2. Studies of Cancer in Humans

Beryllium was considered previously by three working groups (IARC, 1972, 1980, 1987). The first group (IARC, 1972) found the four epidemiological studies available at that time (Hardy *et al.*, 1967; Stoeckle *et al.*, 1969; Mancuso & El-Attar, 1969; Mancuso, 1970) not to provide evidence of the existence of a possible relationship between exposure to beryllium compounds and the occurrence of cancer in man. The second working group (IARC, 1980) reviewed four subsequent cohort studies (Infante *et al.*, 1980; Mancuso, 1979, 1980; Wagoner *et al.*, 1980) and concluded that the evidence for an increased risk for lung cancer from occupational exposure to beryllium was limited. No new study was available at the time of the third review (IARC, 1987).

2.1 Cohort studies (see Table 12, p. 70)

Mancuso (1979) conducted a retrospective cohort mortality study of workers employed in two beryllium extraction, production and fabrication facilities in the USA: one in Lorain, Ohio, and the other in Reading, Pennsylvania (see Table 13, p. 71, for description). The cohort was limited to workers who had been employed for at least three months during 1942–48. Observed and expected numbers of deaths were compared using a modified life-table analysis. Expected deaths were calculated on the basis of five-year mortality rates for the general white male population of the USA, except that the author did not have access to the actual national mortality rates for 1968–75 and calculated expected deaths for that period by applying US mortality rates for 1965–67. As a consequence of this extrapolation, expected lung cancer death rates for the 1968–75 period were underestimated by a factor of 10% (Saracci, 1985). The standardized mortality ratio (SMR) for lung cancer among the 1222 workers in the Ohio plant was 2.00 (1.8 with Saracci's adjustment; 95% confidence interval [CI], 1.2–2.7); that among the 2044 workers at the Pennsylvania plant was 1.37 (1.25 with Saracci's adjustment; 95% CI, 0.9–1.7). The combined lung cancer SMR (with Saracci's adjustment) for the two plants was 1.42 (95% CI, 1.1–1.8). A consistently greater excess of lung cancer was seen in the two plants among workers who were followed for 15 or more years since first employment; the SMRs (with Saracci's adjustment) were 2.0 (95% CI, 1.3–3.1) for the Ohio plant and 1.5 (95% CI, 1.0–2.1) for the Pennsylvania plant. In the combined cohort, the excess of lung cancer was limited to workers who had been employed for less than five years and followed for 15 or more years since first employment. [The

Working Group noted that no analysis of risk by job title or exposure category was conducted. The period of initial employment of the study cohort preceded the imposition by the US Atomic Energy Commission in 1949 of a 2 $\mu g/m^3$ 8-h time-weighted average limit for occupational exposure to beryllium and a ceiling limit of 25 $\mu g/m^3$, applicable to all beryllium facilities under contract to the Commission (Preuss, 1988).] A study of the beryllium alloy plant in Lorain, Ohio, conducted in 1947–48 by the US Atomic Energy Commission (Zielinski, 1961), showed concentrations of beryllium ranging from 411 $\mu g/m^3$ in the general air surrounding the mixing operation to 43 300 $\mu g/m^3$ in the breathing zone of alloy operatives. Control measures were introduced throughout US plants after 1949, and exposure levels in beryllium facilities were reduced markedly. Extraction plants, for example, were able to maintain exposure levels of 2 $\mu g/m^3$ or less, while certain foundry operations had air concentrations consistently in excess of 2 $\mu g/m^3$, with maximal values greater than 1000 $\mu g/m^3$ during the period 1968–72 in the Pennsylvania plant (Wagoner *et al.*, 1980).

Mancuso (1980) re-analysed mortality in the same Ohio and Pennsylvania beryllium extraction and processing plants, but extended the period of employment of the study cohort to 1937–48 and used as a comparison group viscose rayon industry workers employed at one company during 1938–48. Mortality was followed up through 1976. Among the 3685 cohort members from the two beryllium plants, 80 lung cancer deaths were observed, whereas 57.1 were expected on the basis of the total mortality experience of the viscose rayon workers (SMR, 1.40; $p < 0.01$) and 50.6 deaths were expected on the basis of the mortality experience of viscose rayon workers employed in a single department of the industry (SMR, 1.58; $p < 0.01$). [The Working Group noted that use of the latter reference cohort may introduce a selection bias into the analysis, since the mortality experience of workers who never change departments while employed in the industry may differ from that of the total workforce of the industry, for non-occupational reasons.] Lung cancer SMRs were calculated by duration of employment in comparison with the entire group of viscose rayon employees; these values were 1.38 ($p < 0.05$; 52 observed deaths) for one year or less of employment, 1.06 (14 observed deaths) for more than one year to four years or less, and 2.22 ($p < 0.01$; 14 observed deaths) for more than four years' employment.

Wagoner *et al.* (1980) expanded the cohort mortality study of the same Pennsylvania plant analysed by Mancuso (1979, 1980) to include workers employed at some time during 1942–67 and followed them up to 1 January 1976. [This interval extends across the year 1949 when, as previously noted, the Atomic Energy Commission standard of 2 $\mu g/m^3$ was introduced and a substantial reduction in exposure to beryllium subsequently occurred (US National Institute for Occupational Safety and Health, 1972).] They also used 1965–67 national lung cancer mortality rates to calculate expected lung cancer deaths for the period 1968–75. [The adjustment of Saracci (1985) is thus appropriate in considering these results.] Wagoner *et al.* (1980) observed 47 lung cancer deaths among the 3055 workers in the study cohort, whereas 37.7 were expected (with Saracci's adjustment) on the basis of national mortality experience, yielding an SMR of 1.25 (95% CI, 0.9–1.7). When lung cancer SMRs were calculated by latency, the SMRs were 0.88 (9 deaths) for < 15 years' latency, 1.16 (18 deaths) for 15–24 years' latency and 1.68 (20 deaths) for $\geq$ 25 years' latency, the 95% CI for latter SMR being 1.0–2.6. Within latency categories, there was no pattern of increasing (or decreasing) SMR by duration of employment, dichotomized into less than five and five

years or more. Analysis by duration yields an unstable estimate for longer duration strata owing to small numbers: for $\geq$ 5 years, the SMR is 1.1 (seven deaths) and the 95% CI is 0.4–2.3 (Saracci, 1985). A decline in risk for death from chronic beryllium disease was seen in relation to the same categories of length of employment. The potential for confounding of the SMR by a different distribution of smoking habits in the US population and in the beryllium cohort was calculated on the basis of a 1968 medical survey, in which detailed smoking histories of workers at the Pennsylvania plant were obtained, and of the 1964–65 Health Interview Survey of a probability sample of the US population, in which current and past smoking habits were queried. The overall calculations suggest that reported differences in smoking habits were sufficient to increase the lung cancer risk among the beryllium workers by 14%, in the absence of beryllium exposure; however, as also discussed by Wagoner *et al.* (1980), the white male age-adjusted rate for lung cancer mortality in the county in which the Pennsylvania plant was located (31.8/100 000) was lower than the average annual white male age-adjusted mortality rate for the USA as a whole (38.0/100 000). Wagoner *et al.* (1980) calculated that the risk for mortality from lung cancer in the beryllium cohort, if adjusted for differences in mortality between the County and the USA and for residential stability of cohort members, was underestimated by a factor up to 19%. [The Working Group noted that these two factors—smoking distribution and lower regional lung cancer mortality—bias the SMR estimate in opposite directions.]

Infante *et al.* (1980) analysed the mortality experience of white males entered into the Beryllium Case Registry while alive, with a diagnosis of chronic beryllium disease or acute beryllium-related pneumonitis. The Beryllium Case Registry was established in 1952 to collect data on the epidemiology, diagnosis, clinical features, course and complications of beryllium-related diseases. Individuals who were entered into the Registry were categorized as having either acute beryllium-induced pneumonitis or chronic systemic beryllium diseases (Sprinze & Kazemi, 1980). Individuals who were referred to the Registry for evaluation of beryllium-related diseases were employed in a variety of occupations, but most worked in beryllium extraction and smelting, metal production and fluorescent tube production. A total of 421 white males who entered the Registry alive between July 1952 and December 1975 were followed through to 31 December 1975. Seven deaths from lung cancer were observed and 3.3 were expected, based on national mortality rates for the period 1952–67 (SMR, 2.12, not significant). Since published vital statistics were not available for the period 1968–75, national mortality rates for 1965–67 were applied to 1968–75. If the number of expected deaths is increased by 10%, the expected value becomes [3.63], and the adjusted SMR is [1.93; 95% CI, 0.8–4.0]. For men who were entered into the Registry with a diagnosis of beryllium-related acute pneumonitis, the SMR (with Saracci's adjustment) for lung cancer is 2.86 (95% CI, 1.0–6.2; six cases). For those who were entered with a diagnosis of chronic beryllium disease, one lung cancer death was observed, with 1.52 expected (SMR, 0.66; 95% CI, 0.1–3.7). [The Working Group noted the small expected number of lung cancer deaths, particularly among workers with chronic lung disease, and the relatively short follow-up time for those workers who were entered into the Registry after 1965 ($\leq$ 10 years). Chronic beryllium disease results from hypersensitivity to beryllium and may occur at much lower exposures than acute beryllium pneumonitis. A small number of the cases occurred among people living near the plants but who were not occupationally exposed.]

An extended analysis of mortality among people entered into the Beryllium Case Registry was reported by Steenland and Ward (1991). The study cohort, which now included women (34% of the cohort) and men of all races, numbered 689 people who were alive at entry into the Registry between July 1952 and the end of 1980. Mortality follow-up was extended through 1988 [actual US death rates were available for comparison for all years, eliminating the need for Saracci's adjustment in this and the report of Ward *et al.* (1992)]. Excess mortality was found for all cancers (SMR, 1.51; 95% CI, 1.17–1.91; 70 observed deaths), due primarily to an excess of lung cancer (SMR, 2.00; 95% CI, 1.33–2.89; 28 observed deaths); there were also excess deaths from nonmalignant respiratory disease (SMR, 34.23; 95% CI, 29.1–40.0; 158 observed deaths) and all causes of deaths (SMR, 2.19; 95% CI, 1.17–1.91; 428 observed deaths). The SMR for lung cancer was greater among cohort members with acute beryllium pneumonitis (SMR, 2.32; 95% CI, 1.35–3.72; 17 cases) than among those with chronic beryllium disease (SMR, 1.57; 95% CI, 0.75–2.89; 10 cases) (one death was due to disease of unknown type). The SMRs for nonmalignant respiratory disease were 10 times higher in the chronic disease group (SMR, 68.6) than in the acute disease group (SMR, 6.6). The SMRs for lung cancer varied little by time since first exposure (SMR, 1.95; 95% CI, 0.94–3.59 for $\leq$ 20 years since first exposure; 2.03; 95% CI, 1.20–3.21 for $>$ 20 years) or by duration of exposure. [The Working Group presumed that duration of exposure to beryllium was determined by duration of employment in a beryllium plant, although this is not specified in the published report.] Taking into account the distribution of smoking habits among 32% of the cohort members questioned in 1965 and from a national survey of the US population studied in 1965, Steenland and Ward (1991) concluded that the study cohort smoked less (current smokers, 26%) than the US referent population (39%) in 1965 and that, if the 32% sample were representative of the entire cohort, smoking was unlikely to be a confounder of the observed excess lung cancer. Selection bias was diminished in this study because: people who died before entry into the Registry were excluded; only five individuals who had cancer before entry into the Registry were found in a review of Registry records, and none of these had lung cancer; and if patients with lung cancer had entered the Registry preferentially, the follow-up interval on these subjects would have been short, whereas only three of the 28 observed lung cancer deaths occurred within five years of entry into the Registry. [The Working Group noted that the results of this Beryllium Case Registry cohort study yield a higher lung cancer SMR than was found in other studies of beryllium-exposed workers, particularly among those who were entered with acute beryllium pneumonitis and who could therefore be assumed to have had a higher intensity of exposure to beryllium. This finding is consistent with the assumption that the risk for lung cancer is proportional to the intensity of exposure to beryllium. Furthermore, it provides indirect evidence that beryllium, rather than smoking, explains the findings, as people with acute pneumonitis were unlikely to smoke more than workers with chronic beryllium disease.]

Ward *et al.* (1992) reported the results of a cohort mortality study of 9225 male workers (8905 white, 320 non-white) employed by two companies at seven beryllium plants in Ohio and Pennsylvania. The results are summarized in Tables 12–16 (pp. 70–73). [Two of these plants (in Lorain, OH, and Reading, PA) are the same as those studied by Mancuso (1979, 1980) and Wagoner *et al.* (1980) (see Table 13).] Workers had to have worked for at least two days between 1940 and 1969 to qualify for entry into the study cohort. Mortality follow-up

Table 12. Cohort studies of lung cancer in beryllium workers

Reference	Cohort or plant location	Period of employment	Termination of follow-up	Comparison population	SMR	95% CI	Lung cancers observed
Mancuso (1979)	Lorain, OH	1942–48	1974	US white males	1.8[a]	1.2–2.7	25
	Reading, PA	1942–48	1975		1.25[a]	0.9–1.7	40
	Combined				1.42[a]	1.1–1.8	65
Mancuso (1980)	Lorain, OH Reading, PA	1937–48	1976	Viscose rayon workers	1.40	[1.1–1.7]	80
Wagoner *et al.* (1980)	Reading, PA	1942–67	1975	US white males	1.25[a]	0.9–1.7	47
Infante *et al.* (1980)	Beryllium Case Registry	Entry into Registry 1952–75	1975	US white males	[1.93]	[0.8–4.0]	7
				Acute pneumonitis	2.86[a]	1.0–6.2	6
				Chronic beryllium disease	0.66[a]	0.1–3.7	1
Steenland & Ward (1991)	Beryllium Case Registry	Entry into Registry 1952–80	1988	US men and women (all races)	2.00	1.33–2.89	28
				Acute pneumonitis	2.32	1.35–3.72	17
				Chronic beryllium disease	1.57	0.75–2.89	10
Ward *et al.* (1992)	Seven beryllium processing plants	1940–69	1988	US males, all races	1.26	1.12–1.42	280

SMR, standardized mortality ratio; CI, confidence interval; [ ], calculated by the Working Group
[a]With Saracci's adjustment

was extended through to 1988 and was analysed using standard modified life-table methods. The influence of local differences in mortality was evaluated by comparing SMRs derived from national and from local county mortality rates. The effect of the dissimilar distribution of smoking habits between beryllium workers and the US population was also evaluated. In the total cohort of 9225 workers, there were 3240 deaths (35% of the total) and 269 235 person-years of follow-up, of which 52% were person-years at risk 15 years or more after first employment in the beryllium industry. The SMR for all causes was 1.05 (95% CI, 1.01–1.08), that for all cancers was 1.06 (95% CI, 0.99–1.44), and that for nonmalignant respiratory disease was 1.48 (95% CI, 1.21–1.80). With the exception of that for cancer of the respiratory system, none of the SMRs for cancers at specific sites was significantly different from 1.00. The overall SMR for lung cancer was 1.26 (95% CI, 1.12–1.42; 280 observed deaths, based on US rates). SMRs for cancers of the larynx and of the upper respiratory tract were below 1.00.

Table 13. Years during which major processes were used at the US beryllium plants in the study of Ward *et al.* (1992)

Plant location	Ore refining	Beryllium oxide production	Metal production	Beryllium–copper alloy production	Machining
Lorain, OH	1935–48	1935–48	1935–48	1935–47	–
Reading, PA	1935–66	1035–66	–	1935–present	1938–present
Lucky, OH	1950–58	1950–58	1950–58	–	–
Perkins (Cleveland), OH	1937–55	1937–62	1948–62	–	1941–63
St Clair (Cleveland), OH	–	–	–	–	1963–73
Elmore, OH	1958–77	1958–present	1958–present	1952–present	1958–present
Hazelton, PA	1958–78	1958–78	1958–78	1958–78	1958–78

The dates refer only to the processes and were not used to restrict the cohorts. For example, workers hired at the Lucky plant in 1949 were included in the study, as were a few individuals hired at the Lorain plant in 1949 and early 1950.

The SMRs for lung cancer at individual plants (Table 14) were greater than 1.00 at four of the six locations: two plants near Cleveland, OH—Perkins and St Clair—were combined into one cohort because records of the two plants could not be separately identified. The SMRs were significantly greater than 1.00 only at the Lorain, OH, and Reading, PA, plants [the same facilities studied by Mancuso (1979, 1980) and Wagoner *et al.* (1980)]. It is noteworthy that cohorts in which there was a high SMR for pneumoconiosis and other respiratory diseases, presumably indicating higher exposure to beryllium also consistently had elevated SMRs for lung cancer. When lung cancer SMRs were stratified by latency at each plant, three of the six locations showed higher SMRs for the 15–30-year and > 30-year latency categories compared with the < 15-year latency category (Table 15); however, for the total cohort, lung cancer SMRs increased stepwise with increasing latency (bottom row of Table 15). When SMRs were stratified by decade of hire (Table 16), values greater than 1.00 were seen for all three locations in which workers were hired before 1950 (the period when exposures to beryllium were also greater than subsequently), but SMRs were also greater than 1.00 in four of the five locations where workers were hired between 1950 and 1959.

Table 14. Mortality of workers employed in 1940–69 at the seven US beryllium processing plants in the study of Ward *et al.* (1992)

Plant location	Total no. of workers	Percentage of workers employed for		SMR			No. of lung cancer deaths
		< 1 year	1–5 years	Lung cancer (based on US rates)	Lung cancer (based on county rates)	Pneumoconiosis and other respiratory disease (based on US rates)	
Lorain, OH	1192	84.6	12.8	1.69**	1.60**	1.94**	57
Reading, PA	3569	53.8	22.3	1.24*	1.42**	1.34	120
Cleveland, OH (two plants)	1593	47.3	29.8	1.08	1.05	1.22	44
Lucky, OH	405	62.2	35.8	0.82	0.84	0.87	9
Elmore, OH	1323	29.0	24.9	0.99	1.06	0.69	15
Hazelton, PA	590	19.7	17.8	1.39	1.50	2.00	13
Multiple plants	257	0.8	12.1	1.67	–	2.60	13
Location unknown	296	49.3	41.6	1.33	–	3.47**	9
Total[a]	9225	49.7	23.4	1.26**	1.32*	1.48**	280

*$p < 0.05$; **$p < 0.01$

[a]See also Table 12

As seen in the bottom row of Table 16, decade of hire was one of the strongest correlates of lung cancer mortality risk in the total cohort. Poisson regression analysis, with control for age, race, calendar time and time since first employment, showed an independent effect of decade of hire on lung cancer SMRs in the total cohort. Duration of employment had no effect. [The Working Group noted that, given the much higher exposures to beryllium prior to 1950 and the fact that 73% of the total cohort worked for less than five years, duration of employment does not separate that segment of the cohort which received the highest exposures to beryllium.]

Table 15. Standardized mortality ratios (SMRs) for lung cancer by location of plants and latency since time of first employment in the US beryllium plants in the study of Ward *et al.* (1992)

Location	Latency < 15 years		Latency 15–30 years		Latency > 30 years	
	SMR	Observed deaths	SMR	Observed deaths	SMR	Observed deaths
Lorain, OH	0.38	1	2.09**	21	1.66*	35
Reading, PA	0.78	9	1.17	44	1.40*	67
Cleveland, OH	1.30	9	0.91	20	1.27	15
Lucky, OH	0.96	1	0.85	4	0.76	4
Elmore, OH	0.51	2	1.14	12	1.31	1
Hazelton, PA	1.91	4	1.26	9	–	0
Multiple plants	–	0	1.23	4	2.38*	9
Location unknown	0.64	1	1.28	5	2.30	3
Total	0.89	27	1.20	119	1.46**	134

*$p < 0.05$; **$p < 0.01$

Table 16. Standardized mortality ratios (SMRs) for lung cancer by location of plants and decade of hire in the US beryllium plants in the study of Ward *et al.* (1992)

Location	Hired before 1950		Hired 1950–59		Hired 1960–69	
	SMR	Observed deaths	SMR	Observed deaths	SMR	Observed deaths
Lorain, OH	1.69**	57	–	–	–	–
Reading, PA	1.26*	92	1.42	26	0.35	2
Cleveland, OH	1.06	12	1.32	26	0.63	6
Lucky, OH	–	–	0.82	9	–	–
Elmore, OH	–	–	1.42	12	0.45	3
Hazelton, PA	–	–	1.86	9	0.87	4
Multiple plants	2.53**	12	0.36	1	–	–
Location unknown	2.30	4	0.62	2	1.57	3
Total	1.42**	177	1.24	85	0.62	18

*$p < 0.05$; **$p < 0.01$

When lung cancer SMRs for each of the six locations were based on local county mortality rates (Ward *et al.*, 1992; see Table 14), the SMRs differed only slightly from those based on US rates. The largest difference occurred in the Reading, PA, cohort, in which the SMR based on US rates was 1.24 and that based on county rates was 1.42. For all six locations, the lung cancer SMR based on US rates was 1.26 (95%, 1.12–1.42), while that based on local county rates was 1.32 (95% CI, 1.19-1.46). When lung cancer SMRs were adjusted for the distribution of smoking habits at four of the plants in which a smoking survey was conducted in 1968 [covering 1466 (15.9%) of the 9225 members of the cohort], the SMR for the total cohort changed from 1.26 to 1.12, and the SMRs in two of the largest, oldest plants changed from 1.69 to 1.49 (Lorain, OH) and from 1.24 to 1.09 (Reading, PA). The authors noted that the major difficulty in interpreting the smoking-adjusted SMRs is that data on smoking were collected in the late 1960s, while most (94%) of the lung cancer cases occurred among workers hired in the 1940s and 1950s. Thus, the validity of the adjustment for smoking depends on the assumption that differences in smoking habits between the cohort and the US population were the same in the 1940s and 1950s as they were in the late 1960s and that smoking data obtained from 16% of the workers adequately represented the distribution of smoking in the entire cohort. The authors estimated the contribution of smoking to be 13%, i.e., smoking alone could account for a lung cancer SMR of 1.13 *versus* the 1.26 actually observed.

2.2 Case–control studies

Hinds *et al.* (1985) applied a computerized job–exposure matrix to data from a case–control study of lung cancer among males in Hawaii, USA. Between 1 September 1979 and 31 July 1982, 261 cases of newly diagnosed primary lung cancer among male residents of Oahu, Hawaii, were identified through a population-based tumour registry and a review of pathology records at all major hospitals and interviewed. Controls were identified by random-digit dialling and matched on sex and age. Information on occupation was obtained during the interview and applied to a job–exposure matrix to estimate exposure levels to various agents for each study subject. The job–exposure matrix was constructed from lists of occupational codes by Hoar *et al.* (1980), and these were used to code both the primary and secondary occupations of all subjects according to industry; each code was then linked to various levels of exposure to each agent. Each agent was grouped into three exposure levels (no exposure, low exposure, high exposure). The association of each agent with lung cancer risk was estimated by the odds ratio, which was determined by multiple logistic regression analysis and adjusted for age, ethnicity and smoking status. Excess risk for lung cancer was found to be associated with exposure to beryllium at both low (odds ratio, 1.62; 95% CI, 1.04–2.51) and high levels (1.57; 0.81–3.01). Other exposures considered in the analysis were coal-tar and pitch, petroleum, arsenic, chromium, asbestos and nickel. [The Working Group noted that it is not clear whether the odds ratio for beryllium was simultaneously controlled for the other exposures.]

Carpenter *et al.* (1988) conducted a nested case–control study of cancers of the central nervous system among workers employed at some time between 1973 and 1977 at two nuclear facilities in Oak Ridge, TN (USA); deaths of 72 white males and 17 white females from cancer of the central nervous system were identified from information on death

certificates, and four controls were matched to each case for race, sex, facility at which initially employed, year of birth and year of hire. Each job title and department combination was subjectively evaluated for potential exposure to each of 26 chemicals, including beryllium. The evaluation took into account period of employment, literature on the processes used at each facility, quantities and toxicities of chemicals used in the processes, interviews with workers involved in processes at different time periods, and the results of urine analyses and air monitoring. Each job title/department combination was given a rank for potential exposure to each of the 26 chemicals; rank 0 had probably no exposure, rank 1 had low potential, rank 2 had moderate potential and rank 3 had high potential for exposure to the specified chemical. Matched conditional logistic regression analyses were conducted and included potential confounding factors such as socioeconomic status. On the basis of 26 cases ever exposed to beryllium, the odds ratio for cancers of the central nervous system was 1.5 (95% CI, 0.6–3.9). The matched analysis by highest rank ever held *versus* rank 0 yielded odds ratios of 1.26, 12.8 and 3.29 for ranks 1, 2 and 3, respectively (all odds ratios had a p value of 0.09 or greater). When risk estimates were calculated for a 10-year latency, the odds ratios were 1.13, 0.85 and 1.77 for ranks 1, 2 and 3, respectively. A further analysis based on time spent in ranks 2 and 3, assuming a 10-year latency, yielded odds ratios of 0.77, 0.90, 1.30 and 1.88 ($p > 0.5$) for workers with < 3 years, 3–10 years, 11–20 years and 21 years or more in ranks 2 and 3 compared with ranks 0 and 1. The authors concluded that their study does not support the hypothesis that occupational exposures to any of the 26 chemicals studied appreciably increase the risk for cancers of the central nervous system; they noted specifically that, although a weak association between exposure to beryllium and cancers of the central nervous system was observed, confidence intervals [not given for analyses by rank or latency] were wide and included the null value.

2.3 Childhood cancer

A case–control study on parental occupation and childhood cancer carried out in Denver, CO, USA (Feingold *et al.*, 1992), included 252 cases of childhood cancer diagnosed during 1976–83 and 222 population controls selected by random-digit dialling. A job–exposure matrix was used to assign parental exposures for six months or longer during the year prior to the child's birth on the basis of job titles. Odds ratios were estimated for all cancers, acute lymphocytic leukaemia and brain cancer, after adjusting for age at diagnosis, year of diagnosis, sex, mother's age at time of birth, maternal smoking during pregnancy, birth weight, birth order and indicators of social class. When all cancers were considered, no association was found between childhood cancer and exposure to beryllium or its compounds for either the mother or the father (odds ratio, 1.0; 95% CI, 0.1–7.1; based on two exposed cases; and 1.6; 0.6–4.4; based on 17 exposed cases, respectively). When the exposures of the fathers were analysed for specific types of cancer, an elevated odds ratio was found for brain cancer (2.1; 0.6–7.6; 5 cases) but not for acute lymphocytic leukaemia (1.3; 0.3–5.9; 5 cases). Most of the subjects considered to have been exposed to beryllium were electrical equipment assemblers and installers (67%), metal processes and welders (20%). [The Working Group noted that other occupational exposures were not considered in the analysis.]