## 2. Studies of Cancer in Humans

The occupations covered in the studies reviewed below involve recovery of cadmium from zinc refining, manufacture of cadmium oxide, alloys and pigment and production of nickel–cadmium batteries. The Working Group did not review studies of other occupations, such as electroplating, welding (see IARC, 1990b), painting (see IARC, 1989) and glass-making (see p. 347), in which exposure to cadmium occurs, but which involve lower or more sporadic exposures. The use of cadmium was noted to be increasing in the production of nickel–cadmium batteries (US Occupational Safety and Health Administration, 1992) but decreasing in other applications. In general, the maximal concentrations of cadmium in work-place air decreased by up to 100 times since the 1940s in the work sites studied. Given the long latency of cancer, the health effects noted among long-term workers may reflect former rather than current conditions of exposure.

The Working Group considered other occupational respiratory carcinogens, such as nickel (see IARC, 1990a) in nickel–cadmium battery plants and arsenic (see IARC, 1987c) in localized areas of metallurgical plants, that might introduce a spurious association between exposure to cadmium and lung cancer. Potential confounding by occupational exposures to other substances was not considered in the studies of prostatic cancer.

### 2.1 Descriptive studies

Shigematsu *et al.* (1982) assessed mortality in four pairs of populations in cadmium-polluted and unpolluted areas of four prefectures of Japan during 1948–77, when exposure to cadmium in the polluted areas occurred through ingestion of cadmium-contaminated rice. Average concentrations ranged from 0.2 to 0.7 ppm in the polluted area and from 0.02 to 0.1 ppm in the unpolluted areas. No difference was seen between the two areas in the rate of mortality from cancers at all sites or from cancers of the stomach or liver. The rate of mortality from prostatic cancer was significantly higher (standardized mortality ratio [SMR], 1.66) in the polluted than in the unpolluted area of one prefecture, as was the incidence of hyperplasia of the prostate. Figures for respiratory cancer were not reported.

Bako *et al.* (1982) studied age-adjusted incidence rates for prostatic cancer in various census divisions of Alberta, Canada, in relation to the occurrence of cadmium in the environment, i.e. in samples of flowing fresh water, municipal waste water, soil, and wheat and barley stems. Significantly high and low incidence rates were seen: the city with high incidence, 53.2 cases per 100 000 population, had consistently higher cadmium concentrations in the samples taken (0.006 ppm in waste water, 0.27 in soil, 0.004 in flowing water); and the city with the lowest incidence, 10.6 cases per 100 000 population, had consistently low concentrations (< 0.001, 0.19 and 0.001 ppm, respectively). Other environmental parameters also differed.

Campbell *et al.* (1990) reported analyses of a comprehensive cross-sectional survey of possible risk factors for primary liver cancer in 48 counties in China. County mortality rates were correlated positively with mean daily cadmium intake (0–90 μg/day) from foods of plant origin, as estimated by dietary surveys.

## 2.2 Cohort studies (see Tables 10 and 11, pp. 157 *et seq.*)

The relation between exposure to cadmium and cancers of the lung and prostate has been studied in six occupational cohorts in Europe and the USA, most of which covered overlapping populations, and in one in China. The cohorts are generally small, particularly when restricted to long-term, highly exposed workers with prolonged follow-up. Recent studies have expanded the number of subjects by including many short-term, minimally exposed or recently hired workers, so that the need for subanalyses by dose and latency is increased. In order to facilitate interpretation, the studies are grouped according to plant; the published data on cancer of the lung are summarized in Table 10 and those for prostatic cancer in Table 11.

### 2.2.1 *Nickel–cadmium battery manufacture, United Kingdom*

Workers from two nickel–cadmium battery plants in the United Kingdom, one of which operated from 1923 to 1947 and the other from 1937 to the present, were the subject of a series of studies. The plants were amalgamated in 1947. The concentrations of cadmium in cadmium oxide (hydroxide) dust in high-exposure jobs (plate-making and assembly shops) were 0.6–2.8 mg/m$^3$ [236 mg/m$^3$ in the negative active material department where cadmium oxide is prepared (Potts, 1965)] in 1949, $\leq$ 0.5 mg/m$^3$ between 1950 (when extensive local exhaust ventilation was installed) and 1967 (when a new plate-making department was built), $<$ 0.2 mg/m$^3$ from 1968 to 1975 and $<$ 0.05 mg cadmium/m$^3$ after 1975 (Sorahan & Waterhouse, 1983). [The Working Group noted that the process was probably similar to those in the Swedish study described below, where exposure to nickel hydroxide dust was reported to be higher than that to cadmium oxide.]

Potts (1965) identified three deaths from cancer of the prostate and one from lung cancer out of eight deaths among 74 men who had been exposed to cadmium oxide dust in the plant for at least 10 years before 1965. No referent rates were used to compute the expected number of fatal cancers. [The Working Group had no information on the completeness of ascertainment and whether, therefore, the 74 men were representative of the exposed population.]

Kipling and Waterhouse (1967) assembled a cohort of 248 men with at least one year of exposure to cadmium oxide at the same plants, including the 74 men reported by Potts (1965). [The Working Group had no published information on exposure levels in these jobs; however, in subsequent studies of the same plants, these job titles were classified as involving high exposure.] They compared cancer incidence rates through 1966 with regional rates from the local cancer registry. One new case of prostatic cancer was detected. This case, combined with the three deaths reported by Potts (1965), exceeded the 0.58 expected (standardized incidence ratio [SIR], 6.90 [95% confidence interval (CI), 1.86–17.66]). The incidence of lung cancer was not significantly elevated (5 observed, 4.4 expected; SIR, 1.14 [95% CI, 0.37–2.65]). [The Working Group noted that there was no analysis of incidence by latency or duration of exposure.]

Sorahan and Waterhouse (1983) enlarged the cohort to include 3025 people (2559 men) first employed at the plants between 1923 and 1975 for a minimum of one month. An initial study of mortality from prostatic cancer reported eight deaths between January 1946 and

January 1981, whereas 6.6 were expected on the basis of mortality rates in the general population of England and Wales (relative risk [RR], 1.21 [95% CI, 0.52–2.39]). In a later study, Sorahan and Waterhouse (1985) identified 15 incident cases of prostatic cancer entered into the Birmingham Regional Cancer Registry between 1950 and 1980; comparison with the 11.0 cases expected from regional rates gave an RR of 1.36 [95% CI, 0.76–2.25]. Eight of the cases occurred in a subgroup of 458 workers who had been employed for at least one year in jobs entailing high exposure to cadmium oxide dust (8 observed, 1.99 expected; RR, 4.02 [95% CI, 1.73–7.92]). Four of the eight cases were additional to those reported by Kipling and Waterhouse (1967); this number was greater than that expected but not significant (4 observed, 1.78 expected; RR, 2.25 [95% CI, 0.60–5.75]).

Sorahan (1987) examined lung cancer mortality between 1946 and 1984 in the same workforce of 3025 workers. Overall, 110 deaths from lung cancer were observed, while 84.5 were expected (RR, 1.30 [95% CI, 1.07–1.57]). The RRs for lung cancer in high-exposure jobs were slightly greater (1.3–1.5) than that for workers with no or minimal exposure but did not increase with years of employment in high-exposure jobs (Table 10). [The Working Group noted that the analysis did not incorporate exposure measurements, nor was the intensity of exposure considered simultaneously with duration. Tobacco smoking was controlled for indirectly in internal dose-response comparisons. Exposure to nickel hydroxide could not be controlled for, since few workers were exposed to cadmium in the absence of nickel.]

### 2.2.2 *Nickel–cadmium battery manufacture, Sweden*

Concentrations of cadmium in air containing cadmium oxide dust at a single nickel–cadmium battery plant in Sweden, where a series of studies was done, averaged about 1 mg/m$^3$ before 1947, 0.3 mg/m$^3$ between 1947 and 1962, 0.05 mg/m$^3$ between 1962 and 1974 and 0.02 mg/m$^3$ after 1975 (Elinder *et al.*, 1985). Exposures to nickel hydroxide dust were reported to have been 2–10 times higher than those to cadmium oxide, although no measurements were reported (Kjellström *et al.*, 1977).

Kjellström *et al.* (1979) studied 228 men who had been employed at the plant for five or more years between 1940 and 1959, who were followed up from 1959 to 1975. Incident cancers among the workers were identified from the Swedish National Cancer Registry, which started in 1959, and were compared with national rates of incidence. The numbers of new cases were as follows: lung, 2 observed, 1.35 expected (RR, 1.48 [95% CI, 0.17–5.35]), prostate, 2 observed, 1.2 expected (RR, 1.67 [95% CI, 0.19–6.02]) and nasopharynx, 2 observed, 0.20 expected (RR, 10.0 [95% CI, 1.23–36.1]). [The Working Group noted that cancers of the nasal cavity and sinuses and not nasopharyngeal cancers are associated with exposure to nickel, and that only cases of cancers that occurred after 1959 were included.]

Andersson *et al.* (1984) and Elinder *et al.* (1985) extended the cohort to include 522 male workers who had been exposed to cadmium for at least one year between 1940 and 1980, and who were still alive in 1951; follow-up was from 1951 to 1983. In that period, there were eight deaths from lung cancer (6.01 expected; RR, 1.33 [95% CI, 0.57–2.62]), four from prostatic cancer (3.70 expected; RR, 1.08 [95% CI, 0.29–2.77]) and one from cancer of the nasopharynx (expected near 0). Seven of the eight cases of lung cancer occurred among workers with five or more years of exposure and 20 years' latency (7 observed, 4.0 expected;

RR, 1.75 [95% CI, 0.70–3.61]). [The Working Group noted that the small number of cases precluded a dose–response analysis.]

### 2.2.3 *Copper–cadmium alloy plants, United Kingdom*

Holden (1980a,b) described cadmium exposures at two plants, in rural and urban locations in the United Kingdom, where copper–cadmium alloy was produced from 1922 to 1966 and from 1925 to the present, respectively. The numbers of workers in each plant were not given; a total of 347 workers at the two plants had been employed for at least one year. Exposure to cadmium fume at the urban plant exceeded 1 mg/m$^3$ before 1953, with a peak of 3.6 mg/m$^3$, was < 0.15 mg/m$^3$ from 1953 to 1957 and was < 0.05 mg/m$^3$ thereafter. Although air concentrations at the rural plant were not described, proteinuria was common in workers at both plants before 1950, indicating high exposures to cadmium (Holden, 1980b).

Mortality from respiratory cancer, followed from 1921 to 1978, was higher among urban cadmium workers [number not given] than in the general population of England and Wales (8 observed, 4.50 expected; RR, 1.78 [95% CI, 0.77–3.50]) but was significantly lower among the rural workers [number not given] (2 observed, 7.85 expected; RR, 0.25 [95% CI, 0.03–0.92]). One death from prostatic cancer was observed in the combined workforce (1.58 expected; RR, 0.63 [95% CI, 0.01–3.52]). In the same study, 624 'vicinity' workers from the urban plant, who produced arsenical copper and other alloys in the same workshop, were followed up. Their mean cadmium exposures were low ($\leq$ 0.07 mg/m$^3$; King, 1955), but their arsenic exposures were high [figures not given]. These workers had significantly higher mortality rates from both respiratory (36 observed, 26.08 expected; RR, 1.38 [95% CI, 0.97–1.91]) and prostatic cancer (8 observed, 3.0 expected; RR, 2.67 [95% CI, 1.15–5.26]) than the general population of England and Wales (Holden, 1980a,b). [The Working Group noted that no regional comparison was made, and it is unclear whether the general population is comparable with the rural population with respect to smoking. It is unlikely, however, that urban–rural differences would completely explain the low risk for lung cancer in the rural workers.]

Kazantzis *et al.* (1989) reported briefly the results of a nested case–control study of cancer of the lung in the same copper–cadmium alloy cohort described above. Long-term employees were reported also to have been exposed to arsenic in the production of arsenical copper. An analysis in which 50 lung cancer deaths were compared with 158 controls matched on age and year at hire showed a stronger association between lung cancer and exposure to arsenic (odds ratio, 2.15; 90% CI, 1.22–3.79) than with exposure to cadmium (odds ratio, 1.27; 90% CI, 0.61–2.51). [The Working Group found the report difficult to interpret with respect to cadmium, because it lacks information on exposure classification and no statement is made about control for urban *versus* rural location or simultaneous control of exposure to cadmium and arsenic in the analysis.]

### 2.2.4 *Copper–cadmium alloy plants, Sweden*

Kjellström *et al.* (1979) investigated the incidence of prostatic cancer among 94 workers employed for five or more years between 1940 and 1978 at a cadmium–copper alloy plant in

Sweden. Production of the alloy was begun in the 1930s. The levels of cadmium oxide fume in air were 0.1–0.4 mg/m$^3$ in the 1960s and about 0.05 mg/m$^3$ in the 1970s. Mortality from prostatic cancer between 1940 and 1975 was above that expected from national rates (4 observed, 2.69 expected; RR, 1.49 [95% CI, 0.40–3.81]). A reference group of 328 workers not exposed to cadmium had lower mortality from prostatic cancer than expected (4 observed, 6.42 expected; RR, 0.62 [95% CI, 0.17–1.60]).

### 2.2.5 *Cadmium recovery plant in the USA*

Several mortality studies have been conducted at a US plant where cadmium oxide, sulfide and metal were made from cadmium oxide dust recovered from the waste of nonferrous smelters since 1926 (especially zinc smelters). Estimated average air concentrations of cadmium in dust and fumes in high-exposure departments were 1.16 mg/m$^3$ before 1950, 0.50 mg/m$^3$ in 1950–59, 0.34 mg/m$^3$ in 1960–64 and 0.26 mg/m$^3$ in 1965–76 (Smith *et al.*, 1980). As extensive measurements had been made throughout the plant since 1943, mortality could be analysed by both intensity and duration of exposure to cadmium. Other metals, such as lead, arsenic, indium and thallium, had been produced intermittently in localized areas of the plant, and the facility had been an arsenic smelter in 1918–25 and a lead smelter from 1886 to 1918. Some contamination of incoming feed material with arsenic persisted after 1926: The proportion of arsenic in feedstock was $\geq$ 50% before 1926, about 7% in 1926–27, 1.5–5.6% in 1928–33, 1.9–3.7% in 1934–40 and 1.0–2.0% after 1940 (Thun *et al.*, 1985, 1986). In 1973, arsenic was present at 0.3–1.1 μg/m$^3$ in the pre-melt department and 1.4 μg/m$^3$ in the retort department; the respective values for cadmium were 74.8–90.3 and 1105 μg/m$^3$. Bulk samples of preprocessed ore contained 70% cadmium, 6.0% zinc, 4.3% lead and 0.3% arsenic; after initial roasting, bulk samples contained 42.2% cadmium, 3.53% zinc, no lead and 0.02% arsenic. Additional refining steps reduced the levels of impurities further, so that exposure of workers to trace metals other than cadmium was considered to be insignificant (Lemen *et al.*, 1976).

Lemen *et al.* (1976) studied 292 white male hourly workers exposed for two or more years between 1940 and 1969 and followed from 1940 through to 1973. There were four deaths from cancer of the prostate (1.15 expected; RR, 3.48; [95% CI, 0.94–8.91]). Mortality from this cancer was significantly increased in workers with $\geq$ 20 years latency (4 observed, 0.88 expected [RR, 4.55; 95% CI, 1.22–11.64]). The number of deaths from respiratory cancer also exceeded that expected (12 observed, 5.11 expected; RR, 2.35 [95% CI, 1.21–4.10]). [The Working Group noted that the association with lung cancer was not examined in relation to cumulative exposure to cadmium or exposure to other work-related exposures, including arsenic.]

Thun *et al.* (1985) expanded the cohort to a total of 602 white men who had been employed in cadmium production between 1940 and 1969 for at least six months. Estimates of exposure based on air measurements over time were combined with work exposure categories to estimate cumulative exposures to cadmium. No additional death from prostatic cancer had occurred during the extended follow-up from 1974 to 1978. As the cohort was limited to cadmium production workers, one of the four prostatic cancer deaths observed by Lemen *et al.* (1976) was excluded from the analysis. The remaining three deaths from prostatic cancer occurred among workers with two or more years of employment and 20 or

more years of latency (3 observed, 1.41 expected; RR, 2.13; 95% CI, 0.44–6.22). [The Working Group noted that increased screening for prostatic cancer could result in early detection and therefore greater survival, thus biasing the results of mortality studies of this cancer.]

Lung cancer mortality was examined first through 1978 (Thun *et al.*, 1985) and later through 1984 (Stayner *et al.*, 1992). All analyses of lung cancer mortality in relation to exposure to cadmium were restricted to 576 men who were first employed after 1 January 1926, when the plant ceased arsenic smelting, although (as noted above) some arsenic remained in the material being processed, decreasing with time. Death rates from lung cancer in the overall cohort through 1984 were slightly greater than those expected from US white male rates (24 observed, 16.07 expected; RR, 1.49 [95% CI, 0.96–2.22]), and the RR increased with estimated cumulative exposure to cadmium: 0.34, 1.63, 2.17 and 2.72 in workers with cumulative exposures of $\leq 584$, 585–1460, 1461–2920 and $> 2920$ mg/m$^3$-days (Table 10). The mortality rates for lung cancer among the workers were compared with Colorado State rates for white men for the follow-up period through 1978. The RRs were higher for this follow-up period when compared with local rather than national rates: The RR in the most highly exposed group was 3.87 when compared to State rates (7 observed, 1.81 expected [95% CI, 1.55–7.97]) and 2.80 when national rates were used for comparison (Thun *et al.*, 1986).

Several authors have examined whether exposure to cigarette smoking or arsenic could account for the excess mortality from lung cancer at the US plant. Nearly half of the cadmium workers were men of Mexican–American descent, who in the 1980s smoked fewer cigarettes per day on average and had less than half the incidence of lung cancer of other US white males (US National Cancer Institute, 1986). Lower rates from lung cancer among Mexican–Americans as compared with other whites were also reported in earlier years in Denver, where the plant is located: The RR was about 0.3 in 1969–71 and 0.7 in 1979–81, when men with Latino surnames were compared with other whites (Savitz, 1986). Stayner *et al.* (1992) showed that the excess mortality from lung cancer at the US plant is confined to non-Mexican–American cadmium workers when compared to US white males (21 observed, 9.95 expected; RR, 2.11 [95% CI, 1.31–3.23]), and no excess was seen in Mexican–American workers (3 observed, 6.12 expected; RR, 0.49 [95% CI, 0.10–1.43]). Comparisons with the US population, however, result in overestimates of the expected number of deaths among Mexican–Americans and underestimates of the effect of occupation. The tobacco smoking habits of the non-Mexican–American workers were similar to those of all US white males, yet 11 excess deaths from lung cancer were observed (RR, 2.11; $p < 0.01$) (US Occupational Safety and Health Administration, 1992). [The Working Group noted that confounding by cigarette smoking is unlikely to explain a dose–response relationship and strength of association of this magnitude in an occupational cohort study (Axelson, 1978; Siemiatycki *et al.*, 1988).]

A second extraneous factor that could contribute to mortality from lung cancer at the US plant is arsenic. Three studies were designed to isolate the effect of cadmium from that of arsenic in the cohort by using year of hire before or after 1940 as a proxy for exposure to arsenic. These analyses are based on identical exposure data and overlapping study populations.

Lamm *et al.* (1992) performed a nested case–control analysis in which 25 cases of fatal lung cancer diagnosed through 1982 were each matched with three controls on year of hire; no association was found between exposure to cadmium and risk for lung cancer. The mean cumulative exposure of the cases (9.24 mg/m$^3$-year) was not different from that of the controls (mean, 9.29 mg/m$^3$-year). [The Working Group found the results difficult to interpret, in that exposure data identical to those for the full cohort were used and therefore the same results as in the full cohort should have been obtained. One possible explanation is that matching was done on year of hire, but no matched analysis was done, thereby potentially biasing the results.]

In further analyses, Stayner *et al.* (1992) categorized the 576 cadmium workers employed after January 1926 into pre-1940 and post-1940 and included this variable in Poisson and proportional hazards analyses of lung cancer rates. Dose–response relationships between exposure to cadmium remained significant in nearly all multivariate analyses after controlling for age, Mexican–American ethnicity (a proxy for lighter tobacco use) and period of hire.

As noted by Doll (1992), part of the explanation for the differences between the results of Lamm *et al.* (1992) and Stayner *et al.* (1992) could be that the two studies had only 21 cases in common. Lamm's series also included four cases hired before 1926, which were excluded by Stayner *et al.* Three cases included by Stayner *et al.* died of lung cancer between 1982 and 1984 and were therefore not reported by Lamm *et al.* [The Working Group noted that the methodological differences between the studies of Lamm *et al.* and Stayner *et al.* may account for the contradictory results reported.]

In a subsequent analysis, Stayner *et al.* (1993) conducted a nested case–control analysis using approximately 50 controls per case. The odds ratio increased with increasing cumulative exposure to cadmium, as in the full cohort. They also presented an odds ratio analysis of workers hired after 1940, when arsenic exposures were low. For non-Mexican–Americans, the odds ratio was 0.32 [95% CI, 0.0–1.78] at < 584 mg/m$^3$-days, 2.81 [1.02–6.10] at 585–1460 mg/m$^3$-days and 4.70 [1.51–10.97] at 1461–2920 mg/m$^3$-days. No lung cancer death was observed in the highest exposure category (> 2920 mg/m$^3$-days), but only 0.6 were expected. [The Working Group noted that the dose–response pattern was stronger in workers hired after 1940, indicating that the result was not likely to be due to exposure to arsenic.]

Thun *et al.* (1986) addressed the question of the extent to which exposure to arsenic could be held responsible for the excess of lung cancer observed in the cohort. They estimated average cumulative exposure to arsenic in relation to a potency estimate for exposure to arsenic and lung cancer used by the US Occupational Safety and Health Administration and concluded that 0.77 lung cancer deaths could be attributed to arsenic. In a more detailed analysis, the US Occupational Safety and Health Administration (1992) estimated that exposure to arsenic would have resulted in 0.52–0.97 lung cancer deaths in the cohort.

### 2.2.6 *Cadmium processing plants in the United Kingdom*

Armstrong and Kazantzis (1983) and Kazantzis *et al.* (1988) studied mortality among workers at 17 plants in the United Kingdom where cadmium is produced or used, including

primary production, copper–cadmium alloy production, silver–cadmium alloy production, pigments and oxide production and stabilizer production. The cohort comprised 6958 men born before 1940 and employed for more than one year on or near a cadmium process between 1942 and 1970. The plants at which nickel–cadmium batteries and copper–cadmium alloys were produced and which were described by Sorahan (1987) and Holden (1980b) were excluded. Jobs were assessed for each relevant year as involving high, medium or low exposure to cadmium on the basis of discussions with hygienists and others with knowledge of past working procedures, taking into account available results of biological or environmental monitoring. The years at risk of the study population were divided on the basis of these categories and recorded job histories into three groups; 'ever high' (minimum one year), 'ever medium' (minimum one year) and 'always low'. A total of 198 workers (3%; Kazantzis *et al.*, 1992) were classified as having had 'ever high' exposure, 17% were considered to have had 'ever medium' exposure, and the exposures of 80% were classified as 'always low' (Armstrong & Kazantzis, 1983). Kazantzis *et al.* (1992) stated that in these epidemiological studies consideration should be given to concomitant exposure to other potential carcinogens, in particular to arsenic, but also to beryllium (see p. 41), nickel (see IARC, 1990a), chromium (see IARC, 1990c) and emissions from a variety of heated mineral oils (see IARC, 1987d) in the various plants.

Kazantzis *et al.* (1988) described mortality from 1943 to 1984 in this cohort, and Kazantzis and Blanks (1992) and Kazantzis *et al.* (1992) extended follow-up through 1989 for 6910 workers. No increased risk for death from prostatic cancer was observed in the overall cohort (37 observed, 49.5 expected; RR, 0.75; 95% CI, 0.53–1.03). One death from prostatic cancer was seen in the 'ever high' exposure group (1.0 expected; RR, 0.97), but none was observed in the 'ever medium' group (6.2 expected; RR, 0; 95% CI, 0–0.59). Mortality from lung cancer was significantly increased in the overall cohort (339 observed, 304.1 expected; RR, 1.12; 95% CI, 1.00–1.24), with some evidence of a trend across exposure categories; these do not, however, attain significance (low: 270 observed, 249.9 expected; RR, 1.08; 95% CI, 0.96–1.22; medium: 55 observed, 45.6 expected; RR, 1.21; 95% CI, 0.91–1.57; high: 14 observed, 8.6 expected; RR, 1.62; 95% CI, 0.89–2.73). With regard to duration of exposure, mortality from lung cancer was significantly raised for men employed for 20–29 years in the cohort as a whole (65 observed, 49.6 expected; RR, 1.31; 95% CI, 1.01–1.67) and in the low-exposure category (54 observed, 38.4 expected; RR, 1.41; 95% CI, 1.06–1.84). In the 'ever high' exposure category, mortality from lung cancer was significantly increased among men first employed between 1930 and 1939 (4 observed, 1.0 expected; RR, 3.81; 95% CI, 1.03–9.76). There is suggestive evidence of a relationship with both intensity of exposure and duration of employment for workers employed before 1940, but no such pattern was seen for workers who started work after 1950. A significantly increased risk was observed for stomach cancer in the cohort as a whole (106 observed, 85.3 expected; RR, 1.24; 95% CI, 1.02–1.50), but this was not related to intensity of exposure, with 91 of the deaths occurring in the low-exposure group (71.4 expected; RR, 1.28; 95% CI 1.03–1.57). As in the earlier studies of this cohort, an increased risk significantly related to intensity of exposure was observed only for bronchitis.

Ades and Kazantzis (1988) reported separately on the experience of 4393 men who had been employed for at least one year at a lead–zinc smelter that comprised 64% of the entire

United Kingdom cadmium cohort and at which no exposure was classified as 'ever high'. There was excess mortality from lung cancer overall when compared with regional rates (182 observed, 146.2 expected; RR, 1.25; 95% CI, 1.07–1.44) and when updated by Kazantzis *et al.* (1992): 237 observed, 194.3 expected; RR, 1.22, 95% CI, 1.02–1.39. A significant trend in SMR was seen with increasing duration of employment. A nested case–control analysis and matched logistic regression were used to compare 174 fatal cases of lung cancer with 2717 controls matched to the cases on year of birth, date of starting work (within three years) and length of follow-up (at least 10 years). The odds ratio for lung cancer increased by 1.23 fold per mg/m$^3$-years of exposure to cadmium, but the trend was not significant. The trend in RR was significant for exposure to arsenic and lead. Only 21 (12%) cases had ever worked in the two departments (sinter and cadmium plant) where exposures to cadmium generally exceeded 0.010 mg/m$^3$.

#### 2.2.7 *Smelter in China*

Cancer mortality among male workers employed for at least one year in a smelter in China was followed from 1972 to 1985 and compared with rates for the city in which the smelter was located (Ding *et al.*, 1987). When the plant was divided into five areas, industrial hygiene sampling indicated that exposures to cadmium were highest in the cadmium shop and the sintering shop, with mean air concentrations of 0.186 and 0.014 mg/m$^3$, respectively. The levels in the cadmium shop were reported to have been much higher prior to 1980 (0.535 mg/m$^3$). Exposure to arsenic was also reported to have occurred in the sintering area (0.196 mg/m$^3$ $As_2O_3$). One case of lung cancer (0.15 expected, SMR, 6.65) and two of liver cancer (0.11 expected, SMR, 17.9) were observed among cadmium shop workers. Four lung cancers (0.24 expected, SMR, 16.8; $p < 0.05$), one stomach cancer (0.31, SMR, 3.18) and three liver cancers (0.18 expected, SMR, 17.0) were observed among sintering shop workers. The men who died of cancer were reported to have had 10–30 years of exposure. Mortality from lung cancer was also increased in the other three areas. The authors stated that there was no obvious association with smoking. [The Working Group noted that the numbers of workers employed were not given.]

### 2.3 Case–control studies

Abd Elghany *et al.* (1990) conducted a population-based case–control study of exposure to cadmium based on 358 cases of prostatic cancer newly diagnosed in 1984–85 and 679 controls in four urban Utah (USA) counties. Analyses were also conducted for the subgroup of cases classified as aggressive tumours, in order to differentiate more clearly the cases from the controls (which may have included some latent prostatic tumours). In general, there was little evidence of an increased risk for prostatic cancer associated with occupations with potential exposure to cadmium (odds ratio, 0.9; 95% CI, 0.7–1.2), with cigarette smoking (odds ratio, 1.1; 95% CI, 0.8–1.4) or with diet (odds ratio, 1.4; 95% CI, 1.0–2.1). A composite measure of potentially high exposure to cadmium from any source was not associated with prostatic cancer in general (odds ratio, 1.0; 95% CI, 0.7–1.3) but was associated with aggressive tumours (odds ratio, 1.7; 95% CI, 1.0–3.1).

A hypothesis-generating case–control study of 20 cancer sites was conducted in the Montréal (Canada) metropolitan area (Siemiatycki, 1991) and is described in detail in the

**Table 10. Cohort studies of lung cancer in workers exposed to cadmium**

| Type of plant, country (reference) | Population (duration of exposure) | Lung cancers (obs/exp) | Exposure level | Cadmium levels | | | Relative risk (95% CI[a]) | Comment |
|---|---|---|---|---|---|---|---|---|
| | | | | Years | Estimated levels ($mg/m^3$) | | | |
| **Nickel–cadmium battery (cadmium oxide)** | | | | | | | | |
| United Kingdom | | | | | | | | |
| Potts (1965) | 74 men (≥ 10 years) | 1/NR | Overall | | | | Cannot be calculated | Mortality through 1965 No referent group |
| Kipling & Waterhouse (1967) | 248 men (≥ 1 year) | 5/4.40 | Overall | 1949 | 0.6–2.8 | (Sorahan & Waterhouse, 1983) | 1.14 [0.37–2.65] | Incidence through 1966 at same plant as Potts (1965) |
| Sorahan (1987) | 3025 men and women (≥ 1 month) | 110/84.5 | Overall | 1950–67 | < 0.5 | (Sorahan & Waterhouse (1983) | 1.30 [1.07–1.57] | Mortality 1946–84 |
| | | | None[b] | 1968–75 | < 0.2 | | 1.0 | Dose–response based on years employed in high-exposure jobs. Trend not significant |
| | | | < 2 years | > 1975 | < 0.05 | | 1.4 | |
| | | | 2– | | | | 1.3 | |
| | | | 5– | | | | 1.3 | |
| | | | ≥ 15 | | | | 1.5 | |
| Sweden | | | | | | | | |
| Kjellström *et al.* (1979) | 228 men (≥ 5 years) | 2/1.35 | Overall | < 1947 | 1 | (Elinder *et al.* 1985) | 1.48 (0.17–5.35) | Incidence 1959–75 |
| Elinder *et al.* (1985) | 522 men (> 1 year) | 8/6.01 | Overall | 1947–62 | 0.3 | (Elinder *et al.*, 1985) | 1.33 [0.57–2.62] | Mortality 1940–80 at same plant |
| | | | > 5 years and ≥ 20 years latency | 1962–74 | 0.05 | | 1.75 [0.70–3.61] | |
| | | | | > 1975 | 0.02 | | | |
| **Copper–cadmium alloy** | | | | | | | | |
| United Kingdom | | | | | | | | |
| Holden (1980a) | Urban ≥1 year | 8/4.50 | Overall | < 1953 | 1 | | 1.78 [0.77–3.50] | Mortality, number of workers not stated |
| | Rural ≥1 year | 2/7.85 | Overall | 1953–57 | < 0.15 | | 0.26 [0.03–0.92] | Expected deaths based on national rates |
| | 624 vicinity ≥1 year | 36/26.08 | Overall | > 1957 | < 0.05 | | 1.38 [0.97–1.91] | Vicinity workers also exposed to arsenic |
| **Cadmium recovery** | | | | | | | | |
| USA | | | | | (personal) | (ambient) | | |
| Lemen *et al.* (1976) | 292 men (≥ 2 years) | 12/5.11 | | < 1950 | 1.16 | 1–45 | 2.35 [1.21–4.10] | Mortality 1940–73 |
| | | | | 1950–59 | 0.50 | 0.1–20 | | |
| Stayner *et al.* (1992) | 579 men (≥ 6 months) | 24/16.07 | Overall | 1960–64 | 0.34 | 0.4–0.5 | 1.49 (0.95–2.21) | Mortality 1940–84 |
| | | | ≤ 584[c] | 1965–76 | 0.26 | 0.05–0.6 | 0.34 | Excludes workers hired before 1 January 1926 |
| | | | 585–1460 | | | | 1.63 | Test for trend significant |
| | | | 1461–2920 | | | | 2.17 | |
| | | | > 2920 | | | | 2.72 | |

**Table 10 (contd)**

| Type of plant, country (reference) | Population (duration of exposure) | Lung cancers (obs/exp) | Exposure level | Cadmium levels | | Relative risk (95% CI[a]) | Comment |
|---|---|---|---|---|---|---|---|
| | | | | Years | Estimated levels ($mg/m^3$) | | |
| **Cadmium recovery** (contd) | | | | | | Odds ratio | |
| | | | | | | Non-Mexican-American (no.) | Mexican-American (no.) |
| USA (contd)<br>Stayner *et al.* (1993) | Subgroup of cohort of Stayner *et al.* (1992) hired after 1940 | | < 584<br>584–1460<br>1461–2920<br>> 2920 | | | 0.32 (1)<br>2.81 (6)<br>4.70 (5)<br>0 (0.6 exp.) | 0.42 (1)<br>0 (0 exp.)<br>0.82 (1)<br>2.46 (2) |
| **Cadmium processing** | | | | | | | |
| United Kingdom<br>Kazantzis *et al.* (1992); Kazantzis & Blanks (1992) | 6910 men<br>> 1 year | 339/304.1<br>270<br>55<br>14 | Overall<br>Always low<br>Ever medium<br>Ever high | | | 1.12 (1.00–1.24)<br>1.08 (0.96–1.22)<br>1.21 (0.91–1.57)<br>1.62 (0.89–2.73) | Mortality 1943–89; 17 plants; 3% of workers had ever high exposure. |

NR, not reported

[a]Approximate 95% confidence intervals calculated by the Working Group are given in square brackets.

[b]Referent group includes jobs with no or 'minimal' exposure to cadmium.

[c]Units are $mg/m^3$-days

**Table 11. Cohort studies of prostatic cancer in cadmium workers**

| Type of plant, country (reference) | Population (duration of exposure) | Prostatic cancers (obs/exp) | Exposure level | Relative risk (95% CI[a]) | Comment |
|---|---|---|---|---|---|
| **Nickel–cadmium battery (cadmium oxide)** | | | | | |
| United Kingdom | | | | | |
| Potts (1965) | 74 men (≥10 years) | 3/NR | Overall | Cannot be calculated | Mortality through 1965 No referent group |
| Kipling & Waterhouse (1967) | 248 men (≥1 year) | 4/0.58 | Overall | 6.90 [1.86–17.66] | Incidence through 1966 includes three deaths from Potts (1965). |
| Sorahan & Waterhouse (1983) | 2559 men (≥1 month) | 8/6.6 | Overall | 1.21 [0.52–2.39] | Mortality 1946–80 |
| Sorahan & Waterhouse (1985) | 2559 men (≥1 month) | 15/11.02 | Overall<br>> 1 year and high | 1.36 [0.76–2.25]<br>4.02 [1.73–7.92] | Incidence 1950–80 including 4 cases from Kipling & Waterhouse (1967) |
| Sweden | | | | | |
| Kjellström *et al.* (1979) | 228 men (≥5 years) | 2/1.2 | Overall | 1.67 [0.19–6.02] | Incidence 1959–75 |
| Elinder *et al.* (1985) | 522 men (> 1 year) | 4/3.70 | Overall<br>> 5 years and ≥ 20 years' latency | 1.08 [0.29–2.77]<br>1.48 [0.40–3.79] | Mortality 1951–83 |
| **Copper–cadmium alloy** | | | | | |
| United Kingdom | | | | | |
| Holden (1980a) | 347 male cadmium workers (≥1 year) | 1/1.58 | Exposed | 0.63 [0.01–3.52] | Mortality |
| | 624 vicinity workers (≥1 year) | 8/3.0 | Less exposed | 2.67 [1.15–5.26] | |

**Table 11 (contd)**

| Type of plant, country (reference) | Population (duration of exposure) | Lung cancers (obs/exp) | Exposure level | Relative risk (95% CI[a]) | Comment |
|---|---|---|---|---|---|
| **Copper–cadmium alloy** (contd) | | | | | |
| Sweden | | | | | |
| Kjellström *et al.* (1979) | 94 men (≥ 5 years) | 4/2.69 | Exposed | 1.49 [0.40–3.81] | Mortality 1940–75. Data described as preliminary |
| | 328 controls | 4/6.42 | Unexposed | 0.62 [0.17–1.60] | |
| **Cadmium recovery** | | | | | |
| USA | | | | | |
| Lemen *et al.* (1976) | 292 men (≥ 2 years) | 4/1.15 | Overall | 3.48 [0.94–8.91] | Mortality 1940–73 |
| | | | ≥ 20 years' latency | [4.55 (1.22–11.64)] | |
| Thun *et al.* (1985) | 602 men (≥ 6 months) | 3/1.41 | ≥ 2 years' employment and ≥ 20 years' latency | 2.13 (0.44–6.22) | Mortality 1940–78 |
| **Cadmium processing** | | | | | |
| United Kingdom | | | | | |
| Kazantzis *et al.* (1992); Kazantzis & Blanks (1992) | 6910 men (> 1 year) | 37/49.3 | Overall | 0.75 (0.53–1.03) | Mortality 1943–89 Regional adjustment |
| | | 36 | Always low | 0.85 (0.60–1.18) | |
| | | 0 | Ever medium | 0 (0.0–0.59) | |
| | | 1 | Ever high | 0.97 (0.01–5.40) | |

NR, not reported

[a]Approximate 95% confidence intervals calculated by the Working Group are given in square brackets.

monograph on exposures in the glass manufacturing industry (p. 347). The prevalence of exposure to cadmium compounds was 1%. Bladder was the only cancer site to be associated with exposure to cadmium compounds (six exposed cases; odds ratio, 1.6; 90% CI, 0.7–3.8). When the analysis was restricted to substantial exposure, only four cases of bladder cancer had been exposed (odds ratio, 4.9; 90% CI, 1.2–19.6). No association was found with cancers of the lung or prostate.