WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF CARCINOGENIC RISKS TO HUMANS

Diesel and Gasoline Engine Exhausts and Some Nitroarenes

VOLUME 46

IARC, Lyon, France

1989

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

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

Studies of workers whose predominant engine exhaust exposure cannot be defined

In a cohort of Swedish drivers, a statistically significantly elevated risk for lung cancer was reported. A second cohort study of heavy construction equipment drivers showed significant increasing trends in lung cancer risk with duration of exposure, but the trend in risk for other smoking-related diseases was also increased. Increased risks for lung cancer were seen in three case-control studies of persons with mixed occupational exposures to engine exhausts in the USA, Italy and France; in two of these, the increase was significant.

In the one cohort study that addressed risk for bladder cancer, the risk was elevated, although not significantly so. In three case-control studies of bladder cancer in the USA, Italy and Denmark, modest increases in risk were seen; two showed significant trends with duration of exposure. In two further studies using the same set of controls, significant associations were also seen with multiple myeloma and chronic lymphocytic leukaemia. Three occupational groups in the US Navy with presumed exposure to engine exhausts were found to have a significantly high incidence of testicular cancer, although the influence of other exposures could not be assessed.

Possible associations between parental exposure to engine exhausts and cancer in children were considered in ten studies. No clear pattern of risk emerged.

4.4 Other relevant data

No relevant data were available on the toxic effects or metabolism of engine exhausts in humans, and there was no adequate study to evaluate whether diesel and gasoline engine exhausts induce chromosomal effects in humans.

Prolonged exposure of experimental animals to diesel engine exhaust leads to a number of effects related to the concentration to which they are exposed, including particle accumulation in macrophages, changes in the lung cell population, fibrotic effects and squamous metaplasia, which appear to be correlated with impaired pulmonary clearance. It has also caused exposure-related pathological changes in regional lymph nodes in mice and rats and an apparent increase in immunoglobulin M antibody response.

Prolonged exposure to diesel engine exhaust resulted in DNA adduct formation in rats and protein adduct formation in rats and hamsters.

Exposure of rodents to whole diesel engine exhaust induced sister chromatid exchange but not germ-cell mutations, micronuclei or dominant lethal mutations. Whole diesel engine exhaust induced sister chromatid exchange in cultured human cells. It did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* and gave inconclusive results in an assay for recombination in yeast. Particles or their extracts induced somatic gene mutations and sister chromatid exchange in rodents *in vivo* but did not induce micronuclei. They induced chromosomal aberrations, sister chromatid exchange and gene mutations in cultured human cells and cell transformation, sister chromatid exchange, gene mutations and DNA damage in rodent cells *in vitro* and inhibited intercellular communication. Particles or their extracts were weakly recombinogenic in yeast and induced mutations and DNA damage in bacteria. The gaseous phase was also mutagenic to bacteria.