal-tar derivatives, were not considered to be directly relevant to this monograph. Two of the three studies of thermoelectric power plants used fuel oil or both coal and fuel oil combustion. The one study of coal-fired plants (Petrelli *et al.*, 1989) was of limited power; six lung cancer deaths were observed whereas 4.39 were expected (SMR, 1.36; 95% CI, 0.50–2.97).]

In the meta-analysis of urinary bladder cancer (Armstrong *et al.*, 2002), 27 eligible cohorts were identified and meta-regression results were more heterogeneous between industries than those for lung. Only the overall result for the aluminium industry was statistically significant, with a unit relative risk of 1.42 (95% CI, 1.23–1.65; based on six studies) at 100 μg/m^3–years of benzo[*a*]pyrene. Other unit relative risks were 1.04 (95% CI, 0.79–1.37; based on six studies) for coke ovens, 8.80 (95% CI, 0.08–967.8; based on two studies) for gas works, 4.40 (95% CI, 0.27–70.67; based on three studies) for asphalt and >1000 (95% CI, 0.04–>1000; based on three studies) for tar distillery.

[The studies included in the meta-analyses have been summarized separately in this monograph. The Working Group noted that a number of exposures had to be imputed by the authors. However, it was considered that these meta-analyses added to the information available by providing a comparable exposure metric and unit relative risks across these studies and industrial sectors. Those derived for gasworks, aluminium works and coke ovens were very similar and each was statistically significant in the analysis of lung cancer.]

Ojajärvi *et al.* (2000) conducted a meta-analysis of pancreatic cancer and environmental or occupational exposures. The meta-risk ratio for occupational exposure to PAHs was 1.50 (95% CI, 0.90–2.50) based on the results of two cohort studies (Cammarano *et al.*, 1986; Moulin *et al.*, 1989) and two case–control studies (Siemiatycki, 1991; Kauppinen *et al.*, 1995).

2.4 Dietary exposure to PAHs and cancer

PAHs are formed during the grilling, barbecueing, curing or smoking of meats and other foods (Kazerouni *et al.*, 2001). Few epidemiological studies have investigated directly the association between dietary intake of PAHs and cancer at different sites; however, with the development of targeted meat-cooking questionnaires and PAH databases (CHARRED http://charred.cancer.gov/), results from epidemiological studies are becoming increasingly available (Kazerouni *et al*., 2001; Sinha *et al.*, 2005a).

Three studies of colorectal adenoma and one of colonic cancer have investigated the association between PAH and colonic tumours. A hospital-based case–control study in Maryland, USA, that included 146 cases and 228 negative screening (by sigmoidoscopy or colonoscopy) controls was specifically designed to address the hypothesis that dietary

intake of PAHs is associated with risk for colorectal adenoma (Sinha *et al*., 2005b). The study used a food-frequency questionnaire with a module that contained detailed questions on method and degree of cooking of meat in conjunction with the benzo[*a*]-pyrene database (as a surrogate for total and carcinogenic PAHs) that was derived from the collection and analysis of a wide range of food samples and referred to the time period 1 year before the interview (Sinha *et al*., 2005a). Odds ratios were adjusted for age, gender, total caloric intake, reason for screening (routine or other), level of physical activity, pack–years of cigarette smoking and use of non-steroidal anti-inflammatory drugs. Additional adjustment for consumption of total fat, saturated fat, fruit, vegetables, fibre or alcohol, education, race, body mass index, frequency of bowel movements and family history of colorectal cancer did not alter the findings substantially. The estimated median, 10th and 90th percentiles of benzo[*a*]pyrene intake in controls were 5, 0.2 and 66 ng/day, respectively, from meat and 73, 35 and 140 ng/day, respectively, from all foods. The estimated median, 10th and 90th percentiles of benzo[*a*]pyrene intake in cases were 17, 0.5 and 101 ng/day, respectively, from meat and 76, 44 and 163 ng/day, respectively from all foods. The odds ratios for exposure to dietary benzo[*a*]pyrene from meat with the 1st quintile of intake as the referent group were: 1.19 (95% CI, 0.51–2.80) for the 2nd quintile, 1.71 (95% CI, 0.76–3.83) for the 3rd quintile, 2.16 (95% CI, 0.96–4.86) for the 4th quintile and 2.82 (95% CI, 1.24–6.43) for the 5th quintile (*p* for trend, 0.01). The increased risk for colorectal adenomas was more strongly associated with benzo[*a*]pyrene intake estimated from all foods (odds ratio, 2.61; 95% CI, 1.08–6.29 for the 2nd quintile; odds ratio, 4.21; 95% CI, 1.79–9.91 for the 3rd quintile; odds ratio, 2.45; 95% CI, 0.98–6.12 for the 4th quintile; and odds ratio, 5.60; 95% CI, 2.20–14.20 for the 5th quintile; *p* for trend = 0.002).

[The Working Group noted that one of the strengths of this study was that the questionnaire was designed to investigate the role of carcinogens found in cooked meats. Other strengths were that the cases had adenomas rather than cancer and were thus less likely to have changed their current dietary habits following diagnosis. Furthermore, their responses to questions about usual dietary habits were less likely to be influenced by medical treatment. Finally, cases and controls were recruited from a well-defined base of individuals and the study had high participation rates. One of the limitations for this and other case–control studies is the potential for recall bias because the subjects were interviewed after diagnostic and treatment procedures; this is probably less of a problem when studying pre-malignant tumours compared with malignant lesions. Cases had a colonoscopy while the controls had only a sigmoidoscopy; as a consequence, some controls might have had undetected adenomas in the right-side of the colon. However, when analysis was restricted to cases with left-sided colonic adenomas that were detectable by sigmoidoscopy, the results were essentially unchanged.]

A second study investigated whether the intake of benzo[*a*]pyrene was associated with colorectal adenoma in the context of a polyp-screening study conducted in southern California, USA (Gunter *et al*., 2005). Benzo[*a*]pyrene intake was estimated using a meat-cooking module and CHARRED database. Covariates included were study centre,

age, gender, ethnicity, total calorific intake, consumption of fruit, vegetables, saturated fat and alcoholic beverages, physical activity, past and current tobacco smoking (using separate indicators), use of non-steroidal anti-inflammatory drugs, body mass index and family history of colorectal cancer. There was a 6% increase in risk for large (>1 cm) adenoma per 10 ng benzo[*a*]pyrene consumed per day (odds ratio, 1.06; 95% CI, 1.00–1.12; p for trend = 0.04). Consistent with this finding, an incremental increase of 10 g barbecued red meat per day was associated with a 29% increase in risk for large adenoma (odds ratio, 1.29; 95% CI, 1.02–1.63; p for trend = 0.04). Individuals in the top quintile of barbecued red meat intake were at increased risk for large colorectal adenoma (odds ratio, 1.90; 95% CI, 1.04–3.45) compared with those who never consumed barbecued red meat.

[The Working Group noted that one of the strengths of this investigation was that the study population had participated in a polyp-screening trial; hence, the control group was free of neoplastic lesions in the left-side of the colon. However, the possibility that polyps in the right-side of the colon were undetected cannot be excluded, thus attenuating the results through the assumption that benzo[*a*]pyrene is a risk factor for both left- and right-sided adenomas. Another potential concern is that, although detailed information on meat-cooking practices was given, responses were provided retrospectively, which introduces the potential for recall bias; however, there was no change in the risk estimates when analyses were restricted to those who reported no dietary change. One further limitation of the questionnaire is that participants reported only habitual diet from the past year. This fails to account for dietary patterns in the past, which may be more relevant for the initiating stages of carcinogenesis. Although detailed data on cooking practices were available, the participation rate was low (56% for the cases and 59% for the controls) which raises the possibility of selection bias.]

A large case–control study within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial in the USA investigated the role of benzo[*a*]pyrene in colorectal adenoma in 3696 cases of left-sided (descending and sigmoid colon and rectum) adenoma and 34 817 endoscopy-negative controls (Sinha *et al.*, 2005c). Dietary intake was assessed using a 137-item food-frequency questionnaire with additional questions on meats and meat-cooking practices which was linked to CHARRED to estimate benzo[*a*]pyrene intake. The analyses controlled for ethnicity (American Indian/Alaskan Native, Asian, Hispanic, non-Hispanic black, non-Hispanic white or Pacific Islander), educational attainment (<8 years at school, 8–11 years at school, 12 years at school/high school equivalent, post-high school other than college, some college, college graduate or post-graduate), tobacco use (never, smoked cigar or pipe, quit smoking ≥20 years and smoked ≤1 pack/day, quit ≥20 years and smoked >1 pack/day, quit <20 years and smoked ≤1 pack/day, quit <20 years and smoked >1 pack/day or unknown), alcohol use (<1, ≥1–15, >15–30 or >30 g/day), use of aspirin and ibuprofen separately (no regular use, <2, 2–3, 4, 8, 12–16, 30 or 60 per month), vigorous physical activity (none, <1, 1, 2, 3 or ≥4 h/week), body mass index (calculated as kilograms per square metre), total folate intake (micrograms per day), calcium intake (milligrams per day) and dietary fibre intake

(grams per day). When the 5th quintile was compared with the 1st quintile, benzo[*a*]pyrene resulted in a marginally elevated risk for colorectal adenoma (odds ratio, 1.15; 95% CI, 1.02–1.29). In investigating the subtypes, an increase in risk for adenomas in the descending colon and sigmoid colon were observed for benzo[*a*]pyrene (odds ratio, 1.18; 95% CI, 1.02–1.35) but not in the rectum. In addition, benzo[*a*]pyrene was associated with an increased risk for non-advanced colorectal adenoma (odds ratio, 1.18; 95% CI, 1.02–1.37) and for single adenomas (odds ratio, 1.17; 95% CI, 1.03–1.34).

[The Working Group noted that the Prostate, Lung, Colorectal, and Ovarian Cancer Trial contained a very large number of well-characterized cases of colorectal adenoma, which provided good power to investigate the role of meat and meat-related mutagens as risk factors for colorectal adenoma in relation to various end-points, including location and number of adenomas. This study included detailed questions on meat and meat-cooking methods in the dietary questionnaire which were linked to a database of meat-related mutagens. Although these methods of dietary assessment are the most comprehensive available, they are still probably associated with a degree of measurement error. Random measurement error can lead to attenuated risk estimates and, therefore, the actual risks may be higher. This cross-sectional study may be subject to dietary recall bias, although most participants (89%) completed the questionnaire before or on the same day as sigmoidoscopy screening, and hence before diagnosis. This potential bias was investigated and no appreciable differences were noted in risk estimates for meat intake among participants who completed the dietary questionnaire before, on the day of, or subsequent to the day of the sigmoidoscopy screening, which suggests that the time when the questionnaire was completed did not affect the associations between meat intake and adenoma.]

A population-based case–control study of colon cancer that included 701 African–Americans (274 cases, 427 controls) and 957 whites (346 cases, 611 controls) in North Carolina, USA. This study also used the meat-cooking module and CHARRED database. Covariates included consumption of fruit, vegetables, dietary fibre, total fat and dietary folate, total energy intake, physical activity, height, weight and body mass index (kilograms per square metre); fat intake was adjusted for total caloric intake using the residual method. No overall relationship was observed between benzo[*a*]pyrene intake and colon cancer; however, when stratified by race, an association was seen among African–Americans (odds ratio, 1.7; 95% CI, 0.9–3.2) but not among whites (odds ratio, 0.9; 95% CI, 0.6–1.5) (Butler *et al*., 2003).

[The Working Group noted that the strength of this study was the inclusion of an ethnically diverse population. In this population, African–Americans tended to consume higher levels of total and white meat. However, most notably, no differences in the association were observed between categories of meat intake and colonic cancer by race. Rapid ascertainment was used in an attempt to reduce recall difficulties, and cases were identified within 3 months of diagnosis. Selection bias represents another potential source of error, as indicated by an overall response rate of 61%, with a 10% greater response among cases than among controls.]

A population-based case–control study in Minnesota (USA) of 192 cases of exocrine pancreatic cancer and 670 controls collected information using the meat-cooking module; intake of benzo[*a*]pyrene was estimated using the CHARRED database (Anderson *et al*., 2002, 2005). The median intake of benzo[*a*]pyrene for each quintile was 0.3, 0.8, 1.8, 10.4 and 53.7 ng/day for the 1st, 2nd, 3rd, 4th and 5th quintiles, respectively. The corresponding odds ratios for benzo[*a*]pyrene intake were: 1.6 (95% CI, 0.9–2.8), 1.4 (95% CI, 0.8–2.6); 2.0 (1.1–3.7) and 2.2 (1.2–4.0) with a *p*-value for trend of 0.05. These estimates were adjusted for age, sex, tobacco smoking, education, race and diabetes. Grilled/barbecued red meat as a proxy for PAH intake was also a statistically significant predictor of risk for pancreatic cancer (Anderson *et al.*, 2002).

[The Working Group noted that this study was designed to address the hypothesis that dietary benzo[*a*]pyrene intake is associated with risk for pancreatic cancer. Detailed information on cooking practices and degree of cooking for specific types of commonly consumed meats was collected from direct interviews. This is essential to estimate most accurately the carcinogen intake and mutagenicity index associated with meat consumption. However, similarly to estimates of dietary nutrient intakes, estimates of dietary carcinogen intakes are imperfect and may lead to misclassification of exposure. Because approximately half of all pancreatic cancer cases die within 3 months of diagnosis, case–control studies of this disease are particularly challenging. The proportion of all eligible cases enrolled was low (approximately 30%), thus creating the potential for selection bias. In addition, pancreatic cancer cases who do enroll are usually quite ill and as a result may report their food intake history differently from controls.]

Other studies have investigated the relationship between benzo[*a*]pyrene and prostatic cancer and non-Hodgkin lymphoma but have found no association. In a prospective analysis of prostatic cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, benzo[*a*]pyrene intake was estimated for 29 361 men. During follow-up, 1338 cases of prostatic cancer were ascertained but no association between prostatic cancer and benzo[*a*]pyrene intake was observed (Cross *et al.*, 2005). No association between benzo[*a*]pyrene intake and non-Hodgkin lymphoma was seen in a population-based case–control study in Iowa, Detroit, Seattle and Los Angeles (USA) that included 458 cases and 383 controls (Cross *et al*., 2006).

2.5 References

Ahrens, W., Jockel, K.H., Patzak, W. & Elsner, G. (1991) Alcohol, smoking, and occupational factors in cancer of the larynx: A case–control study. *Am. J. ind. Med*., **20**, 477–493

Alguacil, J., Kauppinen, T., Porta, M., Partanen, T., Malats, N., Kogevinas, M., Benavides, F.G., Obiols, J., Bernal, F., Rifa, J. & Carrato, A. (2000) Risk of pancreatic cancer and occupational exposures in Spain. PANKRAS II Study Group. *Ann. occup. Hyg*., **44**, 391–403

Andersen, A., Dahlberg, B.E., Magnus, K. & Wannag, A. (1982) Risk of cancer in the Norwegian aluminium industry. *Int. J. Cancer,* **29***,* 295–298

Anderson, K.E., Sinha, R., Kulldorff, M., Gross, M., Lang, N.P., Barber, C., Harnack, L., DiMagno, E., Bliss, R. & Kadlubar, F.F. (2002) Meat intake and cooking techniques: associations with pancreatic cancer. Mutat. Res., 506-507, 225-231

Anderson, K.E., Kadlubar, F.F., Kulldorff, M., Harnack, L., Gross, M., Lang, N.P., Barber, C., Rothman, N. & Sinha, R. (2005) Dietary intake of heterocyclic amines and benzo(a)pyrene: Associations with pancreatic cancer. *Cancer Epidemiol. Biomarkers Prev.*, **14**, 2261–2265

Armstrong, B.G., Tremblay, C.G., Cyr, D. & Thériault, G.P. (1986) Estimating the relationship between exposure to tar volatiles and the incidence of bladder cancer in aluminum smelter workers. *Scand. J. Work Environ. Health*, **12**, 486–493

Armstrong, B.G., Tremblay, C., Baris, D. & Thériault, G. (1994) Lung cancer mortality and polynuclear aromatic hydrocarbons: A case–cohort study of aluminum production workers in Arvida, Quebec, Canada. *Am. J. Epidemiol*., **139**, 250–262

Armstrong, B.G., Hutchinson, E. & Fletcher, T. (2002) *Cancer Risk Following Exposure to Polycyclic Aromatic Hydrocarbons (PAHs): A Meta-Analysis* (Rep. No. 068), Sudbury, Health and Safety Executive. Available at: http://.hse.gov.uk/research.rrhtm/rr068.htm [accessed 19 May 2004]

Armstrong, B.G., Hutchinson, E., Unwin, J. & Fletcher, T. (2004) Lung cancer risk after exposure to polycyclic aromatic hydrocarbons: A review and meta-analysis. *Environ. Health Perspect.*, **112**, 970–978

Aronson, K.J., Siemiatycki, J., Dewar, R. & Gérin, M. (1996) Occupational risk factors for prostate cancer: Results from a case–control study in Montréal, Québec, Canada. *Am. J. Epidemiol.*, **143**, 363–373

Axelson, O. & Kling, H. (1983) [Mortality among wood preservers with creosote exposure] (Abstract). In: *32nd Nordic Occupational Hygiene Conference,* Solna, Arbetarskyddsstyrelsen (National Board of Occupational Safety and Health), pp. 125–126 (in Swedish)

Baxter, P.J. & McDowall, M.E. (1986) Occupation and cancer in London: An investigation into nasal and bladder cancer using the Cancer Atlas. *Br. J. ind Med*., **43**, 44–49

Becher, H., Ramroth, H., Ahrens, W., Risch, A., Schmezer, P. & Dietz, A. (2005) Occupation, exposure to polycyclic aromatic hydrocarbons and laryngeal cancer risk. *Int. J. Cancer*, **116**, 451–457

Bender, A.P., Parker, D.L., Johnson, R.A., Scharber, W.K., Williams, A.N., Marbury, M.C. & Mandel, J.S. (1989) Minnesota Highway Maintenance Worker Study: Cancer mortality. *Am. J. ind. Med.*, **15**, 545–556

Berger, J. & Manz, A. (1992) Cancer of the stomach and the colon–rectum among workers in a coke gas plant. *Am. J. ind. Med.*, **22**, 825–834

Bertrand, J.P., Chau, N., Patris, A., Mur, J.M., Pham, Q.T., Moulin, J.J., Morviller, P., Auburtin, G., Figueredo, A. & Martin, J. (1987) Mortality due to respiratory cancers in the coke oven plants of the Lorraine coalmining industry (Houillères du Bassin de Lorraine). *Br. J. ind. Med*., **44**, 559–565

Blot, W.J., Brown, L.M., Pottern, L.M., Stone, B.J. & Fraumeni, J.F., Jr (1983) Lung cancer among long-term steel workers. *Am. J. Epidemiol*., **117**, 706–716

Boffetta, P., Burstyn, I., Partanen, T., Kromhout, H., Svane, O., Langård, S., Järvholm, B., Frentzel-Beyme, R., Kauppinen, T., Stücker, I., Shaham, J., Heederik, D., Ahrens, W., Bergdahl, I.A., Cenée, S., Ferro, G., Heikkilä, P., Hooiveld, M., Johansen, C., Randem, B.G. & Schill, W. (2003a) Cancer mortality among European asphalt workers: An international

epidemiological study. II. Exposure to bitumen fume and other agents. *Am. J. ind. Med.*, **43**, 28–39

Boffetta, P., Burstyn, I., Partanen, T., Kromhout, H., Svane, O., Langard, S., Jarvholm, B., Frentzel-Beyme, R., Kauppinen, T., Stucker, I., Shaham, J., Heederik, D., Ahrens, W., Bergdahl, I. A., Cenee, S., Ferro, G., Heikkila, P., Hooiveld, M., Johansen, C., Randem, B. G. & Schill, W. (2003b) Cancer mortality among European asphalt workers: An international epidemiological study. I. Results of the analysis based on job titles. *Am. J. ind. Med.*, **43**, 18–27

Bonassi, S., Merlo, F., Pearce, N. & Puntoni, R. (1989) Bladder cancer and occupational exposure to polycyclic aromatic hydrocarbons. *Int. J. Cancer*, **44**, 648–651

Bovenzi, M., Stanta, G., Antiga, G., Peruzzo, P. & Cavallieri, F. (1993) Occupational exposure and lung cancer risk in a coastal area of northeastern Italy. *Int. Arch. occup. environ. Health*, **65**, 35–41

Brüske-Hohlfeld, I., Mohner, M., Pohlabeln, H., Ahrens, W., Bolm-Audorff, U., Kreienbrock, L., Kreuzer, M., Jahn, I., Wichmann, H.E. & Jockel, K.H. (2000) Occupational lung cancer risk for men in Germany: Results from a pooled case–control study. *Am. J. Epidemiol.*, **151**, 384–395

Bruusgaard, A. (1959) [Incidence of certain forms of cancer in gas workers.] *Tidsskr. Nor. Laegeforen.*, **79**, 755–756 (in Norwegian)

Butler, L.M., Sinha, R., Millikan, R.C., Martin, C.F., Newman, B., Gammon, M.D., Ammerman, A.S. & Sandler, R.S. (2003) Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. *Am. J. Epidemiol.*, **157**, 434–445

Butlin, H.T. (1892) Three lectures on cancer of the scrotum in chimney sweeps and others. III. Tar and paraffin cancer. *Br. med. J.*, **iii**, 66–71

Bye, T., Romundstad, P.R., Rønneberg, A. & Hilt, B. (1998) Health survey of former workers in a Norwegian coke plant: Part 2. Cancer incidence and cause specific mortality. *Occup. environ. Med.*, **55**, 622–626

Cadez, E. (1983) [Ergebnisse langjähriger Untersuchungen über den Einfluss von Schadstoffen auf die Gesundheit von Schornstein-fegern]. *Staub. Reinhalt Luft*, **43**, 116–117 (in German)

Cammarano, G., Crosignani, P., Berrino, H. & Berra, G. (1986) Additional follow-up of cancer mortality among workers in a thermoelectric power plant. *Scand. J. Work Environ. Health*, **12**, 631–632

Carlsten, C., Hunt, S.C. & Kaufman, J.D. (2005) Carcinoma of the skin and coal tar creosote exposure in a railroad worker. *Environ. Health Perspect*., **113**, 96–97

Carta, P., Aru, G., Cadeddu, C., Gigli, G., Papi, G., Carta, F. & Nurchis, P. (2004) Mortality for [sic] pancreatic cancer among aluminium smelter workers in Sardinia, Italy. *G. Ital. Med. lav. Ergon*., **26**, 83–89

Chau, N., Bertrand, J.P., Mur, J.M., Figueredo, A., Patris, A., Moulin, J.J. & Pham, Q.T. (1993) Mortality in retired coke oven plant workers. *Br. J. ind. Med*., **50**, 127–135

Clavel, J., Mandereau, L., Limasset, J.C., Hemon, D. & Cordier, S. (1994) Occupational exposure to polycyclic aromatic hydrocarbons and the risk of bladder cancer: A French case–control study. *Int. J. Epidemiol*., **23**, 1145–1153

Cocco, P., Ward, M.H. & Dosemeci, M. (1999) Risk of stomach cancer associated with 12 workplace hazards: Analysis of death certificates from 24 states of the United States with the aid of job exposure matrices. *Occup. environ. Med*., **56**, 781–787

Cookson, H.A. (1924) Epithelioma of the skin after prolonged exposure to creosote. *Br. med. J.*, **i**, 368

Costantino, J.P., Redmond, C.K. & Bearden, A. (1995) Occupationally related cancer risk among coke oven workers: 30 years of follow-up. *J. occup. environ. Med.*, **37**, 597–604

Cross, A.J., Peters, U., Kirsh, V.A., Andriole, G.L., Reding, D., Hayes, R.B. & Sinha, R. (2005) A prospective study of meat and meat mutagens and prostate cancer risk. *Cancer Res.*, **65**, 11779–84

Cross, A.J., Ward, M.H., Schenk, M., Kulldorff, M., Cozen, W., Davis, S., Colt, J.S., Hartge, P., Cerhan, J.R. & Sinha, R. (2006) Meat and meat-mutagen intake and risk of non-Hodgkin lymphoma: Results from a NCI-SEER case–control study. *Carcinogenesis*, **27**, 293–297

Davies, G.M. (1977) A mortality study of coke oven workers in two South Wales integrated steelworks. *Br. J. ind. Med.*, **34**, 291–297

Doll, R. (1952) The causes of death among gas-workers with special reference to cancer of the lung. *Br. J. ind. Med.*, **9**, 180–185

Doll, R., Fisher, R.E.W., Gammon, E.J., Gunn, W., Hughes, G.O., Tyrer, F.H. & Wilson, W. (1965) Mortality of gasworkers with special reference to cancers of the lung and bladder, chronic bronchitis, and pneumoconiosis. *Br. J. ind. Med.*, **22**, 1–12

Doll, R., Vessey, M.P., Beasley, R.W.R., Buckley, A.R., Fear, E.C., Fisher, R.E.W., Gammon, E.J., Gunn, W., Hughes, G.O., Lee, K. & Norman-Smith, B. (1972) Mortality of gasworkers — Final report of a prospective study. *Br. J. ind. Med.*, **29**, 394–406

Donato, F., Monarca, S., Marchionna, G., Rossi, A., Cicioni, C., Chiesa, R., Colin, D. & Boffetta, P. (2000) Mortality from cancer and chronic respiratory diseases among workers who manufacture carbon electrodes. *Occup. environ. Med.*, **57**, 484–487

Droste, J.H., Weyler, J.J., Van Meerbeeck, J.P., Vermeire, P.A. & van Sprundel, M.P. (1999) Occupational risk factors of lung cancer: A hospital based case–control study. *Occup. environ. Med.*, **56**, 322–327

Earle, J. (1808) *The Chirurgical Works of Percivall Pott, F.R.S.*, Vol. III, London, Wood & Innes, pp. 176–183

Elci, O.C., Akpinar-Elci, M., Blair, A. & Dosemeci, M. (2003) Risk of laryngeal cancer by occupational chemical exposure in Turkey. *J. occup. environ. Med.*, **45**, 1100–1106

Engholm, G., Englund, A. & Linder, B. (1991) Mortality and cancer incidence in Swedish road paving asphalt workers and roofers. *Eur. Asphalt Mag.*, **1**, 62–67

Evanoff, B.A., Gustavsson, P. & Hogstedt, C. (1993) Mortality and incidence of cancer in a cohort of Swedish chimney sweeps: An extended follow up study. *Br. J. ind. Med.*, **50** 450–459

Franco, F., Chellini, E., Seniori Costantini, A., Giola, A., Carra, G., Paolinelli, F., Martelli, C. & Vigotti, M. (1993) Mortality in the coke oven plant of Carrara, Italy. *Med. Lav.*, **84**, 443–447

Friesen, M.C., Demers, P.A., Spinelli, J.J., Lorenzi, M. & Le, N.D. (2005) Specificity of exposure metric in dose–response relations in a retrospective aluminum smelter cohort. *Occup. environ. Med.*, **62** [http://www.occenvmed.com/cgi/content/full/62/11/e22]

Gallagher, R.P., Bajdik, C.D., Fincham, S., Hill, G.B., Keefe, A.R., Coldman, A. & McLean, D.I. (1996) Chemical exposures, medical history, and risk of squamous and basal cell carcinoma of the skin. *Cancer Epidemiol. Biomarkers Prev.*, **5**, 419–424

Gérin, M., Siemiatycki, J., Kemper, H. & Bégin, D. (1985) Obtaining occupational exposure histories in epidemiologic case–control studies. *J. occup. Med.*, **27**, 420–426

Gibbs, G.W. (1983) Mortality experience in Eastern Canada. In: Hughes, J.P., ed., *Health Protection in Primary Aluminium Production,* Vol. 2, *Proceedings of a Seminar, Montreal, 22–24 September, 1981;* London, International Primary Aluminium Institute, pp. 59–69

Gibbs, G.W. (1985) Mortality of aluminum reduction plant workers, 1950 through 1977. *J. occup. Med*., **27**, 761–770

Gibbs, G.W. & Horowitz, I. (1979) Lung cancer mortality in aluminum reduction plant workers. *J. occup. Med*., **21**, 347–353

Giovanazzi, A. & D'Andrea, F. (1981) [Causes of death among workers in an aluminium electrolytic reduction plant.] *Med. Lav*., **72**, 277–282 (in Italian)

Grandjean, P. & Olsen, J.H. (2004) Extended follow-up of cancer incidence in fluoride-exposed workers. *J. natl Cancer Inst*., **96**, 802–803

Grimsrud, T.K., Langseth, H., Engeland, A. & Andersen, A. (1998) Lung and bladder cancer in a Norwegian municipality with iron and steel producing industry: Population based case–control studies. *Occup. environ. Med*., **55**, 387–392

Gunter, M.J., Probst-Hensch, N.M., Cortessis, V.K., Kulldorff, M., Haile, R.W. & Sinha, R. (2005) Meat intake, cooking-related mutagens and risk of colorectal adenoma in a sigmoidoscopy-based case–control study. *Carcinogenesis*, **26**, 637–642

Gustavsson, P. & Reuterwall, C. (1990) Mortality and incidence of cancer among Swedish gas workers. *Br. J. ind. Med.*, **47**, 169–174

Gustavsson, P., Gustavsson, A. & Hogstedt, C. (1988) Excess of cancer in Swedish chimney sweeps. *Br. J. ind. Med*., **45**, 777–781

Gustavsson, P., Bellander, T., Johansson, L. & Salmonsson, S. (1995) Surveillance of mortality and cancer incidence among Swedish graphite electrode workers. *Environ. Res*., **70**, 7–10

Gustavsson, P., Jakobsson, R., Johansson, H., Lewin, F., Norell, S. & Rutkvist, L.E. (1998) Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: A case–control study in Sweden. *Occup. environ. Med*., **55**, 393–400

Gustavsson, P., Jackobsson, R., Nyberg, F., Pershagen, G., Järup, L. & Schéele, P. (2000) Occupational exposure and lung cancer risk: A population-based case–referent study in Sweden. *Am. J. Epidemiol*., **152**, 32–40

Haldorsen, T., Andersen, A. & Boffetta, P. (2004) Smoking-adjusted incidence of lung cancer by occupation among Norwegian men. *Cancer Causes Control*, **15**, 139–147

Hammond, E.C., Selikoff, I.J., Lawther, P.L. & Seidman, H. (1976) Inhalation of benzpyrene and cancer in man. *Ann. N.Y. Acad. Sci.*, **271**, 116–124

Hansen, E.S. (1983) Mortality from cancer and ischemic heart disease in Danish chimney sweeps: A five-year follow-up. *Am. J. Epidemiol.*, **117**, 160–164

Hansen, E.S. (1989a) Cancer mortality in the asphalt industry: A ten year follow up of an occupational cohort. *Br. J. ind. Med.*, **46**, 582–585

Hansen, E.S. (1989b) Cancer incidence in an occupational cohort exposed to bitumen fumes. *Scand. J. Work Environ. Health*, **15**, 101–105

Hansen, E.S. (1991) Mortality of mastic asphalt workers. *Scand. J. Work Environ. Health*, **17,** 20–24

Hansen, E.S., Olsen, J.H. & Tilt, B. (1982) Cancer and non-cancer mortality of chimney sweeps in Copenhagen. *Int. J. Epidemiol*., **11**, 356–361

Hansen, K.S., Viskum, S. & Pedersen, M.S. (1986) [Mortality among gas workers.] *Ugeskr. Laeger*, **148**, 610–612 (in Danish)

Henry, S.A. (1937) The study of fatal cases of cancer of the scrotum from 1911 to 1935 in relation to occupation, with special reference to chimney sweeping and cotton mule spinning. *Am. J. Cancer*, **31**, 28–57

Henry, S.A. (1946) *Cancer of the Scrotum in Relation to Occupation*, New York, Oxford University Press

Henry, S.A. (1947) Occupational cutaneous cancer attributable to certain chemicals in industry. *Br. med. Bull*., **4**, 389–401

Henry, S.A. & Irvine, E.D. (1936) Cancer of the scrotum in the Blackburn registration district, 1837–1929. *J. Hyg.*, **36**, 310–340

Henry, S.A., Kennaway, N.M. & Kennaway, E.L. (1931) The incidence of cancer of the bladder and prostate in certain occupations. *J. Hyg.*, **31**, 125–137

Hoar, S.K., Morrison, A.S., Cole, P. & Silverman, D.T. (1980) An occupation and exposure linkage system for the study of occupational carcinogenesis. *J. occup. Med*., **22**, 722–726

Hogstedt, C., Andersson, K., Frenning, B. & Gustavsson, A. (1982) A cohort study on mortality among long-time employed Swedish chimney sweeps. *Scand. J. Work Environ. Health*, **8** (Suppl. 1), 72–78

Hrubec, Z., Blair, A.E., Rogot, E. & Vaught, J. (1992) *Mortality Risks by Occupation among U.S. Veterans of Known Smoking Status 1954–80* (NIH Publication No. 92-3407), Bethesda, MD, National Institutes of Health

Hurley, J.F., Archibald, R.M., Collings, P.L., Fanning, D.M., Jacobsen, M. & Steele, R.C. (1983) The mortality of coke workers in Britain. *Am. J. ind. Med*., **4**, 691–704

IARC (1985) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 35, *Polynuclear Aromatic Compounds, Part 4, Bitumens, Coal-tars and Derived Products, Shale-oils and Soots*, Lyon, p. 233

Jensen, O.M., Knudsen, J.B., McLaughlin, J.K. & Sorensen, B.L. (1988) The Copenhagen case–control study of renal pelvis and ureter cancer: Role of smoking and occupational exposures. *Int. J. Cancer*, **41**, 557–561

Karlehagen, S., Andersen, A. & Ohlson, C.G. (1992) Cancer incidence among creosote-exposed workers. *Scand. J. Work Environ. Health*., **18**, 26–29

Kauppinen, T., Partanen, T., Degerth, R. & Ojajärvi, A. (1995) Pancreatic cancer and occupational exposures. *Epidemiology*, **6**, 498–502

Kawai, M., Amamoto, H. & Harada, K. (1967) Epidemiologic study of occupational lung cancer. *Arch. environ. Health*, **14**, 859–864

Kazerouni, N., Sinha, R., Hsu, C.H., Greenberg, A. & Rothman, N. (2001) Analysis of 200 food items for benzo[a]pyrene and estimation of its intake in an epidemiologic study. *Food chem. Toxicol.*, **39**, 423–436

Kennaway, N.M. & Kennaway, E.L. (1936) A study of the incidence of cancer of the lung and larynx. *J. Hyg.*, **36**, 236–267

Kennaway, E.L. & Kennaway, N.M. (1947) A further study of the incidence of cancer of the lung and larynx. *Br. J. Cancer*, **1**, 260–298

Kjuus, H., Andersen, A. & Langård, S. (1986) Incidence of cancer among workers producing calcium carbide. *Br. J. ind. Med.*, **43**, 237–242

Konstantinov, V.G. & Kuz'minykh, A.I. (1971) Tarry substances and 3, 4-benzpyrene in the air of electrolysis shops of aluminum works and their carcinogenic significance. *Hyg. Sanit*., **36**, 368–373

Konstantinov, V.G., Simakhina, P.G., Gotlib, E.V. & Kuz'minykh, A.I. (1974) [Problem of the carcinogenic hazard in aluminium electrolysis halls.] In: *Professional'nyi Rak*, Moscow, Academy of Medical Sciences, pp. 87–91 (in Russian)

Krstev, S., Baris, D., Stewart, P.A., Hayes, R.B., Blair, A. & Dosemeci, M. (1998) Risk for prostate cancer by occupation and industry: A 24-state death certificate study. *Am. J. ind. Med*., **34**, 413–420

Kubasiewicz, M. & Starzynski, Z. (1989) Case–referent study on skin cancer and its relation to occupational exposure to polycyclic aromatic hydrocarbons. I. Study design. *Pol. J. occup. Med*., **2**, 221–228

Kubasiewicz, M., Starzynski, Z. & Szymczak, W. (1991) Case–referent study on skin cancer and its relation to occupational exposure to polycyclic aromatic hydrocarbons. II. Study results. *Pol. J. occup. Med. environ. Health*., **4**, 141–147

Kupetz, G.-W. (1966) [*Tumour of the Respiratory Tract and Chimney Sweep Occupation*], Inaugural Dissertation, Berlin, Humboldt University (in German)

Kuroda, S. & Kawahata, K. (1936) [On the occupational origin of lung cancer among generator gas workers.] *Z. Krebsforsch*., **45**, 36–39 (in German)

Letzel, S. & Drexler, H. (1998) Occupationally related tumors in tar refinery workers. *J. Am. Acad. Dermatol.*, **39**, 712–720

Liu, N., Wang, Z., Dong, D., Chen, K. & Quin, L. (1997) Cancer mortality among carbon workers in China: Retrospective cohort study. *J. occup. Health*, **39**, 325–330

Lloyd, J.W. (1971) Long-term mortality study of steelworkers. V. Respiratory cancer in coke plant workers. *J. occup. Med*., **13**, 53–68

Lloyd, J.W. & Ciocco, A. (1969) Long-term mortality study of steelworkers. I. Methodology. *J. occup. Med*., **11**, 299–310

Lloyd, J.W., Lundin, F.E., Redmond, C.K. & Geiser, P.B. (1970) Long-term mortality study of steelworkers. IV. Mortality by work area. *J. occup. Med*., **12**, 151–157

van Loon, A.J., Kant, I.J., Swaen, G.M., Goldbohm, R.A., Kremer, A.M. & van den Brandt, P.A. (1997) Occupational exposure to carcinogens and risk of lung cancer: Results from the Netherlands cohort study. *Occup. environ. Med*., **54**, 817–824

Maclaren, W.M. & Hurley, J.F. (1987) Mortality of tar distillation workers. *Scand. J. Work Environ. Health*, **13**, 404–411

Maizlish, N., Beaumont, J. & Singleton, J. (1988) Mortality among California highway workers. *Am. J. ind. Med.*, **13**, 363–379

Mandel, J.S., McLaughlin, J.K., Schlehofer, B., Mellemgaard, A., Helmert, U., Lindblad, P., McCredie, M. & Adami, H.O. (1995) International renal-cell cancer study. IV. Occupation. *Int. J. Cancer*, **61**, 601–605

Manz, A., Berger, J. & Waltsgott, H. (1983) [*Occupational Cancer in Gas Industry Worker.*], (Wirtschaftsverlag, NW, Report No. 352) Bremerhaven, German Federal Department for Worker Safety and Accident Research, (in German)

Martin, J.C., Imbernon, E., Goldberg, M., Chevalier, A. & Bonenfant, S. (2000) Occupational risk factors for lung cancer in the French electricity and gas industry. *Am. J. Epidemiol.*, **151**, 902–912

Mazumdar, S., Redmond, C., Sollecito, W. & Sussman, N. (1975) An epidemiological study of exposure to coal tar pitch volatiles among coke oven workers. *J. Air Pollut. Control Assoc*., **25**, 382–389

McLaughlin, J.K., Mandel, J.S., Blot, W.J., Schuman, L.M., Mehl, E.S. & Fraumeni, J.F., Jr (1984) A population-based case–control study of renal cell carcinoma. *J. natl. Cancer Inst*., **72**, 275–284

Menck, H.R. & Henderson, B.E. (1976) Occupational differences in rates of lung cancer. *J. occup. Med*., **18,** 797–801

Merlo, D.F., Garattini, S., Gelatti, U., Simonati, C., Covolo, L., Ceppi, M. & Donato, F. (2004) A mortality cohort study among workers in a graphite electrode production plant in Italy. *Occup. environ. Med*., **61**, e9

Milham, S. (1982) *Occupational Mortality in Washington State 1950–1979*, Prepared under Contract No. 210-80-0088, Cincinnati, OH, National Institute for Occupational Safety and Heath

Milham, S., Jr (1976) Cancer mortality pattern associated with exposure to metals. *Ann. N.Y. Acad. Sci*., **271**, 243–249

Milham, S., Jr (1979) Mortality in aluminum reduction plant workers. *J. occup. Med*., **21**, 475–480

Moolgavkar, S.H., Luebeck, E.G. & Anderson, E.L. (1998) Estimation of unit risk for coke oven emissions. *Risk Anal*., **18**, 813–825

Morabia, A., Markowitz, S., Garibaldi, K. & Wynder, E.L. (1992) Lung cancer and occupation: Results of a multicentre case–control study. *Br. J. ind. Med.*, **49**, 721–727

Mori, I. (2002) Cancer mortality among man-made graphite electrode manufacturing workers: Results of a 38 year follow up. *Occup. environ. Med*., **59**, 473–480

Moulin, J.J., Mur, J.M., Wild, P., Demonchy, A., Eloy, E., Jeannot, A. (1988) [Epidemiological study of mortality among coal tar distillery workers]. *Rev. epidemiol. Santé publique,* **36**, 99–107 (in French)

Moulin, J.J., Wild, P., Mur, J.M., Lafontaine, M., Lefer, M., Mercier-Gallay, M., Villemot, P., Whebi, V. & Coulon, J.P. (1989) Risk of lung, larynx, pharynx and buccal cavity cancers among carbon electrode manufacturing workers. *Scand. J. Work Environ. Health*, **15**, 30–37

Moulin, J.J., Clavel, T., Buclez, B. & Laffitte-Rigaud, G. (2000) A mortality study among workers in a French aluminium reduction plant. *Int. Arch. occup. environ. Health*, **73**, 323–330

Mur, J.M., Moulin, J.J., Meyer-Bisch, C., Massin, N., Coulon, J.P. & Loulergue, J. (1987) Mortality of aluminium reduction plant workers in France. *Int. J. Epidemiol*., **16**, 257–264

Nadon, L., Siemiatycki, J., Dewar, R., Krewski, D. & Gérin, M. (1995) Cancer risk due to occupational exposure to polycyclic aromatic hydrocarbons. *Am. J. ind Med*., **28**, 303–324

O'Donovan, W.J. (1920) Epitheliomatous ulceration among tar workers. *Br. J. Dermatol. Syphilis*, **32**, 215–228

Ojajärvi, I.A., Partanen, T.J., Ahlbom, A., Boffetta, P., Hakulinen, T., Jourenkova, N., Kauppinen, T.P., Kogevinas, M., Porta, M., Vainio, H.U., Weiderpass, E. & Wesseling, C.H. (2000) Occupational exposures and pancreatic cancer: A meta-analysis. *Occup. environ. Med.*, **57**, 316–324

Parent, M.E., Siemiatycki, J. & Fritschi, L. (2000) Workplace exposures and oesophageal cancer. *Occup. environ. Med.*, **57**, 325–334

Partanen, T. & Boffetta, P. (1994) Cancer risk in asphalt workers and roofers: Review and meta-analysis of epidemiologic studies. *Am. J. Ind. Med.*, **26**, 721–740

Partanen, T., Heikkila, P., Hernberg, S., Kauppinen, T., Moneta, G. & Ojajärvi, A. (1991) Renal cell cancer and occupational exposure to chemical agents. *Scand. J. Work Environ. Health*, **17**, 231–239

Pesch, B., Haerting, J., Ranft, U., Klimpel, A., Oelschlagel, B. & Schill, W. (2000) Occupational risk factors for renal cell carcinoma: Agent-specific results from a case–control study in Germany. MURC Study Group. Multicenter urothelial and renal cancer study. *Int. J. Epidemiol*., **29**, 1014–1024

Petrelli, G., Menniti-Ippolito, F., Taroni, F., Raschetti, R. & Magarotto, G. (1989) A retrospective cohort mortality study on workers of two thermoelectric power plants: Fourteen-year follow-up results. *Eur. J. Epidemiol.*, **5**, 87–89

Pott, P. (1775) *Chirurgical Observations Relative to the Cataract, the Polypus of the Nose, the Cancer of the Scrotum, the Different Kinds of Ruptures, and the Mortification of the Toes and Feet*, London, Hawes, Clarke & Collins

Pukkala, E. (1995) *Cancer Risk by Social Class and Occupation*, Vol. 7, *Contributions to Epidemiology and Biostatistics*, Basel, Karger

Redmond, C.K. (1983) Cancer mortality among coke oven workers. *Environ. Health Perspect*., **52**, 67–73

Redmond, C.K., Ciocco, A., Lloyd, J.W. & Rush, H.W. (1972) Long-term mortality study of steelworkers. VI. Mortality from malignant neoplasms among coke oven workers. *J. occup. Med*., **14**, 621–629

Reid, D.D. & Buck, C. (1956) Cancer in coking plant workers. *Br. J. ind. Med*., **13**, 265–269

Risch, H.A., Burch, J.D., Miller, A.B., Hill, G.B., Steele, R. & Howe, G.R. (1988) Occupational factors and the incidence of cancer of the bladder in Canada. *Br. J. ind. Med*., **45**, 361–367

Rockette, H.E. & Arena, V.C. (1983) Mortality studies of aluminum reduction plant workers: Potroom and carbon department. *J. occup. Med*., **25**, 549–557

Romundstad, P., Andersen, A. & Haldorsen, T. (2000a) Cancer incidence among workers in six Norwegian aluminum plants. *Scand. J. Work Environ. Health*, **26**, 461–469

Romundstad, P., Haldorsen, T. & Andersen, A. (2000b) Cancer incidence and cause specific mortality among workers in two Norwegian aluminum reduction plants. *Am. J. ind. Med*., **37**, 175–183

Romundstad, P., Haldorsen, T. & Andersen, A. (2000c) Lung and bladder cancer among workers in a Norwegian aluminium reduction plant. *Occup. environ. Med*., **57**, 495–499

Rønneberg, A. & Andersen, A. (1995) Mortality and cancer morbidity in workers from an aluminium smelter with prebaked carbon anodes — Part II: Cancer morbidity. *Occup. environ. Med.*, **52**, 250–254

Rønneberg, A., Haldorsen, T., Romundstad, P. & Andersen, A. (1999) Occupational exposure and cancer incidence among workers from an aluminum smelter in western Norway. *Scand. J. Work Environ. Health*, **25**, 207–214

Sakabe H., Tsuchiya K., Takekura N., Nomura S., Koshi S., Takemoto K., Matsushita H. & Matuso Y. (1975) Lung cancer among coke oven workers. *Ind. Health*, **13**, 57–68

Schoenberg, J.B., Stemhagen, A., Mason, T.J., Patterson, J., Bill, J. & Altman, R. (1987) Occupation and lung cancer risk among New Jersey white males. *J. natl Cancer Inst.*, **79**, 13–21

Schumacher, M.C., Slattery, M.L. & West, D.W. (1989) Occupation and bladder cancer in Utah. *Am. J. ind. Med*., **16**, 89–102

Schunk, W. (1979) [Zur Frage der Beziehung zwischen der Exposition gegenüber polyzyklischen Kohlenwasserstoffen und der Häufigkeit von Krebserkrankungen in zwei Chemiebetrieben Thüringens]. *Z. ärztl. Fortbild.*, **73**, 84–88 (in German)

Sharpe, C.R., Rochon, J.E., Adam, J.M. & Suissa, S. (1989) Case–control study of hydrocarbon exposures in patients with renal cell carcinoma. *Can. med. Assoc. J.*, **140**, 1309–1318

Shimauchi, T., Rikihisa, W., Yasuda, H., Yamamoto, O. & Asahi, M. (2000) [A case of squamous cell carcinoma that developed on chronic tar dermatosis.] *J. UOEH*, **22**, 183–187 (in Japanese)

Siemiatycki, J. (1991) *Risk Factors for Cancer in the Workplace*, Boca Raton, FL, CRC Press

Simonato, L. (1981) Carcinogenic risk in the aluminium production industry: An epidemiological overview. *Med. Lav.*, **72**, 266–276

Sinha, R., Cross, A., Curtin, J., Zimmerman, T., McNutt, S., Risch, A. & Holden, J. (2005a) Development of a food frequency questionnaire module and databases for compounds in cooked and processed meats. *Mol. Nutr. Food Res.*, **49**, 648–655

Sinha, R., Kulldorff, M., Gunter, M.J., Strickland, P. & Rothman, N. (2005b) Dietary benzo[a]pyrene intake and risk of colorectal adenoma. *Cancer Epidemiol. Biomarkers Prev.*, **14**, 2030–2034

Sinha, R., Peters, U., Cross, A.J., Kulldorff, M., Weissfeld, J.L., Pinsky, P.F., Rothman, N. & Hayes, R.B. (2005c) Meat, meat cooking methods and preservation, and risk for colorectal adenoma. *Cancer Res.*, **65**, 8034–8041

Spinelli, J.J., Band, P.R., Svirchev, L.M. & Gallagher, R.P. (1991) Mortality and cancer incidence in aluminum reduction plant workers. *J. occup. Med.*, **33**, 1150–1155

Steineck, G., Plato, N., Alfredsson, L. & Norell, S.E. (1989) Industry-related urothelial carcinogens: Application of a job–exposure matrix to census data. *Am. J. ind. Med.*, **16**, 209–224

Stern, F.B., Ruder, A.M. & Chen, G. (2000) Proportionate mortality among unionized roofers and waterproofers. *Am. J. ind. Med.*, **37**, 478–492

Swaen, G.M.H. & Slangen, J.M.M. (1997) Mortality in a group of tar distillery workers and roofers. *Int. Arch. occup. environ. Health*, **70**, 133–137

Swaen, G.M.H., Slangen, J.J.M., Volovics, A., Hayes, R.B., Scheffers, T. & Sturmans, F. (1991) Mortality of coke plant workers in the Netherlands. *Br. J. ind. Med.*, **48**, 130–135

Teta, M.J., Ott, M.G. & Schnatter, A.R. (1987) Population based mortality surveillance in carbon products manufacturing plants. *Br. J. ind. Med.*, **44**, 344–350

Thériault, G., De Guire, L. & Cordier, S. (1981) Reducing aluminum: An occupation possibly associated with bladder cancer. *Can. med. Assoc. J.*, **124**, 419–422, 425

Thériault, G., Tremblay, C., Cordier, S. & Gingras, S. (1984) Bladder cancer in the aluminium industry. *Lancet*, **323**, 947–950

Tornqvist, S., Norell, S., Ahlbom, A. & Knave, B. (1986) Cancer in the electric power industry. *Br. J. ind. Med.*, **43**, 212–213

Tremblay, C., Armstrong, B., Thériault, G. & Brodeur, J. (1995) Estimation of risk of developing bladder cancer among workers exposed to coal tar pitch volatiles in the primary aluminum industry. *Am. J. ind. Med.*, **27**, 335–348

Watkins, D.K., Chiazze, L., Jr, Fryar, C.D. & Fayerweather, W. (2002) A case control study of lung cancer and non-malignant respiratory disease among employees in asphalt roofing manufacturing and asphalt production. *J. occup. environ. Med*, **44**, 551–558

Wigle, D.T. (1977) Bladder cancer: Possible new high-risk occupation. *Lancet*, **ii**, 83–84

Wong, O. & Harris, F. (2005) Retrospective cohort mortality study and nested case–control study of workers exposed to creosote at 11 wood-treating plants in the United States. *J. occup. environ. Med.*, **47**, 683–697

Wu W. (1988) Occupational cancer epidemiology in the People's Republic of China. *J. occup Med.*, **30**, 968–974

Wu-Williams, A.H., Xu, Z.Y., Blot, W.J., Dai, X.D., Louie, R., Xiao, H.P., Stone, B.J., Sun, X.W., Yu, S.F., Feng, Y.P. *et al*. (1993) Occupation and lung cancer risk among women in northern China. *Am. J. ind. Med*., **24**, 67–79

Zahm, S.H., Brownson, R.C., Chang, J.C. & Davis, J.R. (1989) Study of lung cancer histologic types, occupation, and smoking in Missouri. *Am. J. ind. Med.*, **15**, 565–578