3.3 Epidemiological studies of carcinogenicity to humans

(*a*) *Introduction*

Although population-based studies to detect a possible association between exposure to engine exhausts and cancer in humans are the most direct methods for detecting human carcinogenesis, for low levels of risk the approach is complicated by several factors. These factors can be divided broadly into problems related to the documentation of levels of exposure and the potential for unidentified confounding factors to influence the results.

Nonoccupational exposure to engine exhaust is nearly ubiquitous in urban areas and in the vicinity of vehicles. Because emissions are diluted in the nonoccupational environment, it is unlikely that investigations of the general population would reveal risks when groups with heavy exposure show only a small risk.

'Unexposed' reference populations used in epidemiological studies are likely to contain a substantial number of subjects who are exposed nonoccupationally to engine exhausts. The 'exposed' group is often defined on the basis of job title, which may be an inadequate surrogate for exposure to exhaust emissions, and this may lead to an underestimation of risk. The situation is further complicated by the presence of possible confounding factors, such as smoking and other exposures (e.g., asbestos in railroad yards), which may influence results, especially when lung and bladder cancers are being studied. In addition, in many studies of the occupational setting, there is an inextricable link between exposure to exhaust emissions and to vapours from the fuels themselves. Some occupational groups, such as car-park attendants and toll-booth workers, which might be thought to be a source of more direct information due to their heavy exposure, are usually too small and/or too transient for a population-based study of cancer to be feasible.

Another important consideration is that occupational cohorts tend to have below-average mortality, both from all causes and from various major categories of specific causes. These deficits are, typically, manifestations of a selection process based on health status, referred to as the 'healthy worker effect'. In view of this overall deficit in cancer mortality in working cohorts, conventional statistical evaluation of site-specific standardized mortality ratios (SMRs) is usually conservative. That is, comparison of the SMR with an 'expected' value of 100 derived from the general population - rather than from some defined internal unexposed comparison group — may result in an underestimation of the true magnitude of any occupation-related increase in risk for specific cancers.

In the studies reviewed, retrospective assessment of an individual's exposure to engine exhausts is necessarily indirect, since there are generally no systematic or quantitative records of work-place or ambient exposures. In some studies, the title of a job or occupation with known or presumed exposure is used as a simple surrogate measure of exposure, and the cancer risk of groups of individuals in such jobs is compared with that of the general population or of persons in unrelated jobs. In some other studies, mainly of case-control design, each individual's past exposure is assessed by the use of a job-exposure matrix. In its simplest form, a job-exposure matrix is a two-way table in which each job or occupation is assigned a code indicating the presence (and sometimes the magnitude) of substances to which persons in that job would be exposed, on the basis of contemporary measurements and knowledge of working practices. The job history obtained from the subject is then used

to construct his or her record of past exposure from the matrix. Among the limitations of this approach is the fact that individual exposures may differ widely even within narrowly defined occupations, because of differences in working practices between individuals and work sites, from country to country and over time. It should be noted, however, that while such problems in exposure assessment reduce the precision with which any effect can be measured, they are not likely to give rise to a spurious association where none exists; consistency of results between different studies of this kind is therefore of particular importance in assessing the relationship between exposure and disease.

Several of the available case-control studies are hospital-based rather than population-based; i.e., the control group consists of subjects hospitalized for diseases different from those of the cases. Because little is known about the etiology of many diseases, some of which may be associated with exposure to engine exhaust, it is difficult to rule out bias resulting from the choice of specific sets of controls.

(*b*) *Mortality and morbidity statistics*

The Working Group noted that surveys of mortality or morbidity statistics suffer from many limitations, which reduce their usefulness in the evaluation of carcinogenic risks. Comparison of the results of different studies is complicated by the varying definitions and groupings of occupations and cancer sites. Generally, these studies have been designed to generate hypotheses about potentially exposed groups. For example, a striking difference in the male:female sex ratio for tumours unrelated to hormonal status within a specific geographical region might suggest an area that should be explored in either cohort or case-control studies, in which exposure can be assessed more readily.

Studies of this type that may relate to exposure to exhaust fumes include the following: Menck and Henderson (1976), Decouflé *et al.* (1977), Office of Population Censuses and Surveys (1978), Petersen and Milham (1980), Howe and Lindsay (1983), Milham (1983), Dubrow and Wegman (1984), Malker and Weiner (1984), Baxter and McDowall (1986) and Olsen and Jensen (1987).

(*c*) *Cohort studies*

(i) *Railroad workers*

Kaplan (1959) evaluated 6506 deaths among railroad workers from the medical records of the Baltimore and Ohio Railroad relief department between 1953 and 1958, 818 of which were due to cancer and 154 of which were lung cancer. The cases were categorized into three groups by exposure to diesel exhaust. In comparison with national death rates, none of the groups had an excess risk for lung cancer. [The Working Group noted that, since changeover to diesel engines began in 1935 and was 95% complete by 1959 (Garshick *et al.*, 1988), few if any of the lung cancer deaths could have occurred in workers with more than ten years' exposure to diesel exhaust; in addition, smoking habits were not considered.]

Howe *et al.* (1983) studied a cohort of 43 826 male pensioners of the Canadian National Railway Company consisting of retired railroad workers who were known to be alive in 1965 plus those who retired between 1965 and 1977. Of the total of 17 838 deaths that

occurred in 1965–77, 16 812 (94.4%) were successfully linked to a record in the Canadian mortality data base. The expected number of cancer deaths was estimated from that of the total Canadian population, adjusted for age and calendar period. Available information included birth date, province of residence, date of retirement and occupation at time of retirement. Occupational exposures were classified into three types: 'diesel fumes', coal dust and other. The two statistically significant results for the whole cohort were deficits in deaths from all causes (SMR, 95 [95% confidence interval (CI), 93–96]) and from leukaemia (SMR, 80 [95% CI, 65–97]). For exposure to diesel engine exhaust, the risk for cancer of the trachea, bronchus and lung increased with likelihood of exposure: the relative risks were 1.0 for unexposed, 1.2 [1.1–1.3] for 'possibly exposed' and 1.4 [1.2–1.5] for 'probably exposed' (p for trend < 0.001). The SMR for bladder cancer was 103 [88–119]. Similar results were found for the risk for cancer of the trachea, bronchus and lung from exposure to coal dust. Since there was considerable overlap in exposures to diesel fumes and coal dust, the risk was evaluated by calendar time during which one of these exposures predominated. The risk was largely accounted for by exposure to diesel exhaust. Since exposure to asbestos occurs during locomotive maintenance, workers thought to have had such exposure were removed from the analysis, with little effect on the risk associated with exposure to diesel engine exhaust. Exclusion of workers exposed to welding fumes did not alter the result. The authors noted that the data presented and the risks observed probably represent an underestimate of the true risk, for at least two reasons: exposure misclassification because of the use of job held last and failure to determine the cause of death for 5.6% of cases. [The Working Group noted that no data were available on duration of exposure, usual occupation or smoking habits and recognized the potential for competing biases in the way in which the cohort was composed.]

Garshick *et al.* (1988) studied a cohort of 55 407 white male railroad workers aged 40–64 in 1959 who had started railroad service ten to 20 years earlier. The cohort was traced from records of the pension scheme for US railway workers through to 1980; it was estimated that less than 2% left the industry during the period covered by the study. Death certificates were available for 88% of the 19 396 deaths, of which 1694 were from lung cancer; decedents for whom a death certificate was not obtained were classified as having died of unknown causes. Records of railroad jobs from 1959 through to death, retirement or 1980 were also available from the records of the pension scheme. Jobs were divided into regular exposure to diesel exhausts (train crews, workers in diesel repair shops) and no exposure (clerks, ticket and station agents, and signal maintenance workers). Job categories with recognized asbestos exposure, such as car repair and construction trades, were excluded from those selected for study. Information was available on duration of exposure. There was a significant excess risk for lung cancer in the groups exposed to diesel engine exhaust; this risk was highest in those who had the longest exposure: aged 40–44 (relative risk, 1.5; 95% CI, 1.1–1.9) and 45–49 (1.3; 1.0–1.7) and exposed to diesel exhaust in 1959. The groups aged 50–54 and 55–59 in 1959 also had excess risks, of 1.1 and 1.2, respectively, although these were not statistically significant. When workers with further potential asbestos exposure (shop workers) were excluded, similarly elevated lung cancer rates were observed. Although smoking habits were not considered directly, the authors pointed out that there was no

difference in smoking habits by job title in comparison studies of current workers or in a case-control study in which smoking was assessed. [The Working Group noted that exclusion of shop workers would also have excluded men exposed to welding fumes.]

As part of this study, exposure was assessed on the basis of several hundred time-weighted samples of respirable dust taken in the early 1980s both at stationary sites in parts of four existing, smaller railroad yards and with personal samplers carried by railroad workers in different job categories (Woskie *et al.*, 1988a). Samples were taken from workers in 39/155 Interstate Commerce Commission job codes, and the results were used to classify the jobs; these 39 categories were subsequently combined into 13 job groups, which could be further combined into five: clerks, signal maintenance, engineers/firers, brakers/-conductors and shop workers. The nicotine content was used to adjust the extractable respirable particulate content of each sample to account for the portion contributed by cigarette smoking. Mean exposure levels by national career groups in the five major categories of exposure suggested a five-fold range of exposure to respirable particles between clerks and shop workers (Woskie *et al.* 1988b). These values confirmed the a-priori assignment of the categories of diesel exposure used in the cohort study (Garshick *et al.*, 1988) and the assignment to appropriate exposure categories for the case-control study (Garshick *et al.*, 1987; see p. 140).

(ii) *Bus company employees*

Raffle (1957) determined deaths, retirements and transfers due to lung cancer in London Transport employees aged 45–64 years in jobs with presumably different exposures to exhaust fumes in 1950–54 and compared the figures with those for lung cancer mortality for men in England and Wales or in Greater London. No relationship between presumed exposure and lung cancer incidence was noted. In a subgroup of bus and trolley bus engineering staff aged 55–64, 30 deaths from lung cancer occurred while 21.2 were expected (observed:expected, 1.4) on the basis of the experience of other London Transport employees. [The Working Group noted that no information on smoking habits was available, and that all the deaths occurred in men over 55 years of age.] Waller (1981) compared lung cancer deaths and retirements or transfers to alternative jobs due to lung cancer in men aged 45–64 employed within five job categories of London Transport (bus drivers, bus conductors, engineers (garages), engineers (central works) and motor men and guards) to lung cancer mortality (age- and calendar time-adjusted) for men in Greater London. The study covered 25 years, ending in 1974, thus including some of the data described by Raffle (1957). A total of 667 cases of lung cancer were observed; although the risk was not elevated for any of the five job categories, the highest SMR occurred in the group that was presumably most heavily exposed to diesel exhaust (bus garage workers). [The Working Group noted that no data on smoking habits were available, and neither duration nor latency was examined.]

Rushton *et al.* (1983) examined a cohort of 8684 men employed as maintenance workers in 71 bus garages in London for at least one year in 1967–75. Follow-up until 31 December 1975 was completed for 8490 (97.8%) workers, and cause of death was known for 701 of 705 who had died. The SMRs were 84 [95% CI, 78–91] for all causes and 95 [83–109] for all

neoplasms, 101 [82–122] for lung and pleural cancer, 151 [60–307] for leukaemia, 121 [49–250] for central nervous system tumours and 139 [72–244] for bladder cancer. None of the rates for cancer at individual sites was statistically significantly increased. The authors noted the short follow-up period.

Edling *et al.* (1987) studied 694 men, five of whom (0.7%) were lost to follow-up, who had been employed as clerks, bus drivers or bus garage workers in five bus companies in south-eastern Sweden at any time between 1950 and 1959, and followed for 1951–83. The SMRs, based on age-, sex- and calendar time-adjusted national rates, were 80 (195 deaths observed; 95% CI, 70–90) for deaths from all causes and 70 (50–90) for deaths from malignancy. Dividing the data by exposure category, exposure time or latency did not appreciably change the risk ratios. The small sample size did not allow detailed examination of cancers at specific sites, although six lung cancer cases were observed compared to nine expected. [The Working Group noted that smoking habits were not addressed.]

(iii) *Professional drivers and some other groups exposed to vehicle exhausts*

Ahlberg *et al.* (1981) identified a cohort of Swedish drivers said by the authors to be exposed to diesel exhaust (1865 or 1856 [*sic*] fuel oil tanker drivers and 34 027 other truck drivers) from the national census of 1960. In this cohort, 1143 cancers were registered within the Swedish Cancer Registry in 1961–73. The reference population consisted of 686 708 blue-collar workers from the 1960 census who were thought to have had no exposure to petroleum products or chemicals. The data were adjusted for age and residence. The relative risk for lung cancer was elevated in the whole cohort (1.3; 95% CI, 1.1–1.6) and in Stockholm truck drivers in particular (1.6; 1.2–2.3). From a questionnaire study of 470 professional drivers in Stockholm, it was noted that 78% of fuel truck drivers and 31% of other truck drivers smoked. The authors cited an unpublished study indicating that the comparable smoking rate in Stockholm was 40% and concluded that the results could not be explained by smoking.

Wong *et al.* (1985) studied a cohort of 34 156 male members of a heavy construction equipment operators' union in the USA with potential exposure to diesel exhaust. Cohort members had to have been a union member for at least one year between 1 January 1964 and 31 December 1978, by which time 3345 had died and 1765 (5.2%) could not be traced. Death certificates were obtained for all but 102 (3.1%) decedents. No information was available for jobs held before 1967 and limited information was available on jobs held between 1967 and 1978. The SMRs, based on national figures, adjusted for age, sex, race and calendar time, were 81 (95% CI, 79–84) for all causes, 93 (87–99.6) for all cancers, 99 (88–110) for lung cancer (ICD7 162–163) and 118 (78–172) for bladder cancer. The data were also analysed by duration of union membership, latent period, retirement status, job category and exposure status. Significant upward trends in risk were detected for lung cancer with duration of union membership, used as a surrogate for duration of potential exposure to diesel exhaust, with SMRs for lung cancer of 45 [22–83], 75 [49–111], 108 [81–141], 102 [78–132] and 107 [91–125] for workers with <5, 5–9, 10–14, 15–19 and ≥ 20 years of union membership, respectively. A significant upward trend was also noted for lung cancer with latent period. Mortality from cancers of the digestive system (SMR, 142; 116–173) and

respiratory system (SMR, 162; 138–190) and from lymphosarcoma and reticulosarcoma (SMR, 231; 111–425) was elevated in retirees. Exclusion of early retirees did not remove the risks for respiratory cancer or lymphatic cancer. In general, groups with jobs with presumed high exposure to diesel fumes did not show the excesses reported above. A random sample of union members was surveyed to determine smoking habits, and no significant difference between members and the general population was revealed.

In a review, Steenland (1986) presented data on a preliminary study of the mortality experience of about 10 000 teamsters (truck drivers, dock workers, mechanics and jobs outside the trucking industry) who had died in 1982–83 and had worked for at least ten years in a teamster job. Using occupational data on death certificates, proportionate mortality ratios were calculated for lung cancer for 255 mechanics (226; 95% CI, 162–309), 5834 truck drivers (154; 144–166), 490 dock workers (132; 99–175) and 1064 others (116; 95–142). [The Working Group noted that this was an interim report and that judgement should be reserved until the final results are available.]

Gustafsson *et al.* (1986) studied 6071 Swedish 'dockers' assumed by the authors to have been exposed to diesel exhaust and first employed before 1974 for at least six months. The group had been followed for death from 1 January 1961 or from the date of first employment (if this date occurred later) through to 1 January 1981. Age-, calendar time- and region-specific rates were used to generate expected numbers of deaths. The SMRs were 89 (95% CI, 84–94) for all causes, 103 for all cancers, 132 for lung cancer (105–166) and 110 (85–142) for urogenital tract cancer. Cancer morbidity was determined among 6063 workers who had been alive and without cancer on 1 January 1961 and were followed through to 1 January 1980; a standard morbidity ratio of 110 (101–120; 452 cases) was seen for cancers at all sites and of 168 (136–207; 86 cases) for lung cancer. [The Working Group noted that there was no consideration of duration, intensity or latency of exposure or of smoking habits in this study.]

Stern *et al.* (1981) examined mortality patterns among 1558 white male vehicle examiners who had been employed in New Jersey, USA, for at least six months between 1944 and 1973. The vital status of all but eight (0.5%) of these was ascertained as of 31 August 1973; these eight were assumed to be alive. Approximately 63% of the cohort members had begun employment prior to 1957. A modified life-table analysis was used to generate the expected number of cause-specific deaths on the basis of national rates, adjusting for age and calendar time. There were 52 deaths from cancer (47.8 expected [SMR, 109; 95% CI, 81–143]). The SMRs for malignant disease increased significantly with latency: 0–9 years, 69 [25–151]; 10–19 years, 98 [56–159]; 20–29 years, 107 [62–171]; >30 years, 189 [101–323]. Cancer at no specific organ site accounted for this excess. The exposure of interest was carbon monoxide, but the authors speculated that other components of automobile exhaust might have been responsible. No information on smoking habits was available for deceased workers, but COHb levels in currently nonsmoking workers increased during the work shift, indicating exposure to exhaust.

In a cohort study of white men enlisted in the US Navy (Garland *et al.*, 1988), 143 cases of testicular cancer were identified in the period 1974–79; age-specific incidence rates were similar to those for the US population, derived from the US National Cancer Institute

Surveillance, Epidemiology and End Results (SEER) programme for 1973–77. Of 110 occupational groups in the Navy, three involving maintenance of gasoline and diesel engines and daily exposure to their exhaust emissions (aviation support equipment technicians, enginemen and construction mechanics) had significantly high standardized incidence ratios for testicular cancer: 3.4 (95% CI, 1.9–5.6) in comparison to SEER rates, and 3.8 (2.1–6.3) in comparison to men in the US Navy as a whole, based on 15 cases. The authors noted that this was a hypothesis-generating study and that the men also had potential daily exposure to solvents and other chemicals.

(iv) *Miners*

Although diesel engines have been used in many mines for a number of years, the Working Group decided not to consider all groups of miners because they may be exposed concurrently to other potential lung carcinogens such as radon decay products, heavy metals and silica, and there was no way that the possible confounding effects of such factors could be determined from the data available in published reports.

Waxweiler *et al.* (1973) studied potash miners and millers, who are exposed to no known carcinogens in the ore, who had been employed for at least one year between January 1940 and July 1967 by eight companies. The vital status of the cohort was identified to July 1967. Of a total of 3886 men, 31 could not be traced and were assumed to be alive. Causes of death were compared with those of the general US population, standardized for age, race, sex and calendar time. Of the cohort, 2743 men had worked at least one year underground and less than one year on the surface and 1143 men had worked at least one year on the surface and less than one year underground. In only two of the eight mines were diesel engines used; one mine changed to diesel in 1949 and the other in 1957. Death certificates were available for 433 of the 438 workers who had died. The effect of smoking was taken into account. No excess mortality from lung cancer was seen in either surface or underground miners. Mortality rates did not differ between the mines with diesel vehicles and those without. The authors noted the short follow-up, the small expected numbers of deaths and the broad classification of causes of death.

(*d*) *Case-control studies*

(i) *Lung cancer*

Williams *et al.* (1977) examined cancer incidence and its relationship to occupation and industry in a study based on the US Third National Cancer Survey. In this study, detailed personal interviews were sought for 13 179 cancer patients (a random 10% sample of all incident invasive tumours occurring in three years in eight areas in the USA) and obtained for 7518 (57%). The numbers of cases of cancer at various anatomical sites were compared with that of cases at all other sites combined. The interview included occupational history (main employment and recent employment), other demographic data and information on smoking and drinking habits; the analysis also controlled for age, sex, race and geographical location. A statistically nonsignificant lung cancer excess (odds ratio, 1.5; [CI could not be calculated]) was observed for truck drivers, which could not be accounted for by smoking.

Intensity, duration of exposure and latency were not evaluated. [The Working Group noted the potential for bias due to the relatively low level of compliance with the questionnaire.]

In a population-based case-control study, Coggon *et al.* (1984) used the data on occupation on the death certificates of all men under the age of 40 years in England and Wales who had died of tracheobronchial carcinoma during the period 1975–79; 598 cases were detected, 582 of which were matched with two and the rest with one control who had died from any other cause, for sex, year of death, local authority district of residence and year of birth. Occupations were coded using the Office of Population Census and Surveys 1970 classification of occupations, and a job-exposure matrix was constructed by an occupational hygienist, in which the occupations were grouped according to likely exposure to each of nine known or putative carcinogens. All occupations entailing exposure to diesel fumes were associated with an elevated odds ratio for bronchial carcinoma (1.3; 95% CI, 1.0–1.6); however, for occupations with presumed high exposure, the odds ratio was 1.1 (0.7–1.8). [The Working Group noted the limited information on occupation from death certificates, the young age of the subjects and the consequent short times of exposure and latency, and the lack of information on smoking habits and on the possible confounding effects of other carcinogenic exposures.]

In a hospital-based case-control study (Hall & Wynder, 1984) in 18 hospitals in six US cities, 502 men with histologically confirmed primary lung cancer (20–80 years old) and 502 control patients, matched for age, race and hospital were identified. Patients were interviewed between December 1980 and November 1982. Half of the controls had cancer; patients with tobacco-related diseases were excluded. The questionnaire included items on smoking habits, demographic variables and usual occupation. Occupations were grouped either dichotomously as exposed to diesel exhaust (warehousemen, bus drivers, truck drivers, railroad workers and heavy equipment repairmen and operators) or nonexposed, or, in a separate evaluation, in three presumed categories of frequency of exposure in the job (high, moderate, little). Using the dichotomous division, the exposed group had a significantly elevated odds ratio (2.0; 95% CI, 1.2–3.2), which, however, decreased to 1.4 (0.8–2.4; not significant) when adjusted for smoking. The crude odds ratios were 1.7 (0.6–4.6) for a high probability of exposure to diesel exhaust and 0.7 (0.4–1.3) for a moderate probability of exposure. [The Working Group questioned the possible consequences on risk estimates of excluding patients with tobacco-related diseases from the control group.]

In a hypothesis-generating case-control study, Buiatti *et al.* (1985) investigated the occupational histories of histologically confirmed cases of primary lung cancer among residents of metropolitan Florence, Italy, diagnosed during 1981–83 in the regional general hospital and referral centre for lung cancers in the Province of Florence. For the 376 cases (340 men, 36 women), 892 controls (817 men, 75 women), matched by sex, age, date of admission and smoking status in seven categories, were selected from the medical service of the same hospital, excluding patients with lung cancer, attempted suicides and patients not resident in metropolitan Florence. Each case and control completed a structured questionnaire on demographic variables and on all jobs held for more than one year. The jobs were classified into 21 major classes and 251 subclasses, using the International Labour Office

classification. Odds ratios for industries and occupations (ever *versus* never worked) were calculated using logistic regression, in which age and smoking status were included. Taxi drivers had an elevated relative risk for lung cancer after adjusting for tobacco smoking (1.8; 95% CI, 1.0–3.4). [The Working Group noted that multiple comparisons were made, increasing the probability that statistically significant results would be found.]

In a case-control study in northern Sweden, Damber and Larsson (1987) analysed the association between lung cancer and occupation. The cases were 604 male lung cancers reported to the Swedish Cancer Registry during 1972–77 and who had died before May 1979. For each case, a control was drawn from the National Registry for Causes of Deaths, and was matched for sex, year of death, age and municipality; cases of lung cancer and attempted suicide were excluded as controls. In addition, for each case, one living control (less than 80 years old) was drawn from the National Population Registry, matched for sex, year of birth and municipality. Information on residence, occupation, employment and smoking habits was collected by a questionnaire mailed to surviving relatives and to living controls; the response rates were 98% for cases and 96% and 97% for dead and living controls, respectively. Information was requested on all jobs held for at least one year and on lifetime smoking history. A linear logistic regression model, using three discrete levels of employment (<1 year, 1–20 years, and >20 years) and four levels of lifetime tobacco consumption, was used to calculate odds ratios. For professional drivers with more than 20 years' employment, the unmatched odds ratio was 1.5 (95% CI, 0.9–2.6) in comparison with dead controls; this was reduced to 1.2 (0.6–2.2) after adjustment for smoking. The figures obtained in comparison with living controls were 1.7 (0.9–3.2) and 1.1 (0.6–2.2), respectively.

Garshick *et al.* (1987) performed a case-control study on lung cancer deaths among employed and retired US male railroad workers with ten or more years of service, who had been born on 1 January 1900 or after and who had died between 1 March 1981 and February 1982. Cases of primary lung cancer (1256) were matched to two controls by age and date of death. Workers who had died from cancer, suicide, accident or unknown causes were not included among controls. Potential exposure to diesel exhaust was assigned on the basis of an industrial hygiene evaluation of the >150 railroad jobs and areas described by the US Interstate Commerce Commission. Job codes for each worker were available from the US Railroad Retirement Board starting in 1959 and ending with death or retirement. For workers who had retired between 1955 and 1959, the last railroad job held was available. Asbestos exposure prior to 1959 was categorized by job held in 1959 (end of steam locomotive era) or by the last job before retirement, if this was before 1959. Smoking history was obtained by questionnaire from the next-of-kin. Using multiple conditional logistic regression analysis to adjust for smoking and asbestos exposure, workers 64 years of age or younger at time of death who had worked in a diesel exhaust-exposed job for 20 years had a significantly elevated odds ratio for lung cancer (1.4; 95% CI, 1.1–1.9). No such effect was observed among older workers (0.91; 0.71–1.2), many of whom had retired shortly after the transition to diesel-powered locomotives and were therefore not exposed.

In a population-based case-control study (Lerchen *et al.*, 1987), all white and Hispanic white residents of New Mexico, USA, aged 25–84 years, with primary lung cancer,

excluding bronchioalveolar carcinoma, diagnosed between 1 January 1980 and 31 December 1982, were identified from the New Mexico Tumor Registry. The cases (333 men and 173 women) were frequency matched with controls selected randomly from the telephone directory or, for persons 65 years or older, from the roster of participants in a health insurance scheme, for sex, ethnic group and ten-year age band at a ratio of approximately 1.5 controls per case (449 men and 272 women). Detailed occupational and smoking histories were obtained by personal interview, with response rates of 89% for cases and 83% for controls. Next-of-kin provided interviews for 50% of the male and 43% of the female cases and for 2% of the controls; the authors recognized the possible bias introduced by this practice. The odds ratio for exposure to diesel exhaust fumes, adjusted for age, ethnic group and smoking, was 0.6 (95% CI, 0.2–1.6). [The Working Group noted the possible bias in choosing controls from the telephone directory when cases are not required to have a telephone or to be listed.]

In a case-control study of lung cancer in France (Benhamou *et al.*, 1988), 1625 histologically confirmed cases and 3091 controls, matched for sex, age at diagnosis, hospital admission and interviewer, completed a questionnaire on residence, education, occupation, and smoking and drinking habits. All occupations held for more than one year were recorded and coded without knowledge of the case status of the patient, using the International Standard Classification of Occupations and according to chemical or physical exposures. The analysis was limited to men (1260 cases and 2084 controls); adjustment was made for age at starting smoking, amount smoked and duration of smoking. Several occupations were associated with increased odds ratios for lung cancer, including miners and quarry men (2.1; 95% CI, 1.1–4.3) and transport equipment operators (1.4; 1.1–1.8); the subcategory of motor vehicle drivers also had an increased risk (1.4; 1.1–1.9).

(ii) *Bladder cancer*

In a population-based case-control study in Canada (Howe *et al.*, 1980), all patients with bladder cancer newly diagnosed in three Canadian provinces between April 1974 and June 1976 were identified; 77% of the patients were interviewed, and for each patient one neighbourhood control, individually matched for age and sex, was interviewed. In the analysis, 632 case-control pairs (480 male and 152 female) were included. Lifetime smoking and employment histories were obtained, and exposure to dusts and fumes was elucidated. Elevated odds ratios were observed for railroad workers [not further defined] (9.0; 95% CI, 1.2–394.5; nine exposed cases) and for exposure to diesel and traffic exhaust (2.8; 0.8–11.8; 11 exposed cases).

In a death certificate-based case-control study (Coggon *et al.*, 1984; for details, see description on p. 139), the occupations of 291 bladder cancer cases and 578 hospital controls were compared. The odds ratio for all diesel fume-exposed occupations was 1.0 (95% CI, 0.7–1.3) and that for occupations with high exposure was 1.7 (0.9–3.3). [The Working Group had the same reservations about this study as expressed on p. 139.]

In a population-based case-control study, the relationship between truck driving and bladder cancer was investigated (Hoar & Hoover, 1985). Cases consisted of all white residents of New Hampshire and Vermont, USA, who had died from bladder cancer in

1975–79. One control per case was selected randomly from all other deaths among residents, excluding suicides, and matched for state, sex, age, race and year of death. A second control per case was selected with the additional matching criterion of county of residence. There were 230 and 210 eligible cases in the two states, respectively; the rate of response to interview was 87% for New Hampshire and 58% for Vermont, and the non-respondents were similar to the respondents with respect to case-control status, sex, age and county of residence. The odds ratio for ever having been a truck driver was 1.5 (95% CI, 0.9–2.6), and there was a significant trend between bladder cancer risk and number of years of truck driving: odds ratios, 1.4 (0.6–3.3), 2.9 (1.2–6.7) and 1.8 (0.8–4.1) for those employed as truck drivers for 1–4, 5–9 and >10 years, respectively. Additional adjustment for age, county, coffee drinking or cigarette smoking (six categories) did not alter these crude odds ratios. [The Working Group noted the nonlinearity of the trend.]

In a hospital-based case-control study in Turin, Italy (Vineis & Magnani, 1985), 512 male cases and 596 male controls randomly selected from among other patients in the main hospital of the city of Turin between 1978 and 1983 were interviewed for lifetime occupational and smoking histories. Occupations were coded using the International Labour Office classification, and associations between specific chemicals and bladder cancer were studied using a job exposure matrix. Adjusting for age and smoking, the odds ratio for bladder cancer for truck drivers was 1.2 (95% CI, 0.6–2.5).

In a hospital-based case-control study, Wynder *et al.* (1985) examined the occupational histories and life style factors (smoking, alcohol and coffee consumption, demographic factors) of 194 male cases of histologically confirmed bladder cancer, 20–80 years of age, diagnosed during two-and-a-half years (January 1981–May 1983) in 18 hospitals in six US cities, and of 582 controls, matched by age, race, year of interview and hospital of admission, hospitalized during the same period for diseases not related to tobacco use. The participation rate among eligible subjects was 75% among cases and 72% among controls. 'Usual' occupation was coded according to an abbreviated list of the US Bureau of Census codes. No significant association was detected between bladder cancer and occupations presumed to involve exposure to diesel exhaust: warehousemen and materials handlers, bus and truck drivers, railroad workers, heavy equipment operators and mechanics (odds ratio, 0.87; 95% CI, 0.47–1.6). [The Working Group questioned the possible consequences on risk estimates of excluding patients with tobacco-related diseases from the control group.]

Data from all ten areas of the US National Bladder Cancer Study were used to evaluate the association of motor exhausts with bladder cancer (Silverman *et al.*, 1986). The study group comprised 1909 white male cases with histologically confirmed bladder carcinoma or papilloma not specified as benign and 3569 frequency-matched controls. Significantly elevated age- and smoking-adjusted odds ratios for bladder cancer were observed for truck drivers or delivery men, and for taxi drivers or chauffeurs: 1.5 (95% CI, 1.1–2.0) and 6.3 (1.6–29.3) for 'usual' occupation, 1.3 (1.1–1.4) and 1.6 (1.2–2.2) for 'ever' occupation. For bus drivers, the odds ratios did not reach significance (1.3, 0.9–1.9 and 1.5, 0.6–3.9 for 'ever' and 'usual', respectively). When allowance was made for a 50-year latency, a significant trend with increasing duration of employment as a truck driver was observed: 1.2, 1.4, 2.1 and 2.2 for a duration of employment of <5, 5–9, 10–24 and >25 years, respectively

($p<0.0001$). Information on subsets of this cohort has been published elsewhere (Silverman *et al.*, 1983; Schoenberg *et al.*, 1984; Smith *et al.*, 1985). In the Detroit subset (Silverman *et al.*, 1983), the adjusted odds ratio for bladder cancer for truck drivers who had never driven a vehicle with a diesel engine was 1.4 (0.7–2.9) and that for men who had ever driven a vehicle with a diesel engine was 11.9 (2.3–61.1).

Occupational risk factors were investigated as part of a population-based case-control study in Copenhagen, Denmark (Jensen *et al.*, 1987). Between May 1979 and April 1981, a total of 412 live patients with bladder cancer (invasive tumours and papillomas) were reported in the study, 389 of whom were interviewed. Live controls were selected at random from the municipalities where the cases lived, and the sample was stratified to match the cases with regard to sex and age in five-year groups. Among the 1052 controls approached, the overall participation rate was 75%. Cases and controls were interviewed for information on occupational history coded according to the Danish version of the International Standard Industrial Classification. Cigarette smoking was adjusted for in the analysis by using two dichotomous variables (ever/never smoked, current/noncurrent smoker) and a continuous variable (logarithm of pack-years smoked). The adjusted odds ratio for bladder cancer was elevated in land transport workers (1.6; 95% CI, 1.1–2.3). The adjusted odds ratios for bladder cancer for bus, taxi and truck drivers were 0.7 (0.4–1.5), 1.6 (0.8–3.4), 3.5 (1.1–11.6) and 2.4 (0.9–6.6) for durations of employment of 1–9, 10–19, 20–29 and >30 years, respectively, representing a significant trend with duration of employment. The trend was not significant for land transport workers.

In a hospital-based case-control study in Argentina (Iscovich *et al.*, 1987), 120 patients with histologically confirmed bladder carcinoma admitted to ten general hospitals in Greater La Plata between March 1983 and December 1985 were identified. The 117 patients who could be interviewed represented approximately 60% of all incident cases. For each case, a hospital control from the same establishment was selected (patients with diseases associated with tobacco smoking constituted 12% of the control group); a neighbourhood control, matched for age and sex, was also selected. Information on smoking and past and present occupations was collected by questionnaire. An exposure index based on a job-exposure matrix was generated. The adjusted odds ratio for truck and railway drivers was 4.3 [95% CI, 2.1–29.6].

Covering the period 1960–82, Steenland *et al.* (1987) identified 731 male bladder cancer (ICD-9 188) deaths in the Hamilton County, Ohio, region, where there is a known high bladder cancer rate. Six controls were matched to each case on sex and residence in the county at the time of death, year of death, age of death and race. Death certificates and city directories for all residents over 18 were used to identify job history. The first two controls that were listed in the directory within at least five years of the first listing of the cases were selected. Of the 648 cases (89%) listed in the directories, all but 21 had two controls; the remaining 21 had one control. A comparable analysis of all 731 cases and two controls per case was carried out using usual lifetime occupation from the death certificate. A significant increase in the frequency of bladder cancer was found for men with more than 20 years' duration of employment, identified through the city directories as truck drivers (odds ratio, 12.0 [95% CI, 2.3–62.9]; six cases, one control) and railroad workers (odds ratio, 2.2

[95% CI, 1.2–4.0]). Notably, those workers identified as 'drivers not otherwise specified' for ≥20 years had an odds ratio of 0.15 [95% CI, 0–0.8]. In contrast, on the basis of job ever held identified from either the death certificate or the city directory (without taking duration into account), none of the above findings was significant. [The Working Group noted that this study involved application of a new methodology for exposure ascertainment, which requires further validation.]

In a case-control study of bladder cancer incidence in Edmonton, Calgary and Toronto and Kingston, Canada (Risch *et al.*, 1988), 826 cases of histologically verified bladder cancer were compared with 792 population-based controls matched for age, sex and area of residence. Cases were aged 35–79 and had been ascertained between 1979 and 1982. Information was collected by questionnaire, administered by personal interview, covering family, medical, occupational, residential, smoking and dietary histories. Analysis of the occupational data included adjustment for lifetime smoking habits. Among other findings related to occupation and industry was that the 309 men who had had jobs with exposure to engine exhausts had an odds ratio of 1.5 (95% CI, 1.2–2.0) for 'ever' exposure and an odds ratio of 1.7 (1.2–2.3) for exposure during the period eight to 28 years prior to diagnosis. The authors also calculated that there was a significant increase in trend with duration of exposure for each ten years (1.2; 1.1–1.4). This relationship was not seen for women, but only 19 had been exposed. The relationship was also not seen when an analysis was undertaken by exposure to 18 categories of substances, including engine exhaust. [The Working Group found it difficult to interpret the differences in risk seen when exposure was defined in various ways.]

(iii) *Other and multiple sites*

In a hypothesis-generating, hospital-based case-control study in Sweden, Flodin *et al.* (1987) analysed the association between occupation and multiple myeloma. The cases were in persons diagnosed between 1973 and 1983 and still alive during 1981–83. From comparisons with cancer registry data, it was concluded that the cases represented one-third of all cases diagnosed in the area. Controls were drawn randomly from population registers. There were 131 cases and 431 controls for analysis. Information on occupational history, X-ray treatment and smoking habits were obtained by a mailed questionnaire. The crude odds ratio for occupational exposure to engine exhaust was 2.3 (95% CI, 1.4–3.7); this association remained significant after adjusting for confounding variables. In a study using the same set of controls (431) and source of cases, Flodin *et al.* (1988) investigated the association with occupational exposures for 111 cases of chronic lymphatic [lymphocytic] leukaemia. The crude odds ratio for occupational exposure to engine exhausts was 2.5 (95% CI, 1.5–4.0); the association remained significant after adjustment for confounding variables. [The Working Group noted that the study population and control of confounding were not clearly described, and that exposure to engine exhausts was self-reported and not further defined by the authors.]

In a large, hypothesis-generating, population-based case-control study in Canada (Siemiatycki *et al.*, 1988), the associations between ten types of engine exhaust and combustion products and cancers at 12 different sites were evaluated. The 3726 cancer patients

diagnosed in any of the 19 participating hospitals in Montreal were interviewed (rate of response, 82%). The patients were all men aged 35–70 years. For each cancer site, patients with cancers at other sites comprised the control group. The interview elicited a detailed job history, and a team of chemists and industrial hygienists translated each job into a list of potential exposures (Gérin *et al.*, 1985). The probability of exposure ('possible', 'probable', 'definite'), the frequency of exposure (<5, 5–30, >30% working time) and the level of exposure (low, medium, high) were estimated. Separate analyses were performed for oat-cell, squamous-cell, adenocarcinoma and other carcinomas of the lungs. After stratifying for age, socioeconomic status, ethnic group, cigarette smoking and blue-/white-collar job history, an elevated odds ratio was observed for squamous-cell cancer of the lung and exposure to gasoline engine exhaust (OR, 1.2; 90% CI, 1.0–1.4). In a detailed analysis in which all covariables that changed the estimate of the disease-exposure odds ratio by more than 10% were included as confounders, further associations were revealed: long-term high-level exposure to gasoline engine exhaust (1.4; 1.1–1.8) and short-term high-level exposure to diesel engine exhaust (1.5; 0.9–2.7) were associated with squamous-cell cancer of the lung. The odds ratio for squamous-cell cancer of the lung (1.5; 0.9–2.5) was also elevated for bus, truck and taxi drivers (classified as exposed to gasoline engine exhaust) and for mining and quarrying (classified as exposed to diesel engine exhaust; 2.8, 1.4–5.8), but analyses by duration and intensity of exposure did not support a causal association. Marginally elevated odds ratios were also seen for colon cancer and exposure to diesel engine exhaust (1.3; 1.1–1.6); for cancer of the rectum (1.6; 1.1–2.3) and kidney (1.4; 1.0–2.0) with long-term high-level exposure to gasoline engine exhaust; for colon cancer (1.7; 1.2–2.5) with long-term high-level exposure to diesel engine exhaust; and for rectal cancer (1.5; 1.0–2.2) in bus, truck and taxi drivers. [The Working Group noted that 90% CI were used and that, at the 95% level, most of the intervals would have included unity.]

(*e*) *Childhood cancer*

Studies have been carried out to examine the hypothesis that exposure of adults to engine exhaust may result in mutations in germ cells, direct intrauterine exposure or early postnatal exposure.

In a case-control study in Québec, Canada (Fabia & Thuy, 1974), occupation of the father at time of birth was ascertained from the birth certificates of 386 children (out of 402 patients ascertained from death certificates, hospital insurance data and hospital records) who had died from malignant disease before the age of five years in 1965–70 and of 772 control children whose birth registration immediately preceded or followed that of the case in the official records. The occupation of the father was not known for 30 cases or for 56 controls. Father's occupation was recorded as motor vehicle mechanic or service station attendant for 29 (7.5%) cases and 29 (3.8%) controls [odds ratio, 2.1 (95% CI, 1.2–3.4)] and as driver for 19 (4.9%) cases and 49 (6.4%) controls [0.76 (0.4–1.3)].

In a case-control study in Finland (Hakulinen *et al.*, 1976), all 1409 incident cases of cancer in children under 15 years reported to the Cancer Registry in 1959–68 were ascertained. Paternal occupation was obtained from antenatal clinic records for the first trimester of pregnancy. After excluding twins and cases for which the father's occupation

was unobtainable, 852 cases were available for analysis. For each case, a child with date of birth immediately before that of the case and who had been born in the same maternity welfare district was chosen as a control. Leukaemias and lymphomas (339 pairs; 158 under five years of age), brain tumours (219 pairs; 77 under five years of age) and other tumours (294 pairs; 160 under five years of age) were analysed separately; analyses were carried out separately for the whole group (children under 15 years of age) and for children under five years of age at the time of diagnosis. Paternal occupation as a motor vehicle driver was not more frequent in any group of cases than in controls: the odds ratio for leukaemia in children under five (based on 14 cases) was 0.74 (95% CI, 0.34–1.6); that for leukaemia and lymphoma in the whole group (35 cases), 1.1 (0.63–1.8); that for brain tumours in children under five (four cases), 0.17 (0.00–1.4); and that for brain tumours in the whole group (16 cases), 0.67 (0.29–1.5). [The Working Group noted that only 60% of cases were available for analysis.]

In a case-control study in Connecticut, USA (Kantor *et al.*, 1979), paternal occupation was ascertained from birth certificates for all 149 cases of Wilms' tumour (aged 0–19 years) reported to the Connecticut Tumor Registry in 1935–73 and for 149 controls selected from State Health Department files and matched for sex, race and year of birth. The father's occupation was recorded as driver for eight cases and four controls [odds ratio, 2.1 (95% CI, 0.6–6.7)], as motor vehicle mechanic for six cases and one control [6.2 (0.8–49.8)] and as service station attendant for three cases and no control.

In a case-control study on the association between paternal occupation and childhood cancer (Kwa & Fine, 1980), 692 children born in 1947–57 or 1963–67 and who had died of cancer before the age of 15 in Massachusetts, USA, were identified from the National Center for Health Statistics. Two controls were selected from the registry of births for each case — one born immediately before the case and the other immediately after. Paternal occupation was taken from birth certificates and classified into one of nine categories on the basis of the type of chemical exposures involved. Mechanic/service station attendant was recorded as the father's occupation for 21 (4.9%) leukaemia/lymphoma cases [odds ratio, 1.1 (95% CI, 0.7–1.5)], six (4.5%) cases of neurological cancer [1.02 (0.4–2.4)], four (11.8%) cases of urinary tract cancer [2.9 (1.0–8.1); significant], four (4.2%) cases of all other cancers [0.93 (0.34–2.6)] and 61 (4.4%) controls. No excess of leukaemia/lymphoma, neurological cancer, urinary tract cancer or all other cancer was observed in the children of fathers who were motor vehicle drivers.

In a case-control study on associations between childhood cancer and parental occupation (Zack *et al.*, 1980), the parents of 296 children with cancer followed at a haematology clinic in Houston, TX, USA, from March 1976 to December 1977 and three sets of controls were interviewed for demographic information and job history in the year preceding the birth of the child until diagnosis of cancer. The first set of controls comprised 283 fathers and stepfathers and 283 mothers and stepmothers of children without cancer in the same clinic; the second set consisted of siblings of the parents of the case (413 uncles and 425 aunts), matched by age and number of children; and the third set was selected from among residents in the neighbourhood of the cases (228 fathers and 237 mothers). The proportion of cases with paternal occupation as motor vehicle mechanic, service station attendant or

driver did not differ from that in any control group [crude odds ratio in comparison with the first control group, 0.59 (95% CI, 0.28–1.2); that in comparison with the second control group, 0.79 (0.38–1.6); and that in comparison with neighbourhood controls, 0.92 (0.40–2.1)]. [The Working Group noted that the selection criteria were not given for either cases or controls, that it was unclear whether information on exposure was obtained from mothers or fathers or both, and that confounding factors were not taken into consideration.]

Hemminki *et al.* (1981) obtained data from the Finnish Cancer Registry on children less than 15 years old with cancer diagnosed in 1959–75 and on parental occupation, as in the study of Hakulinen *et al.* (1976; see pp. 145–146). The odds ratio for the father of a child with leukaemia in 1969–75 being a professional driver was 1.9 [95% CI, 1.1–3.7].

In a proportionate mortality study in England and Wales (Sanders *et al.*, 1981), paternal occupations recorded on the death certificates of children under 15 years of age during the years 1959–63 and 1970–72 (167 646 deaths; 6920 deaths from neoplasms) were investigated. Proportionate mortality ratios for neoplasms were not elevated for children of fathers employed as 'drivers of stationary engines, cranes, etc.', as transport workers or as warehousemen.

Associations between paternal occupation and childhood leukaemia and brain tumours were investigated in a case-control study in Maryland, USA (Gold *et al.*, 1982). Children under the age of 20 with leukaemia (diagnosed in 1969–74) or brain tumours (diagnosed in 1965–74) were ascertained in the Baltimore Standard Metropolitan Statistical Area from hospital records, death certificates, hospital tumour registries and from the pathology, radiotherapy and clinical oncology records of 21 of 23 Baltimore hospitals. There were two control groups: one consisted of children with no malignant disease, selected from birth certificates at the Maryland State Health Department and matched for sex, date of birth and race; the other group consisted of children with malignancies other than leukaemia or brain cancer, matched for sex, race, date of diagnosis and age at diagnosis. Information on occupational exposures of both parents before the birth of the child and between birth and diagnosis was collected by interviewing the mother. A total of 43 children had leukaemia and 70 had brain tumours. The paternal occupational category that included driver, motor vehicle mechanic, service station attendant or railroad worker was not more frequent for children with leukaemia or brain tumours than for the control children. [The Working Group noted the small numbers involved and found the results difficult to interpret.]

In a case-control study on childhood leukaemia and neuroblastoma (Vianna *et al.*, 1984), children born in 1949–78 who were diagnosed with acute leukaemia during the first year of life and reported to the Tumor Registry of the New York State Health Department or with neuroblastoma up to 12 years of age at diagnosis were identified. Using information from birth certificates, two sets of controls were selected: one was matched by year of birth, sex, race and county of residence; the other was additionally matched for age of the mother and birth order of the child. Information on parental age, race, education and occupation, and medical, obstetrical and therapeutic histories were obtained by telephone interview of the mothers. Of 65 eligible cases of leukaemia, 60, with two controls each, were finally included in the analysis. The odds ratio for acute leukaemia for children with 'high'

presumed paternal exposure to motor exhaust fumes (service station attendants, automobile or truck repairmen, aircraft maintenance personnel) was 2.5 [1.2–5.3] in comparison with the first control group and 2.4 [1.1–3.7] in comparison with the second. For 'lower' presumed exposure (taxi drivers, travelling salesmen, truck or bus drivers, railroad workers, toll-booth attendants, highway workers, police officers), the odds ratio was 3.4 [1.4–10.2] in comparison with the first control group and 1.3 [0.8–2.1] in comparison with the second. For the 103 cases of neuroblastoma, there was no significant difference from controls in the number of fathers who had had 'high' exposure. [The Working Group questioned the categorization of exposures as 'high' and 'lower' on the basis of the jobs listed.]

In a case-control study on paternal occupation and Wilms' tumour (Wilkins & Sinks, 1984), 105 patients were identified through the Columbus, OH, USA, Children's Hospital Tumor Registry during the period 1950–81. For each case, two controls were selected from Ohio birth certificate files; the first control series was individually matched for sex, race and year of birth, and the second series was additionally matched for mother's county of residence when the child was born. Due to changes in birth certification, the study included only the 62 cases and their matched controls for which father's occupation was recorded. The crude odds ratio for Wilms' tumour in children with paternal occupation as motor vehicle mechanic, service station attendant or driver/heavy equipment operator was 1.1 [95% CI, 0.36–3.5 compared to both controls taken together].