IARC MONOGRAPHS

BLADDER CANCER

IARC SUPPLEMENT 7

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WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISKS TO HUMANS

Overall Evaluations of Carcinogenicity: An Updating of *IARC Monographs* Volumes 1 to 42

SUPPLEMENT 7

LYON, FRANCE

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ACRYLONITRILE (Group 2A)

A. Evidence for carcinogenicity to humans (*limited*)

In the USA, 1345 male workers potentially exposed to acrylonitrile in a textile fibre plant and observed for 20 or more years had a greater than expected incidence of lung cancer (8 observed, 4.4 expected). The risk was greater among workers with more than five years' exposure (6 observed, 2.3 expected) or with jobs where exposure was likely to have been heavier (6 observed, 2.7 expected) than among workers with shorter duration of exposure (2 observed, 1.4 expected) or low levels of exposure (2 observed, 1.4 expected)[1,2]. Further follow-up of this cohort until 1981 revealed a continued excess of lung cancer (10 observed, 7.2 expected), although during the actual follow-up period (1976-1981) there was no excess (2 observed, 2.8 expected). The updating also showed, however, a significant excess of cancer of the prostate (6 observed, 1.8 expected)[3]. In a similar study at another US textile fibre plant, an excess of prostatic cancer (5 cases observed, 1.9 expected) was observed, but there was no excess of lung cancer[4]. In the UK, a study of 1111 male workers exposed to acrylonitrile during polymerization between 1950 and 1968 and followed for ten years or more revealed five stomach cancers (1.9 expected), two colon cancers (1.1 expected), two brain cancers (0.7 expected) and nine cancers of the respiratory tract (7.6 expected)[5]. Among 327 rubber workers exposed to acrylonitrile in the USA, excesses were noted for cancers of the lung (9 observed, 5.9 expected), bladder (2 observed, 0.5 expected) and of the lymphatic and haematopoietic system (4 observed, 1.8 expected). The risk for lung cancer was greatest among workers with five to 14 years' exposure and $\geq$15 years of latency (4 observed, 0.8 expected)[6]. Another study of rubber workers in the USA, however, showed no association between exposure to acrylonitrile and lung cancer[7]. In the Federal Republic of Germany, one study of 1469 workers exposed to acrylonitrile in 12 different plants showed excesses of bronchial cancer (11 observed, 5.7 expected) and of tumours of the lymphatic system (4 observed, 1.7 expected)[8].

B. Evidence for carcinogenicity to animals (*sufficient*)

Acrylonitrile was tested for carcinogenicity in rats by oral administration and by inhalation. Following its oral administration, it induced neoplasms of the brain, squamous-cell papillomas of the stomach and Zymbal-gland carcinomas; tumours of the tongue, small intestine and mammary gland were also reported[1,9,10]. Following its inhalation, neoplasms of the central nervous system, mammary gland, Zymbal gland and forestomach were observed[1,11].

C. Other relevant data

Acrylonitrile did not enhance the frequency of chromosomal aberrations in lymphocytes of exposed workers in one study[12].

In animals treated *in vivo*, acrylonitrile did not induce dominant lethal mutations, chromosomal aberrations (in bone-marrow cells or spermatogonia) or micronuclei in mice, or chromosomal aberrations in rat bone-marrow cells. It bound covalently to rat liver DNA

BENZIDINE (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Case reports and follow-up studies of workers in many countries have demonstrated that occupational exposure to benzidine is causally associated with an increased risk of bladder cancer. In one extreme instance, all five of a group of workers continuously employed in the manufacture of benzidine for 15 years or more developed bladder cancer[1]. Earlier data suggesting that the incidence of this cancer in workers decreased after a reduction in industrial exposure[1] have been supported by a study of a cohort of workers at a US benzidine-manufacturing facility, in which major preventive measures were instituted in 1950 to minimize worker exposure. The study period covered 1945-1979, and, overall, there was a clearly significant excess of bladder cancer incidence, which, however, declined in those first employed after 1950[2]. Although a longer follow-up is required to evaluate fully the effect of preventive measures on cancer risks, the causal association is strengthened by these two independent observations. Few other epidemiological studies have examined the cancer risk associated with exposure to benzidine alone. In a study at a dyestuffs factory in Italy, it was possible to distinguish a very high bladder cancer risk (5 deaths observed, 0.06 expected) associated with benzidine production[3]. The study was extended and updated, but the role of exposure to benzidine alone in the dramatically increased bladder cancer risk could not be examined further[4]. Of 25 benzidine 'operators' at a plant in the USA, 13 developed bladder cancer; all cases had been exposed for six years or more[5]. A surveillance programme of 179 active and 65 retired workers in a dyestuffs manufacturing plant in Japan revealed nine cases of bladder cancer that occurred between 1968 and 1981; all of the cases had been engaged in benzidine production[6].

Other investigations have shown high incidences of cancer of the bladder and urinary tract after concomitant exposure to benzidine and 2-naphthylamine (see p. 261) [7,8]. Exposure to these two compounds was also associated with an increase in the occurrence of second primary cancers at sites other than the bladder, including the liver[9].

Among 1601 workers in the chemical-dye industry in China who were exposed to benzidine, methylnaphthylamine and dianisidine (see p. 198), 21 cases of bladder carcinoma were found. All had a history of exposure to benzidine, while no carcinoma was found among workers exposed to methylnaphthylamine or dianisidine. Suggestions of a dose-response relationship were provided by analysis according to length of exposure[10].

Bladder cancer was also found to be increased in ecological studies of areas where benzidine (as well as 2-naphthylamine and other compounds) was used, manufactured or stored[11,12].

B. Evidence for carcinogenicity to animals (*sufficient*)

Benzidine and/or its salts were tested for carcinogenicity by oral administration in mice, rats, hamsters and dogs and by subcutaneous and intraperitoneal injection and inhalation in rats. Following oral administration of benzidine and its hydrochloride, significant increases in the incidences of benign and malignant liver neoplasms were observed in mice and

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[17]*IARC Monographs, Suppl. 6*, 132-135, 1987

CARBON BLACKS (Group 3) and CARBON-BLACK EXTRACTS (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate* for carbon blacks)

Class 2B Carcinogen

One study of the carbon-black producing industry showed a high proportion of cancers of the skin, particularly melanomas, in equal numbers of carbon-black workers and of a comparison group consisting of other workers in the same plant[1]. A study from the UK in which workers were followed up beyond retirement showed excesses of cancers of the lung and bladder. The excess of lung cancer occurred in each of the five plants studied and was concentrated among persons with ten or more years of follow-up. The bladder cancer excess was based on only three deaths but was also concentrated in the group followed up longer[2]. Excesses of stomach cancer were reported in workers in other industries whose employment entailed exposure to dusts that included carbon blacks[1,3].

Product of combustion

B. Evidence for carcinogenicity to animals (*inadequate* for carbon blacks; *sufficient* for carbon-black extracts)

In limited studies by oral administration in mice, carbon blacks were reported not to produce the gastrointestinal tumours seen after administration of solvent (benzene) extracts of one carbon black[1]. No increase in the development of colonic tumours occurred in mice or rats fed carbon black in the diet[4]. Skin-painting studies with carbon blacks showed them to have no tumorigenic activity in mice, while solvent (benzene) extracts induced benign and malignant skin tumours. Inhalation studies in mice, hamsters, guinea-pigs and monkeys with carbon blacks did not demonstrate tumorigenic activity; the studies suffered from many inadequacies, including poor characterization of the carbon-black aerosol. Studies in

infant whose mother had received clomiphene citrate as treatment for infertility[3], a liver-cell adenoma in a women who had received clomiphene citrate for oligomenorrhoea[4], and unilateral testicular neoplasms in two of 650 oligospermic men who had received monthly treatments with clomiphene citrate (daily for three weeks followed by a week of rest) for six to 12 months[5].

B. Evidence for carcinogenicity to animals (*inadequate*)

Clomiphene citrate was tested in an inadequate experiment in newborn rats by single subcutaneous injection; reproductive-tract abnormalities, including uterine and ovarian tumours, were reported[1].

C. Other relevant data

No data were available on the genetic and related effects of clomiphene citrate in humans. It did not induce chromosomal aberrations or micronuclei in bone-marrow cells of mice treated *in vivo*[6].

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[6]*IARC Monographs, Suppl. 6*, 184-185, 1987

COAL GASIFICATION (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Case reports of tumours of the skin (including the scrotum), bladder and respiratory tract in association with employment in industries involving the destructive distillation of coal suggested a link between work in that industry and human cancer. Descriptive epidemiological studies based on death certificates corroborated these early suggestions[1].

A series of detailed analytical epidemiological studies of the British gas industry add further weight to the hypothesis that work in such coal gasification plants carries a risk for tumours of the lung, bladder and scrotum. There appeared to be a relationship between elevated relative risk of tumours and work in retort houses, particularly when the job had entailed exposure to fumes emanating from the retorts[1].

B. Other relevant data

No relevant data were available to the Working Group.

References

[1]*IARC Monographs*, *34*, 65-99, 1984

COAL-TAR PITCHES (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

A mortality analysis in the UK from 1946 showed a greatly increased risk for scrotal cancer among patent-fuel workers; furthermore, a large number of case reports describe the development of skin (including the scrotum) cancer in workers exposed to coal-tars (see p. 175) or coal-tar pitch[1]. Several epidemiological studies have shown excesses of lung and bladder cancer among workers exposed to pitch fumes in aluminium production plants[2]. A slight excess of lung cancer was found among furnace and maintenance workers exposed to coal-tar pitch fumes in a calcium carbide production plant[3]. A cohort study of US roofers indicated an increased risk for cancer of the lung and suggested increased risks for cancers of the oral cavity, larynx, oesophagus, stomach, skin and bladder and for leukaemia. Some support for excess risks of lung, laryngeal and oral-cavity cancer is provided by other studies of roofers. One study showed a small excess of bladder cancer in tar distillers and in patent-fuel workers. An elevated risk of cancer of the renal pelvis was seen in workers exposed to 'petroleum or tar or pitch'[1]. One study of millwrights and welders exposed to coal-tars and coal-tar pitch in a stamping plant showed significant excesses of leukaemia and of cancers of the lung and digestive organs[4].

B. Evidence for carcinogenicity to animals (*sufficient*)

Application of coal-tar pitches and extracts of coal-tar pitches to the skin of mice produced malignant skin tumours. Extracts of coal-tar pitches had both initiating and promoting activities in mouse skin[1,5,6].

C. Other relevant data

No data were available on the genetic and related effects of coal-tar pitches in humans.

Extracts of coal-tar pitches and 'coal-tar' paints (formulated with coal-tar pitches) were mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system. Extracts of emissions from a roofing-tar pot (coal-tar pitch-based tar) enhanced viral transformation in Syrian hamster embryo cells but did not cause DNA strand breaks. The same material induced sister chromatid exchanges and mutation in cultured rodent cells, both in the presence and absence of an exogenous metabolic system, and was mutagenic to *S. typhimurium* in the presence of an exogenous metabolic system[7].

urinary bladder and the adrenal glands; however, because of the lack of matched controls, it could not be concluded whether tumour induction was due to a combined effect of the three chemicals or of any one of them[4].

C. Other relevant data

Neither chromosomal aberrations (in two patients) nor sister chromatid exchanges (in three patients) were induced following administration of 5-fluorouracil[5].

5-Fluorouracil induced micronuclei but not specific locus mutations in mice treated *in vivo*. It induced aneuploidy, chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster cells. It did not induce sex-linked recessive lethal mutations in *Drosophila*, but caused genetic crossing-over in fungi. Studies on mutation in bacteria were inconclusive[5].

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[5]*IARC Monographs*, *Suppl. 6*, 316-318, 1987

FORMALDEHYDE (Group 2A)

A. Evidence for carcinogenicity to humans (*limited*)

A number of epidemiological studies using different designs have been completed on persons in a variety of occupations with potential exposure to formaldehyde[1-24]. Cancers that occurred in excess in more than one study are: Hodgkin's disease, leukaemia, and cancers of the buccal cavity and pharynx (particularly nasopharynx), lung, nose, prostate, bladder, brain, colon, skin and kidney[1]. The studies reported are not entirely independent; the plant studied by Liebling *et al.*[2] and Marsh[1,3] is also included in the study by Blair *et al.*[4]; the case-control study of Fayerweather *et al.*[5] includes some subjects who were later studied by Blair *et al.*[4]. Detailed estimates of formaldehyde exposure levels were made in the studies of British chemical workers[6], US formaldehyde producers and users[4], Finnish wood workers[7] and US chemical workers[5], and for the case-control studies of Vaughan *et al.*[8,9] and Hayes *et al.*[10].

Class I carcinogen Prod. of Combustion

In the study of US producers and users of formaldehyde, 11% of the subjects were not exposed, 12% had an estimated time-weighted average (TWA) exposure of <0.1 ppm (<0.12 mg/m^3), 34% a TWA of 0.1-<0.5 ppm (0.12-<0.6 mg/m^3), 40% a TWA of 0.5-<2 ppm

LEAD AND LEAD COMPOUNDS:
LEAD AND INORGANIC LEAD COMPOUNDS (Group 2B)
ORGANOLEAD COMPOUNDS (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Three epidemiological studies of workers exposed to lead and lead compounds were reviewed previously[1]: one on smelters and battery workers in the USA, one on workers exposed to tetraethyllead in the USA, and one on copper smelters in the USA; data on the first of these populations have been updated[2]. A study on battery workers in the UK[3] is now available, and studies of a US lead smelter[4] and of a Swedish copper smelter[5] have also been reported. A statistically significant excess of cancers of the digestive system (21 observed, 12.6 expected) was found in the study of battery workers in the UK, spanning 1925-1976, although the excess was confined to the years 1963-1966[3]. Significant excesses of stomach cancer (34 observed, 20.2 expected) and of respiratory cancers (116 observed, 93.5 expected) were seen in the study of US battery plant workers[2], although there was a downward trend in standardized mortality ratio by number of years of employment; in the lead production facilities, the excesses noted for stomach and respiratory cancers were not significant[2]. A nonsignificant excess of respiratory cancer (41 observed, 36.9 expected) was reported in one of the studies of smelters[4], with 28 observed and 25.7 expected in the group with high exposure to lead. Excesses were also noted in this study for kidney cancer (6 observed, 2.9 expected) and bladder cancer (6 observed, 4.2 expected)[4]. A small study of workers at a Swedish smelter[5] with long-term exposure to lead demonstrated a nonsignificant excess of lung cancers (8 observed, 5 expected). Two cases of kidney cancer in lead smelter workers have also been reported[6,7].

The excesses of respiratory cancer in these studies were relatively small, showed no clear-cut trend with length or degree of exposure, and could have been confounded by factors such as smoking or exposure to arsenic (see p. 100).

A study of workers manufacturing tetraethyllead revealed excesses of respiratory cancer (15 observed, 11.2 expected) and brain cancer (3 observed, 1.6 expected)[8].

B. Evidence for carcinogenicity to animals (*sufficient* for inorganic lead compounds; *inadequate* for organolead compounds)

Lead acetate and lead subacetate were tested for carcinogenicity by oral, subcutaneous and intraperitoneal administration in rats, lead phosphate was tested by subcutaneous and intraperitoneal administration in rats, and lead subacetate was tested by oral administration in mice. Renal tumours were produced in animals of each species by each route of administration. Rats given lead acetate or lead subacetate orally developed gliomas. Lead subacetate also produced an increased incidence of lung adenomas in mice after its intraperitoneal administration[1]. Oral administration of lead dimethyldithiocarbamate (ledate) increased the incidence of reticulum-cell sarcomas in male mice of one strain[9] but was not carcinogenic to mice or rats in another experiment[10].

TRICHLOROETHYLENE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

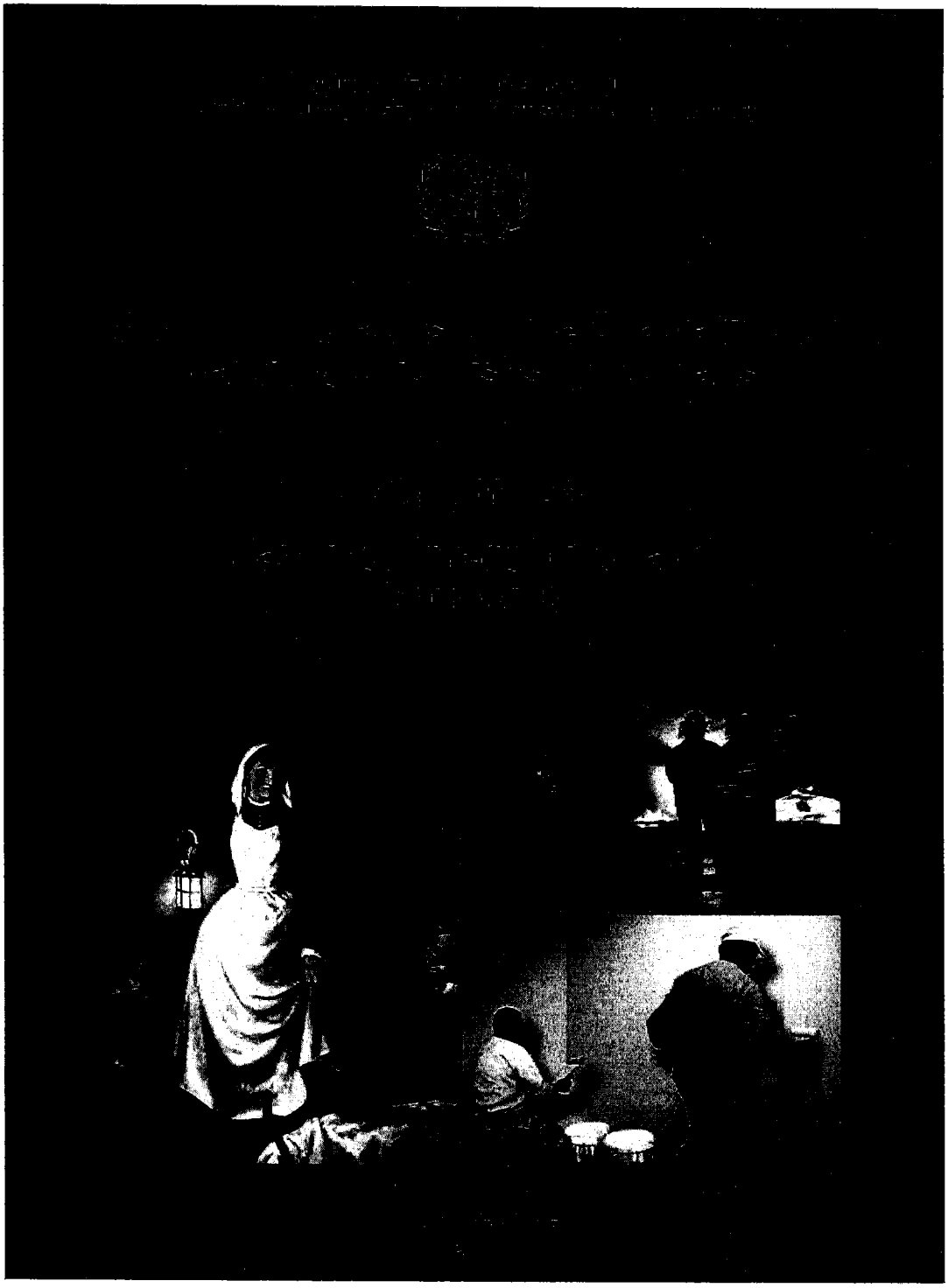
Three cohort studies have been reported, two of which showed no excess of cancer[1,2]; the third[3], in an extended and updated version[4], showed slightly increased incidences of cancer of the bladder (3 observed, 0.8 expected) and prostate (4 observed, 2.4 expected) and of lymphoma (2 observed, 0.3 expected). Two case-control studies of lymphoma have been reported: one on Hodgkin's lymphoma, in which three of 25 cases and none of 50 controls had had exposure to trichloroethylene[5], and the other on Hodgkin's and non-Hodgkin's lymphomas combined in which seven of 169 cases and three of 338 controls had been exposed[6]. Four studies of liver cancer have indicated no clear association with exposure to trichloroethylene[7-10]. A few more cases than controls were exposed in two of the studies, especially when the two studies were analysed together[7,9]. In a proportionate mortality study of polishers and platers with potential exposure to trichloroethylene, but also to chromates (see p. 165) and nickel (see p. 264), there were excesses of oesophageal and primary liver cancers. There were also slight excesses of cancers of the buccal cavity and pharynx, pancreas and larynx and of lymphoma (Hodgkin's and non-Hodgkin's lymphomas combined, 13 observed, 9.3 expected)[11].

Exposure to trichloroethylene may occur to some extent in laundry and dry-cleaning work, although exposure to tetrachloroethylene (see p. 355) probably predominates. Decaffeinated coffee, which is often extracted with trichloroethylene, appeared to be a risk factor for pancreatic cancer in one study, as did dry-cleaning[12].

The inconsistent relationship between liver cancer and dry-cleaning is considered in the summary on tetrachloroethylene. Even if there is some consistency among several studies with regard to an association between lymphatic malignancies and exposure to trichloroethylene, the small numbers involved do not permit any definite conclusion to be drawn about a causal association.

B. Evidence for carcinogenicity to animals (*limited*)

Trichloroethylene was tested for carcinogenicity by oral administration in mice in one experiment and in rats in two experiments. In mice, it produced hepatocellular carcinomas and lung tumours in both males and females. One study in rats was considered to be inadequate, and the other showed equivocal evidence of carcinogenicity[3]. Inhalation studies with trichloroethylene have been conducted in mice, rats and hamsters[13,14]. In one study in female mice, it caused lung tumours[13], but it gave negative results in the other study in mice and in rats and hamsters. Administration by skin painting and by subcutaneous injection to mice also gave negative results[15]. In inhalation experiments using two strains of mice, trichloroethylene increased the incidences of liver tumours in males of one strain and in males and females of the other strain, and of lung tumours in males of one strain and in females of the other. In rats, a low incidence of adenocarcinomas of the renal tubules was observed following exposure to trichloroethylene by inhalation[16]. In mice, oral administration of trichloroethylene containing epichlorohydrin (see p. 202) as a stabilizer induced



2. Studies of Cancer in Humans

2.1 Cohort, record linkage and proportionate mortality studies

2.1.1 *Background*

In 1989, the International Agency for Research on Cancer (IARC) classified painting as an occupation as *carcinogenic to humans* (Group 1) (IARC, 1989, Volume 47). At the time, the epidemiological evidence for the evaluation was primarily based on a total of eight studies (five record linkage and three cohort studies), listed in Table 23 of that volume. The primary findings in these data were relatively consistent excesses for all cancers (standardized mortality ratio [SMR] 1.21, 9100 cases), and for cancer of the lung (SMR 1.41, 468 cases). The lung cancer excess was noted to be above what could reasonably be expected to be due to confounding by smoking. Other findings which drew comment in Volume 47 were excesses for cancers of the oesophagus, stomach, and bladder, although these excesses were smaller than for cancer of the lung and were less consistent across studies. It was noted that results from a few studies showed excesses of leukaemia, and cancers of the buccal cavity, and of the larynx.

Cohort studies generally represent a stronger study design than record linkage studies. In the latter, the exposure is often taken from census employment data, is typically less accurate than the employment records upon which cohort studies are usually based, and does not usually take into account duration of employment. However, in the case of the cohort and record linkage studies listed in Table 23 by IARC in 1989, findings from both types of studies were reasonably consistent.

2.1.2 *Cohort studies since IARC Monograph Volume 47* (Table 2.1)

Yin *et al.* (1987) studied workers who were employed at least 6 months within different factories in the People's Republic of China. They compared 13 604 benzene-exposed painters to 28 257 production workers without occupational benzene exposure with a similar sex and age distribution. Mortality follow-up occurred from 1972–1981, and the authors presented the leukaemia mortality rates separately for painters (15.9/100 000 person–years) and the comparison cohort (2.01/100 000 person–years). [The painters, not including paint-production workers, had a mortality rate ratio of [7.9] (14 leukaemia deaths) compared to workers in other production jobs without benzene exposure (four leukaemia deaths). This high rate ratio is presumably due to the selection of these painters for specifically benzene exposure.] No other cancer outcomes were presented.

Hrubec *et al.* (1995) followed a cohort assembled from a roster of approximately 300 000 caucasian, male WWI and WWII veterans for mortality from 1954–1980. These men served in the US Armed Forces at some time during 1917–1940, and held active

Other cancer categories had very few deaths and provided little information. More detail can be found in Table 2.1.

Steenland & Palu (1999) updated a previous large cohort study of US painters by Matanoski *et al.* (1986): 42 170 painters and 14 316 non-painters were assembled from union records and followed for mortality through local and national registries from 1975–1994. The update added 15 years of follow-up during which time the number of deaths increased from 5313 to 23 458. When painters were compared to the general US population, the updated data showed significant but modest excesses for all cancers (SMR, 1.12; 95% CI: 1.09–1.15; 4674 deaths), cancers of the lung (SMR, 1.23; 95% CI: 1.17–1.29; 1746 deaths), of the bladder (SMR, 1.23; 95% CI: 1.05–1.43; 166 deaths), of the stomach (SMR, 1.39; 95% CI: 1.20–1.59; 197 deaths), and of the liver (SMR, 1.25; 95% CI: 1.03–1.50; 119 deaths). In an additional analysis comparing painters and non-painters directly at other anatomical sites, the standardized rate ratios (SRRs) were 1.23 (95% CI: 1.11–1.35) for cancer of the lung, 1.77 (95% CI: 1.13–2.77) for cancer of the bladder, 0.92 (95% CI: 0.68–1.25) for cancer of the stomach, and 1.36 (95% CI: 0.87–2.11) for cancer of the liver. Further analyses restricted to painters with at least 20 years of membership in the union, showed reductions in the SRRs for cancers of the bladder, stomach, and liver while the SRR for cancer of the lung increased slightly (to 1.32). Both painters and non-painters showed significant excesses of cirrhosis compared to the US population (SMRs, 1.21; 95% CI: 1.07–1.35, and 1.26; 95% CI: 1.03–1.51, respectively), suggesting an excess of alcohol consumption compared to the US population; nonetheless, as noted above, the excess of liver cancer persisted in a direct comparison of painters to non-painters.

The data were also adjusted indirectly for smoking using detailed information on smoking in the general population from two large US surveys (see Axelson & Steenland (1988) for the description of methods). The authors found that confounding by smoking when comparing painters to the US population would have resulted in a rate ratio of 1.14 for lung cancer and 1.05 for bladder cancer, compared to the observed SMRs of 1.23 and 1.23, respectively. While this suggested that confounding by smoking may have accounted for some of the lung cancer excess, the case for an occupational etiology was strengthened by the finding of an SRR of 1.23 (95% CI: 1.11–1.35) through a direct comparison painters to non-painters in the same union as both these groups were expected to have similar smoking habits.

The same Dutch cohort described by van Loon *et al.* (1997) was studied for incident cancers of the bladder (532 cases, 1630 subcohort members) and of the prostate (830 cases, 1525 subcohort members), using the same case–cohort design (Zeegers *et al.*, 2001, 2004). Using a case by case expert assessment, and adjustment for age, other occupational exposures as well as the amount and duration of cigarettes consumed, a positive trend for exposure to paint components was observed, with incident rate ratios of 1.00, 0.75 (95% CI: 0.33–1.72), 1.78 (95% CI: 0.94–3.37), and 1.31 (95% CI: 0.72–2.40) for increasing levels of estimated exposure (none, low, medium and high, respectively; *P*-value for trend, 0.09), based on 483, 8, 20, and 19 bladder cancer cases, respectively (Zeegers *et al.*, 2001). For the 765 prostate cancer cases that reported occupational history, job titles were coded using the

La Vecchia *et al.* (1990) conducted a hospital-based case–control study of bladder cancer in the greater Milan area, Italy. The study included 263 cases and 287 controls. While patients diagnosed with acute, non-neoplastic or urinary tract diseases were used as controls, a relative risk of 1.8 (90% CI: 0.8–3.7) was observed for those who worked in the painting (including spraying) industry. Those who had been occupationally exposed to dyes/paints for more than 10 years had an almost 5-fold increased risk of bladder cancer (RR, 4.8; 90% CI: 1.7–13.9), and this risk increased significantly with increasing duration of exposure to dyes/paints (P for trend = 0.04).

Myslak *et al.* (1991) conducted a hospital-based case–control study in the East Ruhr area, a major industrial area of Germany. The cases included in the study were 403 male bladder cancer patients, and the controls were 426 patients diagnosed with benign prostate disease from the same hospital. The study authors reported an increased RR of bladder cancer of 2.76 (95% CI: 1.21–6.28; 21 cases) for painters. [It should be noted, however, that, while smoking information was collected in this study, there was no indication that the study actually controlled for potential confounding effect from smoking.]

In Volume 47 (IARC, 1989), Claude *et al.* (1986, 1988) reported results from a hospital-based case–control study for cancer of the lower urinary tract in northern Germany. Their results showed a significantly increased risk of lower urinary tract cancers associated with exposure to lacquer, paint, and spray paints. With additional cases and controls, Kunze *et al.* (1992) reported an OR of 2.9 (95% CI: 1.7–4.9; adjusted for tobacco consumption) for having ever been exposed to spray paints. The risk of bladder cancer increased significantly with increasing duration of exposure to spray paints in this study (P for trend = 0.004).

Cordier *et al.* (1993) conducted a hospital-based case–control study in five regions of France. This study involved 765 cases (658 men and 107 women), and the same number of controls. Controls were patients admitted to the same hospital as the cases for causes other than cancer, respiratory disease or symptoms suggestive of bladder cancer. Controls were matched 1:1 to cases by sex, age, ethnic origin, and place of residence. This study did not find any association between employment as a painter and a risk of bladder cancer (RR, 0.97; 95% CI: 0.50–1.88; 19 cases). An OR of 6.41 (95% CI: 0.79–51.85), however, was observed for spray painters, based on eight cases and one control.

Barbone *et al.* (1994) conducted a hospital-based case–control study of bladder cancer in northeastern Italy. The study included 273 bladder cancer cases and 573 controls. Controls were patients without bladder cancer, but admitted for trauma, non-traumatic musculoskeletal conditions, acute surgical conditions, eye diseases, and other conditions such as diseases of the ears, nose, throat or mouth. Cases and controls were interviewed at hospitals. A non-significantly increased risk of bladder cancer was found for men employed in the painting industry (RR, 3.1; 95% CI: 0.7–13; six cases) after controlling for major potential confounders, including cigarette smoking.

Hours *et al.* (1994) conducted a case–control study of bladder cancer in Lyon, France between 1984–1987 involving 116 cases (97 male, 19 female) and 232 hospital-based controls matched by gender, hospital, age, nationality. Job history was obtained from in-person interviews. Painting (regular leisure-time activity) was associated with a non-

1.2 Composition of fire smoke

1.2.1 *Fire chemistry*

Smoke from fires comprises suspended liquid and solid particulate matter, gases and vapours that result from the combustion or pyrolysis of material. There is a very large number of toxic components in smoke (for reviews, see Tuve, 1985; Meyer, 1989; DiNenno *et al.*, 2002; Côté, 2003). The basic form of the overall combustion reaction of organic (carbon-containing) compounds is illustrated by the burning of methane:

$$CH_4 + 2O_2 + \text{Energy of activation} \rightarrow CO_2 + 2H_2O + \text{Heat of combustion} + \text{Light}$$

Given the appropriate ratio of fuel (wood, solvent, plastic, rubber), oxygen, and combustion temperature, the products of combustion should be only water and carbon dioxide (CO_2).

Complete combustion is approached only under carefully controlled conditions. Uncontrolled or unintentional combustion tends to be "fuel rich" and therefore incomplete. The combustion of methane (CH_4) illustrates the formation of free radicals in an 11-step chain reaction, the first two of which are:

$CH_4 \rightarrow CH_3^{\bullet} + H^{\bullet}$

$H^{\bullet} + O_2 \rightarrow OH^{\bullet} + O^{\bullet}$

The free radicals formed during combustion are very reactive and side reactions are propagated to yield hundreds of chemical products, and smoke.

Most polymers found in buildings will burn or thermally degrade to simpler monomers. Thermal degradation products include methane, ethane, ethylene, benzene, toluene, and ethylbenzene in addition to the following monomers: ethylene, vinyl chloride, acrylonitrile, tetrafluoroethylene, styrene, methyl methacrylate, ethylene glycol, terephthalic acid, phenol, formaldehyde, hexamethylenediamine, adipic acid, propene, vinyl chloride, vinyl acetate, vinylidene chloride, chloroprene, 1,3-butadiene, ethyl acrylate, ethylene oxide, methylacrylate, urea, phenol, and isoprene.

The burning of plastics typically produces voluminous amounts of soot, together with higher levels of hydrogen cyanide (HCN), hydrochloric acid (HCl) and acrolein (CH_2=CHCHO) than the burning of materials such as wood, and fossil fuels. More smoke evolves from fires involving aromatic polymers, such as polystyrene, compared to aliphatic polymers, such as polyethylene.

In addition to the chemical agents described above, particulate matter is produced under conditions of incomplete combustion. The particulate matter is an aerosol consisting of condensed phase components of the products of combustion and finely divided carbon particulates that have not undergone combustion but remain suspended in the air. Although the particles themselves are microscopic in size (0.3–1.6 μm), they

rapidly coalesce and thereby become visible. These particles are also adsorbents (similar to activated charcoal) and are an additional vehicle for the transport and inhalation of toxic combustion products. Smouldering yields a substantially higher conversion of fuel to toxic compounds than does flaming, although it occurs more slowly (Ohlemiller, 2002).

1.2.2 *Modern versus pre-modern fires*

All types of fire release toxic and carcinogenic substances, including benzene, 1,3-butadiene, and formaldehyde. The focus has generally been on substances having short-term acute effects: carbon monoxide (CO), carbon dioxide, hydrogen cyanide, nitrogen oxides (NO_x), sulfur dioxide (SO_2) and hydrogen chloride. With the increasing use of polymers in building construction and furnishings, there is concern that the burning of these new materials might release large quantities of other highly toxic substances (Austin *et al.*, 2001b).

Combustion and pyrolysis products from newer building materials and furnishings were believed to be more toxic than smoke from fires in buildings built before these materials became commonplace, and more toxic than smoke from wildland fires (Betol *et al.*, 1983; Alarie, 1985). However, many of the carcinogenic products of combustion identified are volatile organic compounds and are common to most burning materials. In a more recent study, no new or unusual non-polar volatile organic compounds (VOCs) were observed in current structural fires compared to the combustion of wood (Austin *et al.*, 2001b, 2001c). Adding polyvinyl chloride (PVC) to the fire load at simulated apartment fires was observed to significantly increase levels of polychlorinated phenols (IARC Group 2B), while polycyclic aromatic hydrocarbon (PAH) levels remained essentially unchanged (Ruokojärvi *et al.*, 2000). The increases in levels of polychlorinated biphenyls (PCBs, 0.021 to 0.031 mg/m^3), polychlorinated benzenes (0.002 to 0.010 mg/m^3) and I-TEQs [or PCDD/F] (3.5 to 5.4 ng/m^3) as products of combustion were not significant [possibly due to the small sample size]. In another study, proportionately higher levels of ethyl benzene (IARC Group 2B) were found at an electronics factory fire when compared to levels at residential and mixed occupancy fires (Austin *et al.*, 2001b).

The emission of combustion products (in mg per kg of material burned) for the same material varies greatly depending on combustion conditions such as ventilation (oxygen supply), temperature, and heating rate. Nonetheless, the relative amounts of the various non-polar VOCs found in smoke at municipal structural fires have been found to be remarkably similar from fire to fire, namely with the same 14 of 144 target compounds, dominated by benzene (IARC Group 1), toluene and naphthalene (IARC Group 2B) (Austin *et al.*, 2001b, 2001c).

1.2.3 *Carcinogens found in smoke at fires*

Table 1.1 lists the agents in Groups 1, 2A, and 2B that have been detected at fires in one or more studies, together with corresponding IARC evaluations, human and animal evidence of carcinogenicity, and for the agents in Group 1, the cancer sites in humans.

Table 1.1. IARC evaluations and cancer sites in humans of chemicals measured at fires

Chemicals measured at fires	Overall evaluation	Human evidence	Animal evidence	Volume	Cancer sites in humans (For Group 1 agents only)
Acetaldehyde	2B	Inadequate	Sufficient	36, Suppl. 7, 71	
Arsenic	1	Sufficient	Limited	23, Suppl. 7	Skin, lung, liver (angiosarcoma)
Asbestos	1	Sufficient	Sufficient	14, Suppl. 7	Lung, mesothelioma, larynx, gastrointestinal tract
Benz[*a*]anthracene	2B	Inadequate	Sufficient	32, Suppl. 7, 92	
Benzene	1	Sufficient	Limited	29, Suppl. 7	Leukaemia
Benzo[*b*]fluoranthene	2B	No data	Sufficient	32, Suppl. 7, 92	
Benzo[*k*]fluoranthene	2B	No data	Sufficient	32, Suppl. 7, 92	
Benzofuran (coumarone)	2B	No data	Sufficient	63	
Benzo[*a*]pyrene	1	No data	Sufficient	32, Suppl. 7, 92	Lung, bladder, skin
1,3-Butadiene	1	Sufficient	Sufficient	71, 97	Lymphohaematopoietic system
Cadmium	1	Sufficient	Sufficient	58	Lung
Carbon black (total)	2B	Inadequate	Sufficient	65, 93	
Chrysene	2B	Inadequate	Sufficient	3, 32, Suppl. 7, 92	
Dibenz[*a*,*h*]anthracene	2A	Inadequate	Sufficient	32, Suppl. 7, 92	
Dichloromethane (methylene chloride)	2B	Indadequate	Sufficient	71	
Ethylbenzene	2B	Inadequate	Sufficient	77	
Formaldehyde	1	Sufficient	Sufficient	88	Nasopharynx; (nasal sinuses and leukaemia, suggested)
Furan	2B	Inadequate	Sufficient	63	

Table 1.1 (contd)

Chemicals measured at fires	Overall evaluation	Human evidence	Animal evidence	Volume	Cancer sites in humans (For Group 1 agents only)
Indeno-1,2,3-[*cd*]pyrene	2B	Inadequate	Sufficient	32, Suppl. 7, 92	
Isoprene	2B	Not available	Sufficient	60, 71	
Lead				23, Suppl. 7, 87	
Lead compounds, organic	3	Inadequate	Inadequate	23, Suppl. 7, 87	
Lead compounds, inorganic	2A	Limited	Sufficient	23, Suppl. 7, 87	
Naphthalene	2B	Inadequate	Sufficient	82	
2-Nitroamisole	2B	Inadequate	Sufficient	65	
Polychlorophenols	2B	Limited		41, Suppl. 7, 53, 71,	
Pentachlorophenol			Sufficient		
2,4,6-Trichlorophenol			Limited		
Polychlorinated biphenyls (aroclor; 54%) (chlorodiphenyl)	2A	Limited	Sufficient	18, Suppl. 7	
Polychlorinated dibenzodioxins[a]: see TCDD					
Radioactivity (γ activity)	1	Sufficient	Sufficient	78	All sites combined
Radionuclides (α-particle-emitting)	1	Sufficient	Sufficient	78	All sites combined
Radionuclides (β-particle-emitting)	1	Sufficient	Sufficient	78	All sites combined
Silica (crystalline)	1	Sufficient	-	68	Lung
Silica (amorphous)	3	Inadequate	Inadequate	68	

Table 1.1 (contd)

Chemicals measured at fires	Overall evaluation	Human evidence	Animal evidence	Volume	Cancer sites in humans (For Group 1 agents only)
Styrene	2B	Limited	Limited	60, 82	
Sulfuric acid[b]	1	Sufficient	No data	54	
2,3,7,8-tetrachloro dibenzo-*para*-dioxin	1	Limited	Sufficient	69	All sites combined, lung, non-Hodgkin lymphoma, sarcoma
Tetrachloroethylene (perchloroethylene)	2A	Limited	Sufficient	63	Cervix, oesophagus, non-Hodgkin lymphoma
Toluene diisocyanates	2B	Inadequate	Sufficient	39, Suppl. 7, 71	
Trichloroethylene	2A	Limited	Sufficient	63	Liver and biliary tract, non-Hodgkin lymphoma, renal cell
Trichloromethane (chloroform)	2B	Inadequate	Sufficient	73	
Triphenylene	3	Inadequate	Inadequate	32, Suppl. 7, 92	

[a] Polychlorinated dibenzo-*para*-dioxins as a group are classified in Group 3
[b] Evaluation of occupational exposures to strong inorganic acid mists containing sulfuric acid

Vital status was determined for 99% of the cohort, resulting in 470 observed deaths. Significantly elevated SMRs were found for benign neoplasms (SMR, 417), cancer of the colon (SMR, 183), and cancer of the bladder (SMR, 286). Cause-specific mortality was presented by the number of years employed, calendar year of death, year of hire, and latency. Cancer mortality was significantly higher in the long-term firefighters, and risk of mortality from all malignant neoplasms tended to increase with increasing latency. Statistically significant excesses of colon and bladder cancer were observed among firefighters employed for 40 or more years.

Beaumont *et al.* (1991) calculated mortality rates for 3066 firefighters employed during 1940–1970 at the San Francisco Fire Department, USA. Vital status was ascertained through to 1982, and observed and expected rates were computed using United States death rates. About 3% of the population was lost to follow-up. Mortality was examined by duration of employment as a firefighter. The total number deceased (1186) was less than expected (risk ratio [RR] = 0.90), and there were fewer cancer deaths than expected (RR = 0.95). However, there were significant excess numbers of deaths from oesophageal cancer (12 observed, six expected). A statistically significant excess of biliary and related cancer was observed among firefighters employed for 30 or more years.

Grimes *et al.* (1991) conducted a proportionate mortality study involving all male firefighters with at least one year of service in the fire department of the City of Honolulu, USA. The observed percentage of firefighter deaths from each cause from 1969–1988 was compared statistically to the expected numbers of deaths for all males aged over 20 years in Hawaii's general population. The proportionate risk ratio (PRR) for all malignant neoplasms was 1.19 (95% CI: 0.96–1.49). Significant increases in risk of death were found for brain cancer (PRR, 3.78), prostate cancer (RR, 2.61), and cirrhosis of the liver (PRR, 2.3). [The Working Group noted that it does not appear as though PRRs were standardized by age and calendar period as is standard practice for this type of analysis.]

Heyer *et al.* (1990) examined the mortality among 2289 firefighters from Seattle, Washington, USA employed during 1945–1980. Subsequently, Demers *et al.* (1992a) examined the mortality of 4546 firefighters who were employed by the cities of Seattle and Tacoma (Washington, USA), and Portland (Oregon, USA) for at least one year during 1944–1979. Demers *et al.* (1992b) also examined the cancer incidence in 4528 firefighters from Seattle and Tacoma during 1944–1979. Mortality in these firefighters was compared to United States national mortality rates and to mortality rates of police officers from the same cities. Mortality was examined by the duration of employment as a firefighter (i.e., actually controlling fires) rather than as an inspector or a support person. This mortality was then compared to a reference group of police from the same cities. Complete follow-up was achieved for 98% of the firefighters. During 1945–1989 (the cohort was the same as Demers *et al.* [1992a] but the follow-up lasted until 1989), 1169 deaths occurred in the study population, and 1162 death certificates (99%) were collected. There was no excess risk of overall

Deschamps *et al.* (1995) investigated all professional male members of the Brigade des Sapeurs-Pompiers de Paris ($n = 830$) who served for a minimum of 5 years as of January 1st, 1977. They were monitored for a 14-year period, with follow-up terminating on January 1st, 1991. Cause-specific mortality rates in these firefighters were compared with national mortality data provided by the Institut National de la Santé et de la Recherche Médicale. To assess the occupational exposure as a firefighter, data were collected on duration of employment as an active duty firefighter (as opposed to office work). These 830 firefighters accrued a total of 11 414 person–years of follow-up. Follow-up appears to have been 100% complete. There were 32 deaths in the cohort during the 14-year period of follow-up. When compared to the average French male, they were found to have a far lower overall mortality (SMR, 0.52 [95% CI: 0.35–0.75]). None of the cause-specific SMRs was significant. However, a greater number of deaths than expected was observed for genito-urinary cancer (SMR, 3.29) [based on one bladder cancer, and one testicular cancer], and digestive cancer (SMR, 1.14).

Baris *et al.* (2001) conducted a retrospective cohort mortality study among 7789 firefighters in Philadelphia, Pennsylvania, USA, on males employed during 1925–1986. Vital status was ascertained up until 1986. SMRs and 95% CI were calculated with expected numbers of deaths in the United States white male population, as the overwhelming majority of firefighters were white. Occupational exposure histories were abstracted from detailed records maintained by the Philadelphia Fire Department, and a job–exposure matrix was created for each firefighter. To estimate exposure–response relationships, the study used this matrix to compare mortality among groups of firefighters defined by the estimated number of career runs. There were 2220 deaths and a total of 6.2% of the cohort was lost to follow-up. In comparison with white males in the United States, firefighters had a similar mortality from all causes of death combined (SMR, 0.96), and all cancers (SMR, 1.10). Statistically significant excess risks were observed for colon cancer (SMR, 1.51). The risks of mortality from colon cancer (SMR, 1.68), kidney cancer (SMR, 2.20), non-Hodgkin lymphoma (SMR, 1.72), multiple myeloma (SMR, 2.31), and benign neoplasms (SMR, 2.54) were increased in firefighters with at least 20 years of service.

Bates *et al.* (2001) conducted a historical cohort study of mortality and cancer incidence in all remunerated New Zealand firefighters, who served during 1977–1995. Ascertainment of employment was through a registry maintained by the United Fire Brigades Association of New Zealand. The final cohort comprised 4221 male firefighters. To assess the occupational exposure as a firefighter, data were collected on duration of employment. The 4221 male firefighters in this cohort accrued a total of 58 709 person–years of follow-up. Follow-up was successful in tracing 93.5%. There were 117 deaths up until 1995. Cancer incidence was ascertained during 1977–1996. The SIR for all cancers was 0.95. For most sites, no excesses were observed. The only cancer for which this study provided evidence of an increased risk was

testicular cancer. Eleven testicular cancers were observed versus 7.1 expected (SIR, 1.55; 95% CI: 0.8–2.8). For the years 1990–1996, the SIR for testicular cancer was 3.0 (95% CI: 1.3–5.9).

Ma *et al.* (2005) examined age- and gender-adjusted mortality rates of 36 813 professional firefighters employed during 1972–1999 in Florida, USA, and compared those with that of the Florida general population. The study population consisted of 34 796 male and 2017 female professional firefighters. The racial/ethnic composition was caucasian (90.1%), hispanic (7%), and black (6.5%). Employment as a firefighter was ascertained from employment records in the Florida State Fire Marshall Office. Surrogate information on occupational exposures in firefighting was collected by examining the year of certification and duration of employment as a firefighter. No information was collected on smoking histories. A total of 1411 male and 38 female deaths with known causes were identified in this cohort. In male firefighters, a deficit of overall mortality from cancer was observed (SMR, 0.85). Excess risks were observed for male breast cancer (SMR, 7.41; 95% CI: 1.99–18.96), and thyroid cancer (SMR, 4.82; 95% CI: 1.30–12.34), each based on four cases. Mortality from bladder cancer was increased and approached statistical significance (SMR, 1.79; 95% CI: 0.98–3.00). Female firefighters had similar overall cancer mortality patterns to Florida women (SMR, 1.03), but the numbers were small for specific cancer sites.

In a further analysis of the same cohort, Ma *et al.* (2006) determined the relative cancer risk for firefighters in the State of Florida compared with the Florida general population. Employment as a firefighter was ascertained from employment records in the Florida State Fire Marshall Office. Cancer incidence was determined through linkage to the Florida Cancer Data System, a statewide cancer registry estimated to capture 98% of cancers in Florida residents. No pathological verification of cancer diagnoses was undertaken. A total of 970 male and 52 female cases of cancer were identified; 6.7% of the cohort were lost to follow-up. Male firefighters had significantly increased incidence rates of cancers of the bladder (SIR, 1.29; 95% CI: 1.01–1.62), testis (SIR, 1.60; 95% CI: 1.20–2.09), and of the thyroid (SIR, 1.77; 95% CI: 1.08–2.73). Female firefighters had significantly increased incidence rates of overall cancer (SIR, 1.63; 95% CI: 1.22–2.14), cervical (SIR, 5.24; 95% CI: 2.93–8.65) and thyroid cancers (SIR, 3.97; 95% CI: 1.45–8.65), and Hodgkin disease (SIR, 6.25; 95% CI: 1.26–18.26).

2.2 Case–control studies

Case–control studies have been used to examine the risk of firefighting and its association with various types of cancers. In all but one of these studies, ten or fewer firefighters were included in the case and/or control group. Several studies combined broad occupational categories with heterogeneous exposures such as firefighter and fireman, with the latter not necessarily working as a firefighter. These types of studies may result in exposure misclassification. Even within specific occupational groups such as firefighters, all would not have the same intensity or type of exposures. The

versus 'never' employed as a firefighter were 4.3 (95% CI: 0.7–30.5, four cases and three controls); for working as a firefighter ≥ 10 years, 3.0 (95% CI: 0.2–45.5, two cases and two controls); and for employment ≥ 5 years before the 'reference' date [date of diagnosis], 3.1 (95% CI: 0.4–24.4, three cases and three controls).

Bates (2007) also evaluated 70 firefighters diagnosed with cancer of the testis (SEER code 28020, cohort described above for cancer of the kidney), and found an adjusted OR of 1.54 (95% CI: 1.18–2.02).

Gaertner *et al.* (2004) reported on incident cases of bladder cancer with a histological confirmation, identified through the National Enhanced Cancer Surveillance System programme in seven Canadian provinces. The cases were adults aged 20–74, identified during 1994–1997 and interviewed 2–5 months after diagnosis. Random selections of population controls were included in the programme by frequency-matching age and gender to all cancer cases. Random digit dialling was used during the 1996 calendar year to recruit controls living in Newfoundland and Alberta, while all other provinces used a random sample from the provincial health insurance database. Native Indians and subjects in the military were excluded from the study. Mailed questionnaires with telephone follow-up, as necessary, were used to gather data regarding sociodemographics, occupational history, smoking history, dietary habits, and specific agent exposures. The response rates for the male and female bladder cancer cases were 66% and 72%, respectively, and for the controls, 59% and 65%, respectively. The overall analysis included 887 cases and 2847 controls. In the analysis of firefighters, eight male cases and 13 male controls were considered. the Standardized Occupational Classification system was used to code occupations, with up to 12 occupations coded per person. Data analysis also included demographic information provided from the interviews. An unconditional logistic regression analysis was used adjusting for age, province, race, smoking, ex-smoking, and consumption of fruit, fried food, and coffee. For the analysis of 'ever' or 'never' worked as a firefighter for more than one year, an elevated OR of 1.51 (95% CI: 0.59–3.84) was found. When stratified by duration of employment as a firefighter, the ORs were: 2.0 (95% CI: 0.43–9.49) for > 1–5 years (three cases and four controls); 0.86 (95% CI: 0.708–8.93) for > 5–15 years (one case and three controls); and 1.36 (95% CI: 0.36–5.16) for > 15 years (four cases and six controls).

Bates (2007) assessed 174 firefighters diagnosed with cancer of the bladder (SEER code 29010, cohort described above for cancer of the kidney and Table 2.6), and found an adjusted OR of 0.85 (95% CI: 0.72–1.00).

2.2.2 *Cancer of the brain*

Four studies on brain cancer in relation to firefighting were considered, all from the USA (Tables 2.4 and 2.6).

Brownson *et al.* (1990) evaluated brain cancers using the Missouri Cancer registry. Cancer cases from public and private hospitals have been collected since 1972, and reporting has been mandated since 1984. The group of cases comprised Caucasian

Hansen (1990) performed a study of Danish firefighters employed at the time of the 1970 national census. An analysis was then conducted of 57 deaths (21 from cancer) during 1970–1980 occurring among 886 males who had reported employment as firefighter. Men employed in similar occupations were used as the reference group, and an excess of lung cancer among firefighters over the age of 60 was reported, based on small numbers.

Ma *et al.* (1998) conducted a further analysis of a data set collected by Burnett *et al.* (1994) with additional years of follow-up using 1984–1993 death certificate data from 24 states in the USA. A total of 6607 deaths and 1883 cancer deaths among firefighters were identified based on the occupational titles on death certificates. Race-specific cancer mortality odds ratios (MORs) were calculated with all non-cancer deaths as the reference group. Analyses were adjusted for age and year of death. Among caucasian male firefighters, significant excesses were observed for cancers of the lip, pancreas, lung, prostate, kidney, and soft-tissue sarcoma and non-Hodgkin lymphoma. Among black male firefighters, significant excesses were observed for cancers of the nasopharynx, colon, prostate, and brain.

2.3.2 *Descriptive studies with firefighter results.*

There is a large body of descriptive epidemiology carried out for the purpose of occupational cancer and mortality surveillance. The results of these studies are summarized in Table 2.8.

Berg & Howell (1975) examined the risk of colorectal cancer by occupation using death certificate data from the USA and the United Kingdom and observed an excess among firefighters. [The Working Group noted that there was an overlap between the United Kingdom data included in this study and the meta-analysis by Dubrow & Wegman, 1983].

Williams *et al.* (1977) observed excesses of oral cancer, lung cancer, bladder cancer, and non-Hodgkin lymphoma based on the small number of cancers among firefighters that were included in the Third National Cancer Survey, USA. [The Working Group noted that Williams *et al.* (1977) was included in the meta-analysis conducted by Dubrow & Wegman (1983), but was unique in that occupation was ascertained by interview.]

Dubrow & Wegman (1983) summarized the results of ten early USA and United Kingdom studies and reported the results that appeared to be most consistent between the studies. Among those studies that reported results for firefighters, large intestine cancer and multiple myeloma were significantly elevated.

Morton & Marjanovic (1984) examined the incidence of leukaemia by occupation in the Portland–Vancouver metropolitan area in North-western USA, and excesses were observed among firefighters based on very small numbers.

Mortality among a cohort of 293 958 United States military veterans was examined by occupation and industry (Blair *et al.*, 1985). Usual occupation and industry as well as smoking information was determined from questionnaires

completed in 1954 and 1957, and 107 563 deaths were recorded during 1954–1970. Excesses of rectal, bladder, and brain cancers were observed based on very small numbers.

Gallagher *et al.* (1989) conducted a study of mortality by occupation and industry using death certificate data during 1950–1984 from the Canadian province of British Columbia. There were 1202 deaths among firefighters identified based on occupational titles on death certificates. PMRs were calculated with adjustment for 5-year age and calendar period. There were 197 cancer deaths, and a small excess of overall cancer as well as a significant excess of pancreatic cancer was observed.

In the USA, Sama *et al.* (1990) examined cancer incidence among firefighters using the Massachusetts Cancer Registry records for 1982–1986. Employment as a firefighter was based on the usual occupation reported to the Registry. The analysis was restricted to 315 Caucasian male firefighters. Case–control analyses were conducted for nine different cancer types and two 'unexposed' reference populations were used: policemen and statewide males. Standardized morbidity odds ratios (SMORs) were calculated and significant excesses of malignant melanoma and bladder cancer were observed compared to the general population. Excesses of bladder cancer and non-Hodgkin lymphoma were observed when compared to policemen.

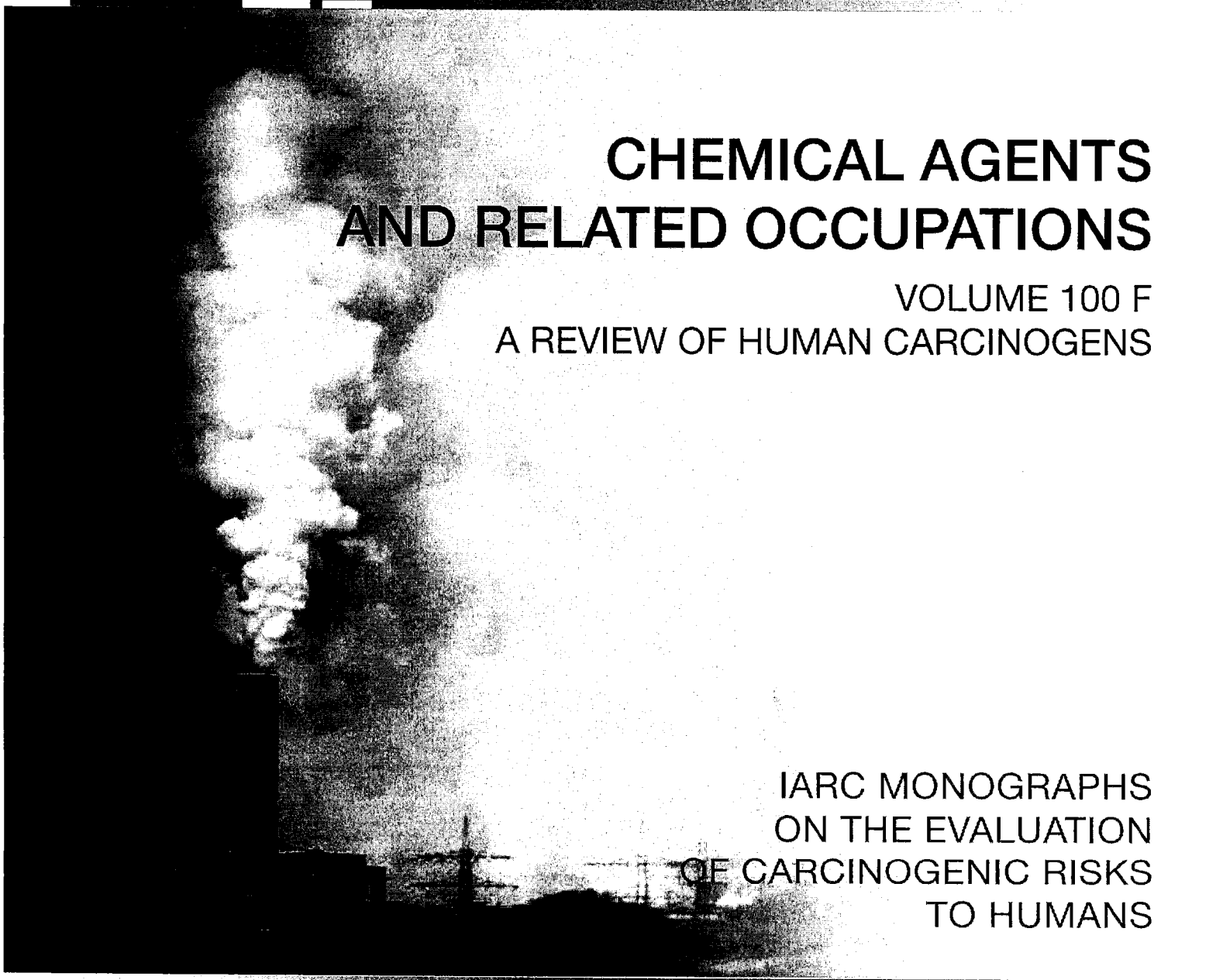
An analysis of deaths in England and Wales (1979–1980 and 1982–1990) were examined by occupation (OPCS, 1995). A total of 2968 deaths among male firefighters and 16 deaths among their female counterparts were observed based on the last occupation listed on death certificates. Only statistically significant results were reported, and excesses of oesophageal, stomach, and gall bladder cancer mortality were observed among men.

A follow-up study was conducted in the Finnish working-age population identified in the 1970 census (Pukkala, 1995). A total of 1436 male firefighters were identified during the follow-up period during 1971–1985 through linkage with the Finnish tumour registry. No statistically significant excesses were observed. The largest excess reported was for non-localized prostate cancer.

In Canada, Finkelstein (1995) examined occupations associated with lung cancer using a case–control study based on death certificates in two Ontario cities, and observed an excess among firefighters based on small numbers.

Milham (1997) conducted a study of mortality by occupation and industry using death certificate data (1950–1989) from the state of Washington, USA. A total of 2266 deaths among firefighters were identified based on the occupational titles on death certificates. PMRs were calculated and adjusted by 5-year age group and calendar period. There were 197 cancer deaths and a small excess of overall cancer was observed as well as significant excesses of melanoma and lympho- and reticulosarcoma. [The Working Group noted that there was an overlap between this and the multistate studies conducted by NIOSH, but that this had the longest follow-up period and was the earliest study of its kind in North America.]

IARC MONOGRAPHS



CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

Specific remarks about some of the agents reviewed in this volume

Four aromatic amines (4-aminobiphenyl, benzidine, 2-naphthylamine, *ortho*-toluidine) and two related industrial processes (auramine production, magenta production) were re-affirmed as Group-1 carcinogens based on *sufficient evidence* that they cause cancer of the urinary bladder in humans. The Group-1 classification of dyes metabolised to benzidine was based on *sufficient evidence* of carcinogenicity for some of these dyes in experimental animals and strong mechanistic evidence indicating that the metabolism of these dyes leads to the release of free benzidine – a re-affirmed Group-1 carcinogen – and to the subsequent induction of chromosomal aberrations in all experimental animal species studied, and in humans exposed to these dyes. Likewise, the Group-1 classification of 4,4′-methylenebis(2-chloroaniline) was based on *sufficient evidence* of carcinogenicity in experimental animals and strong mechanistic evidence, indicating that the toxicological profile of this genotoxic amine is similar to that of *ortho*-toluidine (a re-affirmed Group-1 carcinogen), that it forms DNA adducts in human urothelial cells *in vitro* and haemoglobin adducts in the blood of exposed workers, and that it causes cytogenetic alterations in urothelial cells and lymphocytes of exposed workers.

Exposure to polycyclic aromatic hydrocarbons (PAHs) causes cancers of the skin and lung in humans. Although there are no epidemiological studies of benzo[*a*]pyrene as a single exposure, it is carcinogenic in numerous animal species. There is mechanistic evidence indicating that benzo[*a*]pyrene is metabolized to highly reactive diolepoxides that form covalent DNA adducts, which have been shown to induce mutations in the K-*RAS* oncogene and the *TP53* tumour-suppressor gene in human lung tumours, and in corresponding genes in lung tumours in mice. Exposures to benzo[*a*]pyrene and benzo[*a*]pyrene-containing complex mixtures also induce cytogenetic alterations, DNA breakage, oxidative DNA lesions, and specific mutations in oncogenes and tumour-suppressor genes, all of which can contribute to the carcinogenic effects of benzo[*a*]pyrene and benzo[*a*]pyrene-containing complex mixtures in exposed humans. This consistent and coherent mechanistic evidence from experimental and human studies provides biological plausibility to support the overall classification of benzo[*a*]pyrene as a Group-1 carcinogen.

Two PAH-containing mixtures (chimney soot, coal-tar pitch), and occupational exposures in four PAH-related industries (coal-tar distillation, coal gasification, coke production, aluminium production) were confirmed as Group-1 carcinogens.

Workers in the rubber-manufacturing industry have an increased risk for leukaemia, lymphoma, and cancers of the urinary bladder, lung, and stomach. Due to the diversity and complexity of the exposures during rubber-manufacturing, the Working Group – like the previous one three decades ago (*IARC Monograph* Volume 28, 1982) – could not identify specific causative agents. However, there continues to be strong evidence of genotoxic and cytogenetic effects in workers in this industry.

There is consistent evidence that untreated or mildly treated mineral oils cause cancer of the skin, specifically of the scrotum, in humans. The association is highly unlikely to be due to chance, bias, or confounding, given the large case series, supportive epidemiological evidence, the rarity of scrotal cancer, and the intensity of exposure during the period of interest. Despite the fact that a significant proportion of workers exposed occupationally to mineral oils and shale oils are women, epidemiological studies established a statistically significant risk only for skin cancer in the scrotum, because of the extreme rarity of this type of cancer at this site. This observation does not imply that the skin-cancer hazard is restricted to males.

3.8 Buccal pouch application

Repeated application of benzo[*a*]pyrene to the buccal pouch mucosa of male hamsters resulted in a high incidence of forestomach papillomas (Solt *et al.*, 1987).

3.9 Subcutaneous tracheal grafts transplantation

In one study conducted in rats transplanted with subcutaneous rat tracheal grafts exposed to beeswax pellets containing various amounts of benzo[*a*]pyrene, a high incidence of squamous-cell carcinomas was reported (Nettesheim *et al.*, 1977).

3.10 Intramammilary administration

In three studies in rats, benign and malignant mammary gland tumours developed after intrammilary injection of benzo[*a*]pyrene (Cavalieri *et al.*, 1988a, b, 1991).

3.11 Intracolonic instillation

In three experiments in mice, intracolonic instillation of benzo[*a*]pyrene induced lymphomas and a variety of benign and malignant tumours in various organs including the forestomach (Toth, 1980; Anderson *et al.*, 1983).

3.12 Intravaginal application

Intravaginal application of benzo[*a*]pyrene in mice produced invasive cervical carcinoma; no such tumours were seen in controls (Näslund *et al.*, 1987).

3.13 Intrafetal injection

In one study in male and female Swiss mice, intrafetal injection of benzo[*a*]pyrene produced lung adenomas (Rossi *et al.*, 1983).

4. Other Relevant Data

Benzo[*a*]pyrene is a carcinogen that induces tumours in many animal species. Some of the examples relevant for this review are: lung tumours in mice, rats, and hamsters; skin tumours in mice; liver tumours in mice; forestomach tumours in mice and hamsters; and mammary gland tumours in rats (Osborne & Crosby, 1987; IARC, 2010). In humans, occupational exposures to benzo[*a*]pyrene-containing mixtures have been associated with a series of cancers: coke production: lung; coal gasification: lung, bladder; paving and roofing: lung; coal tar distillation: skin; soots: lung, oesophagus, haematolymphatic system, skin; aluminum smelting: lung, bladder; tobacco smoking: lung, lip, oral cavity, pharynx, oesophagus, larynx, bladder (IARC, 1984, 1985, 1986, 2010).

Class I Prod. of comb.

Studies on the mechanisms of action of benzo[*a*]pyrene have been reviewed (Xue & Warshawsky, 2005; IARC, 2010).

4.1 Metabolism

Benzo[*a*]pyrene is metabolized by both phase-I and phase-II enzymes to form a series of arene oxides, dihydrodiols, phenols, and quinones and their polar conjugates with glutathione, sulfate, and glucuronide (Osborne & Crosby, 1987). Benzo[*a*]pyrene-7,8-diol is a key metabolite that is formed by the action of epoxide hydrolase on benzo[*a*]pyrene-7,8-epoxide. This dihydrodiol can be further metabolized by cytochrome P450s (CYPs) to a series of benzo[*a*]pyrene-7,8-diol-9,10-epoxides, which form one class of ultimate carcinogenic metabolites of benzo[*a*]pyrene.

both in the absence and presence of an exogenous metabolic activation system.

Chemical analyses of high-temperature coal-tar pitches identified several polycyclic aromatic hydrocarbons that are genotoxic and carcinogenic in experimental studies (IARC, 1985). These include benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, dibenz[*a,h*]anthracene, chrysene, and indeno[1,2,3-*cd*]pyrene (IARC, 1983, 2010). These polycyclic aromatic hydrocarbons may contribute to the genotoxic and tumorigenic activities of coal-tar pitches.

4.1.2 Humans

DNA strand-breaks (measured by single-cell gel electrophoresis; comet assay) and the 8-oxo-deoxyguanosine/deoxyguanosine (8-oxo-dG/dG) ratio (measured by means of HPLC with electrochemical detection) were determined in peripheral blood leukocytes of roofers exposed to dust from coal-tar pitch (coal tar) during removal of existing roofs before applying hot asphalt. When the workers were stratified by 1-hydroxypyrene excretion in the urine, the amount of DNA strand-breaks in their leukocytes increased, and the 8-oxo-dG/dG ratio decreased in a dose-dependent manner (Toraason *et al.*, 2001).

4.2 Synthesis

There is strong evidence from experimental data that coal-tar pitch has a genotoxic mechanism of action. There is moderate evidence in humans for a genotoxic mechanism underlying the effects of exposures during roofing and paving with coal-tar pitch, based on one study.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of coal-tar pitch as encountered in paving and roofing. Coal-tar pitch as encountered in paving and roofing causes cancer of the lung.

Also, a positive association has been observed between exposure to coal-tar pitch as encountered in paving and roofing, and cancer of the bladder.

There is *sufficient evidence* in experimental animals for the carcinogenicity of coal-tar pitch.

There is strong evidence from experimental data that coal-tar pitch has a genotoxic mechanism of action. There is moderate evidence in humans for a genotoxic mechanism underlying the effects of exposures during roofing and paving with coal-tar pitch, based on one study.

Coal-tar pitch is *carcinogenic to humans (Group 1).*

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investigated to explain some of the variation in micronucleus formation. The sweeps did not have higher frequencies of micronuclei in either cell type when the results were adjusted for age and smoking, and there was no association between years of work and micronucleus formation (Carstensen *et al.*, 1993).

The same group of workers was studied for the presence of aromatic DNA adducts and micronuclei, and also genotyped for *CYP1A1* and *GST1*. While no specific DNA adducts were identified, the sweeps had higher total DNA-adduct levels in white blood cells, but the increase was not statistically significant. There were no systematic differences in DNA-adduct patterns between the sweeps and the controls. DNA adducts in sweeps were moderately but statistically significantly correlated with micronuclei in both T- and B-lymphocytes. The correlation between adduct-levels and micronuclei was most marked in T-lymphocytes of individuals lacking the *GST1* gene (Ichiba *et al.*, 1994).

Groups of 45 Swedish chimney sweeps and 49 controls were investigated for micronucleus formation in blood lymphocytes stimulated by phytohaemagglutinin or pokeweed mitogen, and by analysis of lymphocyte subgroups and neutrophilic leukocytes. There were higher frequencies of micronuclei among sweeps than in controls, with both methods of stimulation. The effect on micronucleus formation in lymphocytes was more significant in cells stimulated with pokeweed mitogen, suggesting that the T4 lymphocytes were preferentially damaged by the occupational exposure (Holmén *et al.*, 1994).

Analysis of *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adducts in a group of 19 chimney sweeps showed that four of them (21%) had adduct levels exceeding the 95 percentile control-subject value (Pavanello *et al.*, 1999a). These higher levels were associated with the lack of GSTM1 activity: three of the chimney sweeps had the *GSTM1* *0/*0 genotype (Pavanello *et al.*, 1999b).

4.2 Synthesis

Extracts of soots contain carcinogenic polycyclic aromatic hydrocarbons and are genotoxic. Based on a small number of genotoxicity studies in exposed humans, there is moderate evidence of a genotoxic mode of action for the carcinogenic hazards associated with occupational exposures as a chimney sweep. The detection of *anti*-benzo[*a*]pyrene-7,8-diol-9,10-epoxide-DNA adducts in the peripheral blood lymphocytes of chimney sweeps suggests involvement of benzo[*a*]pyrene in the genotoxic effect of this exposure in humans.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of soot as found in occupational exposure of chimney sweeps. Soot, as found in occupational exposure of chimney sweeps, causes cancer of the skin (observed in the scrotum), and of the lung.

Also, a positive association has been observed between exposure to soot as found in occupational exposure of chimney sweeps and cancer of the bladder.

There is *inadequate* evidence in experimental animals for the carcinogenicity of soot.

There is *sufficient evidence* in experimental animals for the carcinogenicity of soot extracts.

Extracts of soots contain carcinogenic polycyclic aromatic hydrocarbons and are genotoxic. Based on a small number of genotoxicity studies in humans there is moderate evidence for a genotoxic mechanism for occupational exposures as a chimney sweep.

Soot as found in occupational exposure of chimney sweeps is *carcinogenic to humans (Group 1).*

2.1 Cancer of the urinary bladder

A large cohort study from Québec, Canada (Gibbs *et al.*, 2007) showed an excess of bladder-cancer mortality with a statistically significant linear trend with cumulative exposure to benzo[*a*]pyrene B[*a*]P (see Table 2.1, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-17-Table2.1.pdf). The excess risk was evident only in workers who had been first employed before 1950, and smaller risks were noted in those first employed later (Gibbs & Sevigny, 2007a, b). An increased risk for bladder cancer and a significant exposure-response trend was found in a cohort study from British Columbia, Canada (Spinelli *et al.*, 2006; Friesen *et al.*, 2007). Both Canadian studies derived smoking-adjusted risk estimates. A significant excess for bladder cancer with a positive exposure-response trend was also found in a study of a Norwegian aluminium smelter (Romundstad *et al.*, 2000). Supporting evidence of a bladder-cancer excess comes from cohort studies from France (Mur *et al.*, 1987; Moulin *et al.*, 2000) and the United States of America (USA) (Rockette & Arena, 1983). A recently reported cohort study from Australia showed no excess of bladder cancer, although the follow-up was relatively short (Friesen *et al.*, 2009; Sim *et al.*, 2009). No bladder-cancer excess was found in a Swedish study (Björ *et al.*, 2008).

2.2 Cancer of the lung

An excess of lung cancer in aluminium-production workers has been reported although the data were less consistent than for bladder cancer. The large Quebec cohort showed a smoking-adjusted excess of lung cancer with an exposure-response trend (Gibbs *et al.*, 2007; Gibbs & Sevigny, 2007b; Armstrong & Gibbs, 2009). An excess of lung cancer, but no clear trend, was noted in the Swedish cohort (Björ *et al.*, 2008). The cohort from British Columbia Canada showed no overall excess of lung cancer, but a trend with increasing cumulative exposure to B[*a*]P (Spinelli *et al.*, 2006; Friesen *et al.*, 2007). The Australian cohort showed no excess but a positive trend with exposure to dust, but not to B[*a*]P (Friesen *et al.*, 2009; Sim *et al.*, 2009). No excess of lung cancer was evident in the studies from France (Mur *et al.*, 1987; Moulin *et al.*, 2000), Norway (Romundstad *et al.*, 2000) or the USA (Rockette & Arena, 1983).

2.3 Synthesis

Overall, the cohort studies strongly support an association between work in aluminium smelters and bladder-cancer risk. Confounding or chance is not likely to explain the findings. There is an increased risk for cancer of the bladder from occupational exposure in aluminium smelters.

An increased risk for lung cancer has been found in several but not all epidemiological studies in the aluminium-production industry. Some studies also show a dose–response trend in terms of B[*a*]P–years. Confounding from smoking or chance is not likely to explain the findings. Based on these observations, there is evidence that risk for cancer of the lung is causally associated with work in aluminium smelters.

The exposure circumstances, especially levels of PAH in aluminium smelters, vary between industrial departments and also depend on the process used. However, data are not sufficient to disentangle the cancer risks associated with these different exposure situations.

3. Cancer in Experimental Animals

Two samples of airborne particulate polynuclear organic matter were collected from two sites in an aluminium-production plant. Each sample was tested by topical application of 50 mg in toluene (1:1) twice weekly to the skin of twenty C3H mice. Samples containing 0.11% and

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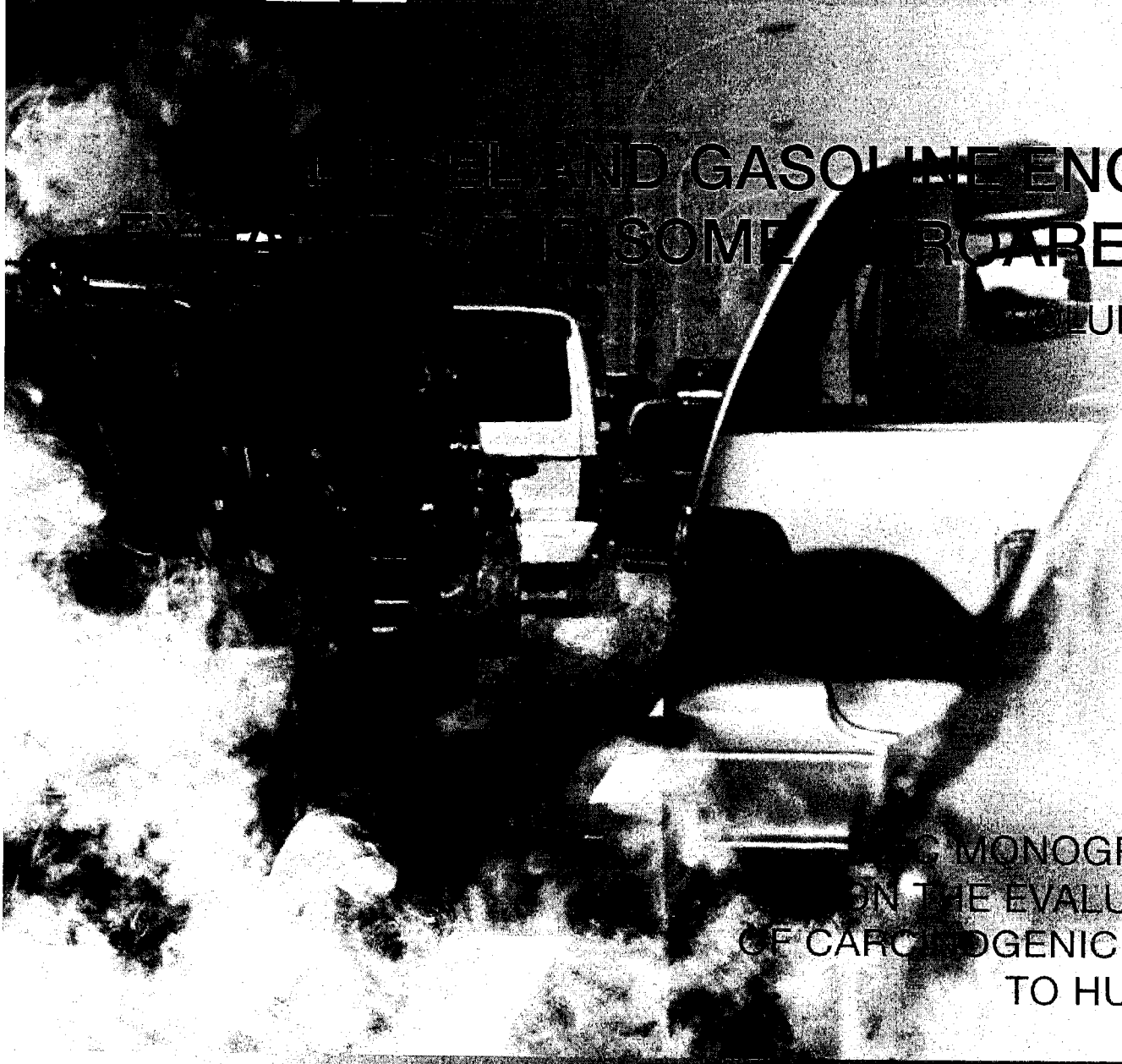

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TO HUMANS

International Agency for Research on Cancer
World Health Organization

who were employed 1900–94. In Copenhagen, the first diesel-powered buses were introduced in 1936, but, during the Second World War, all buses were fuelled with gasoline. Diesel-powered buses gradually replaced gasoline-powered models after that time, and, in the 1960s, they also replaced the trams. Cancer rates were compared with those of the general population of Denmark by linkage to the Danish Cancer Registry and National Death Index to identify cancers that occurred after 1943. Among male workers employed for 3 months or longer, the standardized incidence ratio was 1.6 (95% CI, 1.5–1.8; 473 cases) for lung cancer, 1.0 (95% CI, 0.8–1.3; 82 cases) for stomach cancer, 1.2 (95% CI, 1.0–1.5; 105 cases) for rectal cancer, 1.4 (95% CI, 1.0–1.9; 39 cases) for laryngeal cancer, 1.6 (95% CI, 1.3–1.6; 83 cases) for kidney cancer, 1.4 (95% CI, 1.2–1.6; 177 cases) for urinary bladder cancer, 1.9 (95% CI, 1.2–2.8; 22 cases) for pharyngeal cancer and 1.1 (95% CI, 0.8–1.5; 46 cases) for leukaemia. In women, the standardized incidence ratio for lung cancer was 2.6 (95% CI, 1.5–4.3; 15 cases). In both men and women, a greater risk of lung cancer was observed with longer time since first employment. No trend in lung cancer risk was found based on periods of predominantly gasoline or diesel vehicle use, and the risks were similarly elevated for workers who started before, at the onset, or during the use of diesel buses. [The Working Group noted that no information on specific exposures or tobacco smoking was available and the periods of diesel and gasoline emissions overlapped. Compared with other men in Copenhagen, the smoking rates among the bus drivers were slightly higher during some time periods, suggesting the possibility of some confounding by smoking.]

A nested case–control study (Soll-Johanning *et al.*, 2003) was conducted with 153 cases of lung cancer and 84 cases of urinary bladder cancer included in the cohort of Copenhagen bus drivers and tramway employees. The cases and controls or next of kin were interviewed regarding tobacco smoking history. Deaths from cancer or non-neoplastic respiratory disease were excluded from the control group and cases and controls were matched on date of birth. Both 10-year lag and no lag models, based on duration of employment, were assessed, adjusting for smoking history in seven categories based on pack–years. No consistent increase in lung cancer risk was observed based on categories of duration of employment in either lag model. The risk, although not statistically significant, increased with greater number of years of employment, but then decreased after > 20 years. With a 10-year exposure lag, there was a suggestion of an increased risk for urinary bladder cancer in persons with 10– < 20 years of work (relative risk, 1.61; 95% CI, 0.57–4.55).

In the cohort study described in Section 2.2.1, Guo *et al.* (2004a) reported on lung cancer risk in male bus drivers who had exposure to both gasoline and diesel exhausts; the standardized incidence ratio was not significantly elevated (SIR, 0.89; 95% CI, 0.78–1.00; 253 cases). [The Working Group noted that this study was limited due to the lack of detailed work histories relating to exposures to exhaust and information on tobacco smoking.]

In a separate report, Guo *et al.* (2004b) presented data for other cancers in bus drivers. The risk was elevated for urinary bladder cancer (SIR, 1.29; 95% CI, 1.02–1.62; 75 cases), oesophageal cancer (SIR, 1.10; 95% CI, 0.60–1.85; 14 cases), kidney cancer (SIR, 1.29; 95% CI, 1.00–1.64; 67 cases) and leukaemia (SIR, 1.04; 95% CI, 0.68–1.51; 27 cases). [The Working Group noted that this study was limited due to the lack of detailed work histories relating to exposures to exhaust and information on tobacco smoking.]

Petersen *et al.* (2010) studied the cancer incidence in a cohort, established in 1978, of 2037 male Danish urban bus drivers over a 25-year period of follow-up (1979–2003). In 1978, public bus drivers in the three largest cities of Denmark received a mailed questionnaire on occupational

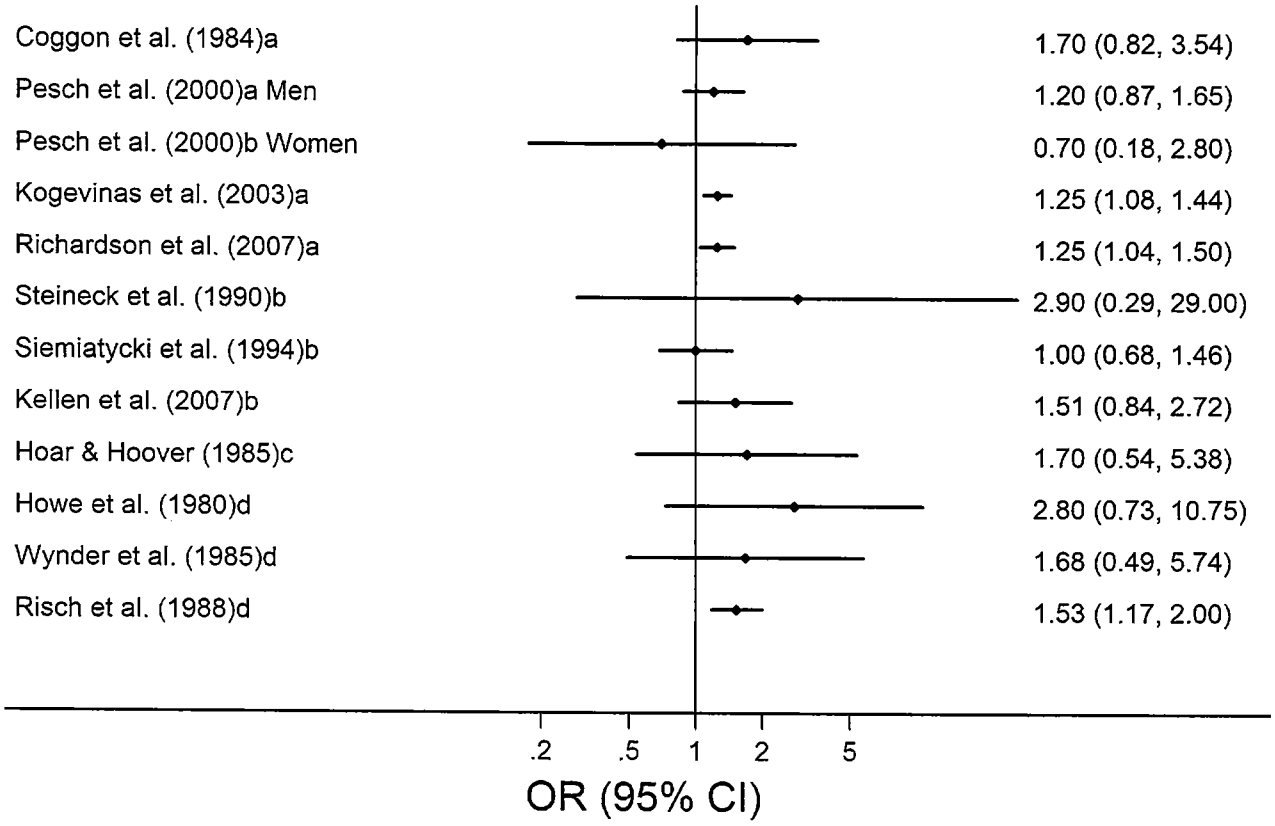
carcinogens showed similar results. Analysis of risk among never-smokers also showed an increased odds ratio in the highest quartile of cumulative exposure to diesel exhaust (OR, 1.26; 95% CI, 0.90–1.78). A positive and significant trend with duration of exposure was observed among those exposed to low ($P < 0.01$) and high levels ($P < 0.01$) of diesel motor exhaust. The risk estimates were similar for population-based and hospital-based case–control studies, and no significant heterogeneity for the effect of diesel motor exhaust in the highest quartile of cumulative exposure was found across studies ($P = 0.29$). [The Working Group noted that this study was based on a very large data set with detailed information on job histories and smoking habits. Exposure was coded in a standardized manner by the application of a JEM, although temporal changes in exposure were not taken into account. Although this study base partially overlapped with some earlier publications, these present findings were considered to be independent in so far as a new exposure assessment was used. The association between exposure to diesel motor exhaust and the risk for lung cancer reported here probably could not be explained by bias or confounding.]

Pintos *et al.* (2012) reported an expansion (Montreal II) of an earlier case–control study from the Montreal area, Canada (Siemiatycki *et al.*, 1987; Parent *et al.*, 2007; Montreal I), and covered the findings from Montreal I and Montreal II, as well as those from the pooled data set. Cancer cases were identified from area hospitals and population controls were recruited from electoral lists. Subjects or proxies were interviewed regarding lifetime occupational history, including data on work site and work tasks, and several other risk factors, including tobacco smoking. Exposure to diesel exhaust and several other occupational exposures were coded by expert assessment which was improved in relation to the method employed in the original study (Siemiatycki *et al.*, 1987). Odds ratios were adjusted for age, ethnicity, level of education, socioeconomic status, smoking, respondent status and occupational carcinogens. Study I (sampled in 1979–86) comprised 857 cases and 533 population controls; study II (sampled in 1996–2001) comprised 736 cases and 894 population controls, all of whom were men. An increased odds ratio of 1.34 (95% CI, 1.1–1.7) was found for subjects ever-exposed versus those never-exposed to diesel motor exhaust; for substantial cumulative exposure, the odds ratio was 1.80 (95% CI, 1.3–2.6). The findings were essentially similar for study I and study II when analysed separately. An analysis of risk in relation to histological type of lung cancer showed that the risks were more pronounced for squamous cell carcinomas (OR, 2.09; 95% CI, 1.3–3.2) for ever exposure to substantial levels of diesel exhaust but were lower for adenocarcinomas (OR, 1.17; 95% CI, 0.7–1.9). An intermediate risk was reported for small cell carcinomas (OR, 1.52; 95% CI, 0.8–2.7). A previous analysis based on the subjects in study I (Parent *et al.*, 2007) investigated the risk of lung cancer in relation to diesel exhaust and gasoline exhaust. No excess risk was found with exposure to gasoline exhaust. [The Working Group noted that this large study showed an increased risk of lung cancer after occupational exposure to diesel motor exhaust. A detailed exposure assessment and adjustment for potential confounders was applied, and the findings were internally consistent between the two sampling periods. The study showed a stronger effect for squamous cell carcinoma than for other histological types.]

2.3.2 Cancer of the urinary bladder

Numerous case–control studies that evaluated the risk for urinary bladder cancer and potential occupational exposure to diesel or motor exhaust were identified. The major limitation of the studies reviewed was the small number with well characterized exposure to

Fig. 2.1 Case–control studies of urinary bladder cancer with odds ratios for the highest exposure to diesel exhaust



a Job–exposure matrix
b Expert assessment
c Proxy
d Combined jobs
CI, confidence interval; OR, odds ratio

diesel or gasoline exhaust. A few studies used JEMs or experts to assess exposure, while others provided risk estimates for exposure to diesel exhaust for combined occupations based only on job titles or proxy exposure, and a large number of studies reported risk estimates for occupations that had potential for exposure to diesel exhaust. These studies are discussed in Section 2.3.2(a–c), and are summarized in Table 2.3. Odds ratios are plotted in Fig. 2.1. The use of expert or JEM assessment of exposure to diesel exhaust increased the probability of distinguishing exposed workers from unexposed workers, and these studies were most influential in the evaluation of risks for urinary bladder cancer. Studies that used job titles alone as a surrogate for exposure to diesel exhaust were less informative with regard to specific exposure to diesel or gasoline exhaust; however, some studies that provided a more focused analysis of HGV drivers were given more weight. Studies that reported risk estimates for specific occupations are described by occupation in Table 2.4, and the findings across studies are briefly discussed in Section 2.3.2(d). The odds ratios for urinary bladder cancer by occupational title are plotted in Fig. 2.2–2.7.

duration of employment as an HGV driver, and Pesch *et al.* (2000), which used a different JEM to assess exposure to exhaust, these studies were not reviewed independently because their findings were captured in the pooled analyses. The analysis included 3346 male incident cases and 6840 male controls, aged 30–79 years. Controls from populations and hospitals were matched to the cases on age and geographical area. Information on every job held for more than 6 months was available from 10 studies and for the longest-held job from one study. The FINJEM was applied to evaluate exposure to diesel exhaust. Risk estimates were calculated by job duration, calendar year of first employment and age at diagnosis for all occupations with at least 10 subjects; individuals never employed in the occupation or any of the a-priori defined high-risk occupations were used as the unexposed population. Odds ratios were adjusted for age, tobacco smoking and study centre. Associations with diesel exhaust were presented in graphical form (Fig. 2.1), which showed an odds ratio of approximately 1.25 (95% CI, ~1.05–1.4) for urinary bladder cancer among subjects with the highest tertile of exposure to diesel exhaust compared with the unexposed; odds ratios were less than 1.0 for medium and low exposure to diesel exhaust. [The Working Group noted that this was one of the more informative case–control studies for evaluating the potential risk for urinary bladder cancer from exposure to diesel exhaust because it was large and used high-quality exposure assessment. The number of exposed subjects in each diesel exhaust exposure category was not reported. The study provided some evidence for an association between exposure to diesel exhaust and the risk of urinary bladder cancer.]

Richardson *et al.* (2007) investigated the risks of exposure to specific chemicals using the same cancer registry database as an earlier study in British Columbia, Canada, which found an association between several occupations with potential exposure to diesel engine emissions and an excess incidence of urinary bladder cancer (Band *et al.*, 2005). Self-administered questionnaires were completed by 15 463 men (response rate, 60.1%), aged 20 years or older, diagnosed with cancer from 1983 to 1990. Complete occupational histories were available for 1062 cases of urinary bladder cancer (94% transitional cell carcinoma) and 8057 cancer controls, matched to cases by year of birth and year of diagnosis. Exposure to specific chemical agents, classified by IARC as definite or probable urinary bladder carcinogens, was assessed using the National Occupational Exposure Survey JEM, which predicts the probability of exposure to a specific substance in a specific job, based on walk-through assessments in a stratified sample of workplaces within the USA during 1981–83. Odds ratios were estimated after matching for age and year of diagnosis and adjusting for ethnicity, years of smoking, alcohol consumption and questionnaire responder. The odds ratios for urinary bladder cancer for ever and high cumulative exposure to diesel exhaust were 1.18 (95% CI, 1.04–1.35; 604 exposed cases) and 1.25 (95% CI, 1.04–1.49), respectively; a significant exposure–response trend was observed for cumulative exposure (P for trend = 0.01). [The Working Group noted that the advantages of this study were the use of a JEM to assess exposure specific for diesel exhaust and adequate power to evaluate an exposure–response relationship; however, the exposure assessment was not calendar year-specific and was based on occupational data collected over a 3-year period in a different country. Despite its limitations, the study added some support for an association between urinary bladder cancer and exposure to diesel exhaust.]

and matched to cases by sex, age and area of residence. Analyses were performed on 826 cases and 792 controls who completed interviews, during which structured questionnaires were used to obtain information on 26 occupations and exposures to 18 substances. Among men, elevated risks of urinary bladder cancer, adjusted for year of birth and lifetime tobacco smoking, were observed for ever employment (OR, 1.53; 95% CI, 1.17–2.00), employment for 8–18 years before diagnosis (OR, 1.69; 95% CI, 1.24–2.31) and for every 10 years of duration of employment (OR, 1.23; 95% CI, 1.08–1.41) in jobs that entailed contact with 'diesel or traffic fumes'. [The Working Group noted that no information was provided on which occupations were considered to entail exposure to diesel exhaust; this study has limited utility for the evaluation of the risk for cancer.]

Data from the American Health Foundation hospital-based, case–control study of tobacco-related neoplasms were used in two analyses of the relationship between exposure to diesel and traffic fumes and the risk for urinary bladder cancer (Wynder *et al.*, 1985; Iyer *et al.*, 1990). Both analyses included cases of histologically confirmed urinary bladder cancer diagnosed from 1981 to 1983 and controls with non-tobacco-related diseases (both malignant and non-malignant) at 18 hospitals located in six cities in the USA. [The Working Group was unsure whether the study populations overlapped.] The first analysis by Wynder *et al.* (1985) included 194 male cases and 582 controls matched by age, race, hospital and year of interview, and the second analysis by Iyer *et al.* (1990) included 136 cases and 272 controls matched for sex, age, race, hospital and year of interview. Occupational histories were obtained by in-person interviews using a structured questionnaire. In the first analysis, occupational exposure to diesel exhaust fumes was assessed for specific occupations (titles for usual employment) defined as entailing probable high exposure and for occupations with high, moderate and minimal probable exposure to diesel exhaust, based on the percentage of employees in a given occupation entailing exposure to diesel exhaust. The odds ratios were 1.0 or less for all specific occupations related to diesel exhaust, except for railroad workers (OR, 2.0; 95% CI, 0.34–11.61; two exposed cases) (Wynder *et al.*, 1985). The odds ratio for combined occupations with high probable exposure was 1.68 (95% CI, 0.49–5.73; four exposed cases). In the second analysis, occupations were grouped into low (referent), possible and probable categories of exposure to diesel exhaust according to an a-priori list of job titles. Self-reported exposure to diesel exhaust was also considered. The odds ratio was 1.24 (95% CI, 0.77–2.00; 41 exposed cases) for any exposure to diesel exhaust (including possible or probable exposure classified by job title and self-reported exposure). The odds ratios for possible and probably exposure considered separately were equivalent to unity or below. [The Working Group noted that both studies were limited by small numbers of cases and controls in the categories or occupations with a higher probability of exposure. Although these studies reported risk estimates for different categories of probable exposure to diesel exhaust, the categories appeared to be based on job titles only.]

Dolin & Cook-Mozaffari (1992) did not report an odds ratio because the only available estimate was for low exposure to diesel exhaust, and Pesch *et al.* (2000) reported no odds ratio because the authors reported results for 'exhaust' in general and not diesel exhaust.

(c) *Studies that reported risk estimates from job titles*

Numerous studies of occupation and the risk for urinary bladder cancer have found that reported risk estimates from job titles – either specific occupations or industries with potential exposure to diesel and/or engine exhaust – and comprised the following:

Population-based studies: these included a series of reports that analysed data from the US National Bladder Cancer Study in New Hampshire (Colt *et al.*, 2004), New England (Colt *et al.*, 2011) and Iowa (Zheng *et al.*, 2002), studies from Canada (Gaertner *et al.*, 2004), Limburg, Belgium (Kellen *et al.*, 2005; Reulen *et al.*, 2007) and New Zealand (Dryson *et al.*, 2008) with a similar study design, in which regional or local cancer registries were used to identify cases and matched controls were selected from the same geographical regions, a matched population-based case–control study in two industrial regions in Belgium (Schifflers *et al.*, 1987) and a case–control study in Copenhagen and surrounding areas (Jensen *et al.*,1987).

The US National Bladder Cancer Study was a population-based case–control study comprising all histologically confirmed cases of carcinoma of the urinary bladder diagnosed from 1978 to 1979 identified from 10 cancer registries that participated in the US NCI Surveillance, Epidemiology, and End Results Program. Findings that focused on occupations involving motor vehicles were reported separately for white men (Silverman *et al.*, 1989a), non-white men (Silverman *et al.*, 1989b) and white women (Silverman *et al.*, 1990). Silverman *et al.* (1986) reported findings that focused on motor-related occupations in white men (1909 cases and 3565 controls), and Smith *et al.* (1985) reported findings specific for automobile and HGV mechanics for all men (2108 controls and 4046 cases). Two studies reported findings separately by individual regions: Silverman *et al.* (1983) for men in Detroit and Schoenberg *et al.* (1984) for white men in New Jersey. [Although the latter four populations were included in the larger studies, they are included in the tables because they provided more detailed analyses.]

Studies with hospital or other cancer controls: these included three studies that identified cases of urinary bladder cancer and controls with other cancers from cancer registries in Missouri, USA (Brownson *et al.*, 1987; Brooks *et al.*, 1992), Detroit, USA (Burns & Swanson, 1991), British Columbia, Canada (Band *et al.*, 2005), and the United Kingdom (limited to men aged 18–54 years) (Coggon *et al.*, 1986), a study that used cancer and non-cancer controls (oral cancer or diseases) in Bombay, India (Notani *et al.*, 1993), and four studies that used non-cancer controls in La Plata, Argentina (Iscovich *et al.*, 1987), Spain (Spanish Bladder Study) (Samanic *et al.*, 2008), the USA (Decouflé *et al.*, 1977) and Texas, USA (Cassidy *et al.*, 2009). Brooks *et al.* (1992) reported risks for invasive urinary bladder cancer using the Detroit population.

Mortality studies: two studies that measured mortality were identified, including a study that used city directories and death certificates as a source for occupational information in Ohio, USA (Steenland *et al.*, 1998), and one that provided detailed analyses of HGV drivers in New Hampshire and Vermont, USA (Hoar & Hoover, 1985). For cancers that have higher survival rates, such as urinary bladder cancer, studies that report mortality are less informative than those that report incidence, because mortality studies overlook cases of cancer that do not result in death.

Several other studies of occupations with potential exposure to motor exhaust were identified, but were not reviewed because either the numbers of exposed cases were small (Bonassi *et al.*, 1989; Ahmad & Pervaiz, 2011) or no formal analyses of risk estimates were performed (Tola *et al.*, 1980; Yaris *et al.*, 2006).

The studies on occupational titles were the least informative to evaluate risks specific for exposure to gasoline or diesel exhaust, because job titles alone are a crude surrogate of exposure. Diesel engines were introduced into the workplace at various rates and at different times, and thus the confidence that the individual workers in the study were actually exposed to diesel exhaust was low. Other limitations included potential confounding from co-exposures to