MELANOMA CANCER

IARC SUPPLEMENT 7

PAGES 101, 142, 174, 175, 211, 323, 343, 355, AND 373

IARC 45

PAGES 92, AND 107

IARC 98

PAGES 399, 400, 401, 491, 508, 521, 526, AND 530

IARC 105

PAGES 231, 239 AND 241

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

1987

IARC 105 Chemical List
Found during FIRE'd
Overhaul

solution[1], and further reports have confirmed these findings[2-9]. In some instances, skin cancers have occurred in combination with other cancers, such as liver angiosarcoma (after six months' treatment with Fowler's solution giving a total intake of 0.24 g arsenic)[6], intestinal and bladder cancers[7] and meningioma[9]. Liver angiosarcomas have also been associated with medicinal exposure to arsenic[1,6,10].

Epidemiological studies of cancer following medical treatment with arsenic have shown an excess of skin cancers, but no clear association with other cancers has been obtained[1], as confirmed by a recent cohort study on individuals treated with Fowler's solution[11]. No relation was found between prostatic cancer and treatment of syphilis with arsenicals[12].

An association between environmental exposure to arsenic through drinking-water and skin cancer has been observed[1] and confirmed[13,14]; two cases of bladder cancer were also described, with latent periods of eight to 20 years[15]. The latent periods for two cases of skin cancer related to arsenic in drinking-water were 20 and 23 years, and the concentrations or uptake of arsenic were reported to be 1.2 and 1 mg per day, respectively, with an estimated total ingested dose of about 8 g in one study[14].

Epidemiological studies in areas with different frequencies of black-foot disease and where drinking-water contained 0.35-1.14 mg/l arsenic revealed elevated risks for cancers of the bladder, kidney, skin, lung, liver and colon in both men and women[16,17].

A case of liver angiosarcoma was reported in the 20-month-old child of an exposed worker living in the vicinity of a copper mine and smelter[18]. Four rather inconsistent studies describing the effect of air pollutants containing arsenic[1,19,20] were followed by further reports that indicated an effect on lung cancer incidence of arsenic in polluted air from smelters and pesticide production, with risk ratios of 2.0-2.5 near smelters[21,22]. Two further studies near smelters showed no clear effect[23,24].

Occupational exposure to inorganic arsenic, especially in mining and copper smelting, has quite consistently been associated with an increased risk of cancer[1]. A number of studies of smelter workers relate to populations that have been reported previously[1] and represent both partial[25-27] and total[28,29] updates. An almost ten-fold increase in the incidence of lung cancer was found in workers most heavily exposed to arsenic, and relatively clear dose-response relationships have been obtained with regard to cumulative exposure[29] and especially with 30-day ceiling levels[27]. Sulphur dioxide in the smelter environment appeared to play a minor role, if any, in the development of lung cancer[27]. Other forms of cancer were considered, but their incidences were not found to be consistently increased[28]. Other US smelter worker populations have been shown to have consistent increases in lung cancer incidence, as well as increases of about 20% in the incidence of gastrointestinal cancer and of 30% for renal cancer and haematolymphatic malignancies[30,31]. The observation in an earlier study of an increase in lung cancer risk among a population of Swedish smelter workers[1] has been confirmed, with a risk of six to eight fold among roasters[32].

A decrease in lung cancer risk after cessation of exposure to arsenic has been observed in some studies[30,33], possibly indicating a late-stage effect of arsenic[34,35].

With regard to histological type of lung cancer, a significant, relative excess of adenocarcinomas and a slight excess of oat-cell cancers were seen among smelter workers[36].

[11]Poirier, L.A., Kasprzak, K.S., Hoover, K.L. & Wenk, M.L. (1983) Effects of calcium and magnesium acetates on the carcinogenicity of cadmium chloride in Wistar rats. *Cancer Res., 43*, 4575-4581

[12]Takenaka, S., Oldiges, H., König, H., Hochrainer, D. & Oberdörster, G. (1983) Carcinogenicity of cadmium chloride aerosols in W rats. *J. natl Cancer Inst., 70*, 367-373

[13]Oldiges, H., Hochrainer, D., Takenaka, S., Oberdörster, G. & König, H. (1984) Lung carcinomas in rats after low level cadmium inhalation. *Toxicol. environ. Chem., 9*, 41-51

[14]Hoffmann, L., Putzke, H.-P., Kampehl, H.-J., Russbült, R., Gase, P., Simonn, C., Erdmann, T. & Huckstorf, C. (1985) Carcinogenic effects of cadmium on the prostate of the rat. *J. Cancer Res. clin. Oncol., 109*, 193-199

[15]Löser, E. (1980) A 2 year oral carcinogenicity study with cadmium on rats. *Cancer Lett., 9*, 191-198

[16]Shimkin, M.B., Stoner, G.D. & Theiss, J.C. (1978) Lung tumor response in mice to metals and metal salts. *Adv. exp. Med. Biol., 91*, 85-91

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

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

Product of Combustion
IARC 105-Chemical List

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

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].

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

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)

IARC 105 Chemical List
Exposure during overhaul

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].

References

[1]*IARC Monographs, 35*, 83-159, 1985

[2]*IARC Monographs, 34*, 37-64, 1984

[3]Kjuus, H., Andersen, A. & Langård, S. (1986) Incidence of cancer among workers producing calcium carbide. *Br. J. ind. Med., 43*, 237-242

[4]Silverstein, M., Maizlish, N., Park, R. & Mirer, F. (1985) Mortality among workers exposed to coal tar pitch volatiles and welding emissions: an exercise in epidemiologic triage. *Am. J. public Health, 75*, 1283-1287

[5]Robinson, M., Bull, R.J., Munch, J. & Meier, J. (1984) Comparative carcinogenic and mutagenic activity of coal tar and petroleum asphalt paints used in potable water supply systems. *J. appl. Toxicol., 4*, 49-56

[6]Niemeier, R.W., Thayer, P.S., Menzies, K.T., von Thuna, P., Moss, C.E. & Burg, J. (1987) *A comparison of the skin carcinogenicity of condensed roofing asphalt and coal tar pitch fumes.* In: Cooke, M. & Dennis, A.J., eds, *Proceedings of the 10th International Symposium on Polynuclear Aromatic Hydrocarbons, Chemistry, Characterization and Carcinogenesis*, Columbus, OH, Battelle, pp. 609-647

[7]*IARC Monographs, Suppl. 6*, 186, 1987

COAL-TARS (Group 1) ★

IARC 105 - Chemical List Found in Overhaul Phase

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

There have been a number of case reports of skin cancer in patients who used tar ointments for a variety of skin diseases[1,2]. A mortality analysis in the UK from 1946 showed a greatly increased scrotal cancer risk for 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 or coal-tar pitches (see p. 174)[1]. Several epidemiological studies have shown an excess of lung cancer among workers exposed to coal-tar fumes in coal gasification and coke production[3,4]. 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[5].

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

Coal-tars from blast furnaces, coke ovens and coal gasification plants, as well as pharmaceutical coal-tars, were tested for carcinogenicity by skin application in mice, producing skin tumours. Pharmaceutical coal-tars and tars from coal gasification plants also produced skin tumours when applied to the ears of rabbits. Pharmaceutical coal-tars applied to the skin of rats produced lung tumours but not skin tumours. Inhalation of tar from coke ovens produced benign and malignant lung tumours in mice and rats and skin tumours in mice[1,3,4].

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].

References

[1] *IARC Monographs, 26*, 217-235, 1981

[2] Boice, J.D., Greene, M.H., Keehn, R.J., Higgins, G.A. & Fraumeni, J.F., Jr (1980) Late effects of low-dose adjuvant chemotherapy in colorectal cancer. *J. natl Cancer Inst., 64*, 501-511

[3] Ferguson, T. (1980) Prevention and delay of spontaneous mammary and pituitary tumors by long- and short-term ingestion of 5-fluorouracil in Wistar-Furth rats. *Oncology, 37*, 353-356

[4] Habs, M., Schmähl, D. & Lin, P.Z. (1981) Carcinogenic activity in rats of combined treatment with cyclophosphamide, methotrexate and 5-fluorouracil. *Int. J. Cancer, 28*, 91-96

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

FORMALDEHYDE (Group 2A)

★ IARC IOS Chemical List. Found during FIRE, overhaul and IN diesel Exhaust.

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].

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

IARC 105 Chemical List Found during Smoke in FIRE Phase.

exposed to the compounds accidentally. PCB mixtures may be contaminated with polychlorinated dibenzofurans and polychlorinated dibenzodioxins (see, e.g., p. 350).

A slight increase in the incidence of cancer, particularly melanoma of the skin, was reported in a small group of men exposed to Aroclor 1254, a mixture of PCBs[1]. In a study of over 2500 US workers exposed to a similar mixture of PCBs during the manufacture of electrical capacitors, five deaths due to cancer of the liver and biliary passages were observed, whereas 1.9 would have been expected. This increase was sustained mainly by female workers in one of the two plants in the study (four of the five deaths), and all five workers had first been employed before the early 1950s[2,3]. Another study of workers in a capacitor plant was conducted in Italy. Exposure in the early years of production (until 1964) was to PCB mixtures containing 54% chlorine (mainly Aroclor 1254 and Pyralene 1476), which were later replaced by mixtures containing 42% chlorine (mainly Pyralene 3010 and 3011). Early results showed a significant excess of all cancers among male workers, which was due mainly to cancers of the digestive system and of the lymphatic and haematopoietic tissues. Among female workers, a slight increase in mortality from cancer of the lymphatic and haematopoietic tissues was reported[4]. The study was later enlarged and extended to include 2100 workers and to cover the period 1946-1982. Both male and female workers exhibited significantly increased cancer mortality in comparison with rates for the local population (14 observed, 7.6 expected; and 12 and 5.3, respectively, for men and women). Among male workers, cancers of the gastrointestinal tract (two stomach, two pancreas, one liver and one biliary passages) taken together were significantly increased (6 observed, 2.2 expected). Female workers showed a significant increase in deaths from haematological neoplasms (4 observed, 1.1 expected)[5]. In Sweden, among 142 male workers employed between 1965 and 1978 in a capacitor manufacturing plant when PCB mixtures containing up to 42% chlorine had been used, no significant excess of cancer deaths was noted. Cancer incidence was also examined: the number of cases observed corresponded well to that expected. One individual in a subgroup with higher exposure developed two relatively rare tumours, both of which occurred ten years after the start of exposure: a slow-growing mesenchymal tumour (desmoid) and a malignant lymphoma[6].

After contamination of cooking oil with a mixture of PCBs (Kanechlor 400) in Japan in 1968, a large population was intoxicated ('Yusho' disease). An early report on mortality from 1963-1983 showed a significantly increased risk of all cancers, and an almost five-fold significantly elevated risk of primary liver cancer. The edible rice oil had also been contaminated by polychlorinated quaterphenyls and polychlorinated dibenzofurans. Dose-response relationships were not clarified[7]. A further comprehensive study of 887 male 'Yusho' patients showed statistically significantly increased mortality from all malignancies (33 observed, 15.5 expected), from liver cancer (9 observed, 1.6 expected) and from lung cancer (8 observed, 2.5 expected). Use of local rather than national rates in calculating expected number of deaths decreased the observed:expected ratio for liver cancer from 5.6 to 3.9, which was still statistically significant. A closer look at the geographical distribution of liver cancer cases did not allow exclusion of factors other than PCB poisoning as a possible explanation for this finding. For the 874 female patients examined, none of the noted observed:expected ratios was significant[8]. In a series of ten autopsies of 'Yusho'

References

[1]*IARC Monographs, 42*, 39-143, 1987

[2]Zambon, P., Simonato, L., Mastrangelo, G., Winkelmann, R., Saia, B. & Crepet, M. (1987) Mortality of workers compensated for silicosis during the period 1959-1963 in the Veneto region of Italy. *Scand. J. Work Environ. Health, 13*, 118-123

[3]Koskela, R.-S., Klockars, M., Järvinen, E., Kolari, P.J. & Rossi, A. (1987) Cancer mortality of granite workers. *Scand. J. Work Environ. Health, 13*, 26-31

[4]Lynge, E., Kurppa, K., Kristofersen, L., Malker, H. & Sauli, H. (1986) Silica dust and lung cancer: results from the Nordic occupational mortality and cancer incidence registers. *J. natl Cancer Inst., 77*, 883-889

[5]Thomas, T.L. & Stewart, P.A. (1987) Mortality from lung cancer and respiratory disease among pottery workers exposed to silica and talc. *Am. J. Epidemiol., 125*, 35-43

[6]Hessel, P.A., Sluis-Cremer, G.K. & Hnizdo, E. (1986) Case-control study of silicosis, silica exposure, and lung cancer in white South African gold miners. *Am. J. ind. Med., 10*, 57-62

[7]*IARC Monographs, 34*, 133-190, 1984

[8]*IARC Monographs, Suppl. 6*, 494-496, 1987

SOOTS (Group 1)

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

The carcinogenicity of soot is demonstrated by numerous case reports, dating back over 200 years, of skin cancer, particularly of the scrotum, among chimney-sweeps. More recent cohort studies of mortality among chimney-sweeps in Sweden and Denmark have shown a significantly increased risk of lung cancer. Supporting evidence for an association with lung cancer was provided by two earlier epidemiological studies in the German Democratic Republic and the UK. The potentially confounding and interactive effects of smoking could not be evaluated; however, cigarette smoking is not believed to have seriously biased these estimates. In addition to lung cancer, statistically significant excess mortality from oesophageal cancer, primary liver cancer and leukaemia was found among chimney-sweeps in one study[1].

B. Evidence for carcinogenicity to animals (*inadequate* for soots; *sufficient* for soot extracts)

Coal soot was tested in two experiments in mice by whole-body exposure, but the studies were inadequate for evaluation. Coal-soot extracts applied to the skin of mice produced skin tumours in two studies. A wood-soot extract applied to the skin of mice was inadequately tested. In limited studies, subcutaneous implants of wood soot in female rats produced a few local sarcomas; similar implants in the scrotal sac of rats did not. An extract of fuel-oil soot was inadequately tested by application to the skin of mice. Extracts of soot from the combustion of oil shale produced skin tumours in mice after dermal application and lung

C. Other relevant data

No data were available on the genetic and related effects of 1,1,2,2-tetrachloroethane in humans.

1,1,2,2-Tetrachloroethane did not transform BALB/c 3T3 cells and did not induce sex-linked recessive lethal mutations in *Drosophila*. It induced recombination, gene conversion and mutation in *Saccharomyces cerevisiae* under conditions in which endogenous levels of cytochrome P450 were enhanced. It was not mutagenic to bacteria but caused DNA damage[3].

References

[1]Norman, J.E., Jr, Robinette, C.D. & Fraumeni, J.F., Jr (1981) The mortality experience of army World War II chemical processing companies. *J. occup. Med., 23*, 818-822

[2]*IARC Monographs, 20*, 477-489, 1979

[3]*IARC Monographs, Suppl. 6*, 511-513, 1987

TETRACHLOROETHYLENE (Group 2B)

IARC Chemical List - found during Fire Phase

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

Tetrachloroethylene has been studied by observing laundry and dry-cleaning workers, who may also have been exposed to other solvents, especially trichloroethylene (see p. 364), but also petroleum solvents. In several cohort and proportionate mortality studies, excesses have been reported of lymphosarcomas[1], leukaemias[2] and cancers of the skin[1,2], colon[3], lung[2,4] and urogenital tract[1-5], although in one study no excess of urogenital cancer was seen among persons exposed mainly to tetrachloroethylene[5]. Some excess of lymphomas and of cancers of the larynx and bladder was seen in a large cohort of dry cleaners[6]. A familial cluster of chronic lymphocytic leukaemia has also been related to dry-cleaning[7]. A large case-control study of bladder cancer did not show any clear association with dry-cleaning[8]. In other case-control studies, dry-cleaning appeared to be a risk factor for pancreatic cancer[9] and for liver cancer[10]. Some excess of liver cancer was also seen in one of the proportionate mortality studies[2]. In two case-control studies of liver cancer[11,12], an increased risk with occupational exposure to organic solvents (in one of the studies in women only[12]) was observed; in the first study, one case and no control had had exposure to tetrachloroethylene; in the second, one of six female cases was in dry-cleaning workers. Even if there is some consistency in several studies with regard to an association between lymphatic malignancies and urogenital cancers, taken together, and exposure to tetrachloroethylene, this broad grouping and the small numbers involved do not permit any definite conclusion to be drawn about any causal connection.

Vincristine sulphate induced micronuclei in bone-marrow cells of mice and hamsters treated *in vivo*. Conflicting results were obtained for induction of sister chromatid exchanges in human lymphocytes *in vitro*. It induced aneuploidy in and transformation of Syrian hamster embryo cells, but it did not transform mouse C3H 10T1/2 cells. It did not induce chromosomal aberrations, sister chromatid exchanges or unscheduled DNA synthesis in rodent cells *in vitro*. It induced mutation in mouse lymphoma cells but not in other rodent cells. It did not induce sex-linked recessive lethal mutations in *Drosophila* and was not mutagenic to bacteria[2].

References

[1]*IARC Monographs, 26*, 365-384, 1981
[2]*IARC Monographs, Suppl. 6*, 563-565, 1987

VINYL CHLORIDE (Group 1)

IARC 105 Chemical List
Found during overhaul

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

Vinyl chloride has been associated with tumours of the liver, brain, lung and haematolymphopoietic system[1]. A large number of epidemiological studies[2-12] and case reports[13-25] have substantiated the causal association between vinyl chloride and angiosarcoma of the liver. Several studies also confirm that exposure to vinyl chloride causes other forms of cancer, i.e., hepatocellular carcinoma[13,19,23,26], brain tumours[11,27], lung tumours[12,28-30] and malignancies of the lymphatic and haematopoietic system[11,29,31]. Exposure to polyvinyl chloride dust was associated with an increased incidence of lung tumours in one study; the authors suggested that trapped vinyl chloride monomer was responsible[30]. Melanoma occurred in excess in one study[12] but has not been mentioned in others. Slightly elevated risks for gastric[29] and gastrointestinal cancer (other than liver cancer)[32] were indicated in some studies, but these were not confirmed in others.

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

Vinyl chloride administered orally or by inhalation to mice, rats and hamsters produced tumours in the mammary gland, lung, Zymbal gland and skin and angiosarcomas of the liver[1]. Similar findings were made in more recent studies[33-39]. In one, a combination of oral administration of ethanol and inhalation of vinyl chloride resulted in more liver tumours (including angiosarcomas) than after treatment with vinyl chloride alone[40].

C. Other relevant data

Chromosomal aberrations were induced in peripheral blood lymphocytes of workers exposed to vinyl chloride at levels of 5-500 ppm (13-1300 mg/m^3). Two studies reported negative results for sister chromatid exchanges in exposed workers, while in another study a weakly positive response was found[41].

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF CARCINOGENIC RISKS TO HUMANS

Occupational Exposures in Petroleum Refining; Crude Oil and Major Petroleum Fuels

VOLUME 45

IARC, Lyon, France

1989

In further analyses of the Exxon refineries and chemical plants in Baton Rouge, LA, Baytown, TX, and Bayway/Bayonne, NJ, mortality was examined by occupation and work site (Hanis *et al.*, 1985b). Directly adjusted death rates for each subgroup of interest and for the total US population were calculated using the age, sex, race and calendar year distribution of the total cohort as a standard; thus, direct comparisons could be made between mortality rates in cohort subgroups and in the US population by calculating ratios of the directly adjusted rates. Workers were classified as having been 'potentially exposed' or 'unexposed' on the basis of their longest-held job. The 'exposed' category included those who had worked as process operators, mechanical workers and labourers (75% of the study population); while the 'unexposed' category included primarily white-collar office workers (22% of the population). Cause-specific cancer rates were higher among potentially exposed workers than among the unexposed for every cancer site except brain, but none of the site-specific rate ratios was significantly different from 1.0. Directly adjusted death rates were consistently greater than those for the total US population only for renal cancer in each of the three plants. The death rates for pancreatic cancer were higher than the US rates among employees at the Baton Rouge and Baytown plants only, and elevated rates of large intestinal cancer occurred at the Baytown and Bayway/Bayonne plants.

A series of investigations of mortality has been performed among members of the Oil, Chemical and Atomic Workers international union (OCAW) in Texas (Thomas *et al.*, 1980, 1982a,b, 1984). In all of these reports, proportionate mortality among male members of the OCAW was compared with that among US men, adjusting for age, race and calendar period.

The first report concerned 3105 Union members in Texas whose deaths in 1947–77 while actively employed were reported to OCAW and whose death certificates could be located (90%; Thomas *et al.*, 1980). Of the white OCAW members, 1722 had held blue-collar jobs in petroleum refineries and petrochemical plants, primarily in maintenance and production (Thomas *et al.*, 1982a), and had significant excess frequencies of deaths from cancers of the digestive and respiratory systems, skin and brain (ICD8 191, 192).

Subsequent analyses were limited to three petroleum refineries located in the Beaumont/Port Arthur area of the Texas Gulf Coast (Thomas *et al.*, 1982a,b, 1984) and included 1194 retired workers as well as those who had died while actively employed between 1943 and 1979. Among 2509 deceased men who had been employed by the three refineries combined (Thomas *et al.*, 1982a,b), the adjusted PMRs using national rates for all causes of death were significantly elevated for all cancers as well as for cancers of the stomach, pancreas, skin (ICD8 172, 173), prostate and brain (ICD8 191, 192) and for leukaemia. Nine deaths from multiple myeloma were observed and 4.6 were expected, but the PMR was not significant. When national cancer rates were used to calculate proportionate cancer mortality ratios (PCMRs), these ratios were also elevated but significantly so only for brain and leukaemia in whites. When county cancer mortality rates were used, none of the PCMRs was significantly raised. A detailed examination of brain tumour mortality in whites indicated that OCAW members had had elevated frequencies of mortality from benign and unspecified tumours of the brain as well as those specified on death certificates as malignant. [The Working Group noted that, of the 2509 deaths studied,

distillates [24] and one intermediate catalytically cracked distillate [25] were tested in mice by skin application and induced skin tumours.

Several high-boiling distillates [26] and residues [27] of catalytically cracked oils and several thermally cracked residues [31] were tested in experiments in mice by skin application, producing high incidences of benign and malignant skin tumours.

Thermally-cracked residues [31] originating from two different sources were tested by skin application in rabbits, producing some skin tumours, but the study was considered inadequate for evaluation. In one study in mice, skin application of water-quench pyrolysis fuel oil or oil-quench pyrolysis fuel oil (steam-cracked residues [34]) produced carcinomas and papillomas of the skin.

Effluents

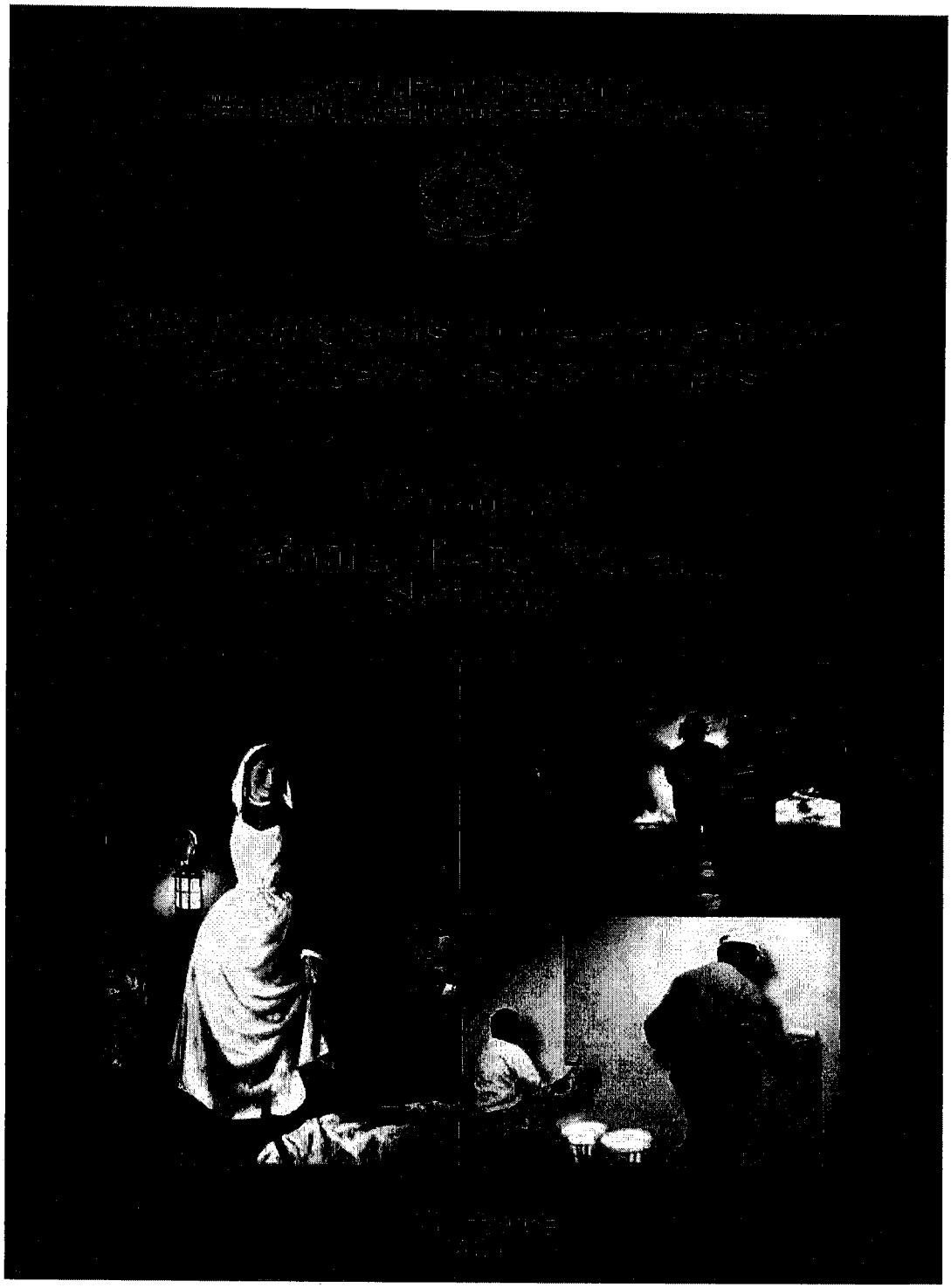
Two studies on petroleum refinery effluents were inadequate for evaluation.

4.3 Human data

Taking into consideration the overlap in cohort studies conducted in the USA, ten separate, company-specific cohorts were studied. Two industry-wide study cohorts from the USA comprised various combinations of these cohorts. The cohorts mentioned hereafter refer to the ten separate US cohorts, two from Canada and one from the UK.

Information on specific jobs or exposures was available in only a few of the epidemiological studies of petroleum refinery workers. Some caution should be applied in interpreting the relative risks for cancer in cohort studies of petroleum refinery workers. As for most cohorts of actively employed persons, the overall risk for cancer in all of the cohort studies reviewed here was lower than that in the general population. Yet, it is the cancer experience of the general population that has been conventionally used, in published papers, in evaluating the rates of specific cancers in refinery workers. Significant deficits were reported for cancers at some sites in certain studies; such findings are mentioned in this summary only when a consistent pattern emerged. Caution should also be applied in interpreting the findings from those case-control studies conducted within the general population setting. Most of the studies reported had positive findings, and are likely to be an incomplete selection of case-control studies in which occupational exposures have been investigated.

One case report and one case series describe clusters of skin cancer cases (squamous-cell carcinoma) among wax pressmen who had been exposed to crude paraffin wax saturated with aromatic oils. Significant excess mortality from skin cancer was reported among three refinery cohorts, one of which included the wax pressmen from the case series. In a second cohort, the overall excess was due to an elevated risk for malignant melanoma. In the third, excess skin cancer risk was experienced primarily by maintenance workers. Skin cancer mortality was elevated in three additional cohorts, but the increase was not significant. A case-control study showed a significantly elevated risk for malignant melanoma among men employed in the coal and petroleum products industry, with a cluster of cases employed in petroleum refineries.



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.

Products of Combustion

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	

magnitude of this form of misclassification is unknown, but it is likely that the resulting misclassification will be non-differential with regard to cases and controls. Another limitation to case–control studies is that cases may be more likely than controls to remember jobs of shorter duration. Those jobs in the more distant past may be more likely recalled by cases than controls resulting in differential bias away from the null. Alternatively, in several of the reported studies, cases were more likely than the controls to provide proxy interviews by their survivors rather than by the cases themselves. Because of the relatively few studies available for individual organ sites, the studies were grouped into four categories including urogenital, brain and central nervous system, larynx and lung, and other.

2.2.1 *Cancers of the urogenital system*

Four cancers of the urogenital organs in relation to employment as a firefighter were considered (Tables 2.3 and 2.6).

Delahunt *et al.* (1995) examined pathologically confirmed incident renal cell carcinomas the New Zealand Cancer Registry during the period 1978–1986. The registry included 95% of those patients diagnosed and treated in both the public and private sector. At time of registration, the current or most recent occupation was recorded. Additional information collected included age, and smoking habits. Renal cell carcinomas with an ICD-9 code of 189.0 (malignant neoplasm of the kidney, excluding the renal pelvis) were evaluated. The control groups were a random sample of registrations drawn from all cases over 20 years of age, having primary tumours from sites other than the urinary tract registered during the same time period. There were a total of 710 male cases and 12 756 controls. There were 52 cases and 737 controls under the occupational classification of "Service" which included firefighters and five other occupational groups. The relative risk for firefighters was 4.7 (95% CI: 2.5–8.9).

Bates (2007) (see Table 2.6) conducted a registry-based case–control study using the California Cancer Registry. Anonymized records of all male cancers for the period 1988–2003 were collected. To identify firefighters, the occupation and industry fields were searched for titles including fire, firefighter, fire fighter, fireman, fire man, and fire chief. If the subjects indicated that they did not carry out firefighting activities, they were not considered. A total of 16 cancer organ sites were examined including kidney, bladder, prostate, and testis. For each analysis, all other cancers were used as controls except for those cancers shown in the initial analysis that had demonstrated a firefighting etiology; these included cancers of the lung, bronchus, bladder, prostate, colorectum, and skin melanomas. Analysis was limited to males aged 21–80 at time of diagnosis. There were 3659 firefighters and 800 448 controls in the analysis after exclusion of 13% of the files ($n = 140\,000$) with no recorded occupation or industry. Logistic regression analyses were performed for each cancer type for which there had been more than 50 cancers recorded in firefighters. This was not done for for cancer of the thyroid ($n = 32$ cases) or multiple myeloma ($n = 37$ cases) as these two were based on prior hypotheses.

For the cases, 220 (32%) were interviewed by proxy. Analyses were adjusted for gender, race, 4-year age groups, and study area. The adjusted OR for employment in firefighting and prevention occupations was 1.9 (95% CI: 0.5–9.4, five cases and five controls), and for the self-reporting category, 2.8 (95% CI: 0.5–14.3, four cases). The OR for firefighters employed < 10 years was 0.9 (95% CI: 0.0–22.3, one case and two controls), while for those employed 10 or more years, the OR increased to 2.9 (95% CI: 0.4–21.6, four cases and three controls).

Bates (2007) also investigated multiple myeloma, non-Hodgkin lymphoma, and leukaemia in firefighters (for full study description see Section 2.2.1 and Table 2.6), for which the ORs were reported as 1.03 (95% CI: 0.75–1.43, 37 cases), 1.07 (95% CI: 0.90–1.26, 159 cases), and 1.22 (95% CI: 0.99–1.49, 100 cases), respectively.

(b) Cancers of the gastrointestinal system and pancreas

Bates (2007) conducted the only study investigating cancers of the gastrointestinal system in firefighters. The ORs for cancers of the stomach were 0.80 (95% CI: 0.61–1.07, 51 cases), of the colorectum 0.90 (95% CI: 0.79–1.03, 282 cases), of the caecum 1.09 (95% CI: 0.82–1.44, 52 cases), and of the pancreas 0.90 (95% CI: 0.70–1.17, 63 cases).

(c) Thyroid cancer

Bates (2007) assessed 32 firefighters with cancer of the thyroid, and found an OR of 1.17 (95% CI: 0.82–1.67).

(d) Melanoma

Bates (2007) investigated firefighters ($n = 323$) diagnosed with melanoma, and found a significant and elevated OR of 1.50 (95% CI: 1.33–1.70).

2.3 Descriptive studies

Several descriptive studies have provided results for firefighters. These have varied in their design including cohort studies based on record linkage, and studies based solely on death certificate or registry data. In some cases, these have been investigations specifically directed at firefighters. They are described in more detail below and in Tables 2.7 and 2.8.

2.3.1 *Cohort and linkage studies of firefighters*

Feuer & Rosenman (1986) conducted a study of deaths among active and retired firefighters from the state of New Jersey, USA, during 1974–1980. Firefighters were identified using pension records, and their duration of employment was also collected. Their mortality was compared to that of the police force, identified in the same manner, and of the general population. Proportionate mortality ratios (PMRs) were calculated based on 263 caucasian male firefighter deaths, and a significant excess of leukaemia was observed using to the police force as reference group.

2.4 Case reports

Individual firefighters have applied for, and sometimes received, workers' compensation for cancer. An apparent cluster of cancer among firefighters was reported in an investigation of a chemical waste dump fire by NIOSH (Hrubec *et al.*, 1992). However, the authors concluded it was not likely to have been related to firefighting. [Given the limitations of these reports and the large number of descriptive, cohort, and case–control studies with data on firefighters, the Working Group did not believe that case reports would contribute to the evaluation.]

2.5 Meta-analyses

Two meta-analyses of studies of firefighters and cancer have been conducted (Howe & Burch, 1990; LeMasters *et al.*, 2006). The most recent meta-analysis included a great majority of the studies considered by the Working Group (LeMasters *et al.*, 2006). Cancer risk was significantly elevated for ten of the 21 cancer types analysed (stomach, colon, rectum, skin, prostate, testis, brain, non-Hodgkin lymphoma, multiple myeloma, and malignant melanoma). With the exception of testicular cancer (summary RR = 2.02), the summary relative risk estimates were moderate, ranging from 1.21 for colon to 1.53 for multiple myeloma. For four of these sites (prostate, testis, non-Hodgkin lymphoma, and multiple myeloma), findings were consistent across study designs and the types of study available. However, since that analysis, two additional large studies of cancer in firefighters had been published (Ma *et al.*, 2006; Bates, 2007). Therefore, another meta-analysis was performed by the Working Group to assess the impact of these recent studies.

Inclusion criteria for studies in this meta-analysis were reported estimates of relative risk with corresponding 95% confidence intervals or information that allowed their computation by the Working Group for 'ever' versus 'never' exposure to firefighting or employment as a firefighter. For those studies that did not report for this category, the relative risks and 95% confidence intervals were estimated by the Working Group from strata-specific relative risk and corresponding number of cases, assuming a normal distribution when possible. Studies that only reported point estimates without confidence intervals were not included. Proportionate mortality studies were also excluded. Statistical heterogeneity among studies was tested with the Q statistic. Summary relative risk estimates were obtained from random-effect models for prostate cancer ($Q = 32.816$, $P = 0.005$), and fixed-effect models for testicular cancer ($Q = 3.928$, $P = 0.560$), and non-Hodgkin lymphoma ($Q = 6.469$, $P = 0.486$). All statistical analyses were performed using STATA (version 9.0; StataCorp, College Station, TX).

Based on the Working Group's meta-analysis, three of the four sites remained statistically significant. Testicular cancer was evaluated based on six studies and

3. Studies of Cancer in Experimental Animals

No data were available to the Working Group.

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

Smoke is a complex mixture of chemicals in aerosol, gas, and vapour forms. The focus of this section of the monograph will be primarily on components of smoke from municipal and wildland fires. There is a paucity of information on the extent of exposure to firefighters from trash fires, vehicle fires, and non-wildfire vegetation fires, during which firefighters typically do not wear respiratory protection. Although not typical of exposures most firefighters encounter, there are published reports on the effects of firefighter exposure to specific incidents, including the World Trade Center fire and collapse, and specific industrial fires or clean-up operations. It should be kept in mind that the magnitude of these exposures are not representative of most fires.

Information on many of the specific chemicals found in smoke is available in previous IARC monographs. The data on absorption, distribution, metabolism, and excretion for select carcinogens contained in fire smoke are listed in Table 4.1. Only inhalation and dermal exposures were considered – the predominant occupational exposure routes in firefighters. One of the difficulties in evaluating the toxicokinetics and metabolism of combustion products in firefighters is the adsorption of chemical components onto particles (Fine *et al.*, 2001). This will alter the absorption kinetics of these combustion products and may also cause a proportionally greater effect in the lungs compared to other tissues. Depending on their volatility, these chemicals may also exist at significant concentrations in the gas phase of smoke exposure as well. No chronic toxicity studies could be found on non-human exposure to combustion products from structural materials. Due to limited data, the toxicokinetics of chemical mixtures are not considered in this monograph, although they are likely to be of significant importance given the multiplicity of chemicals in smoke.

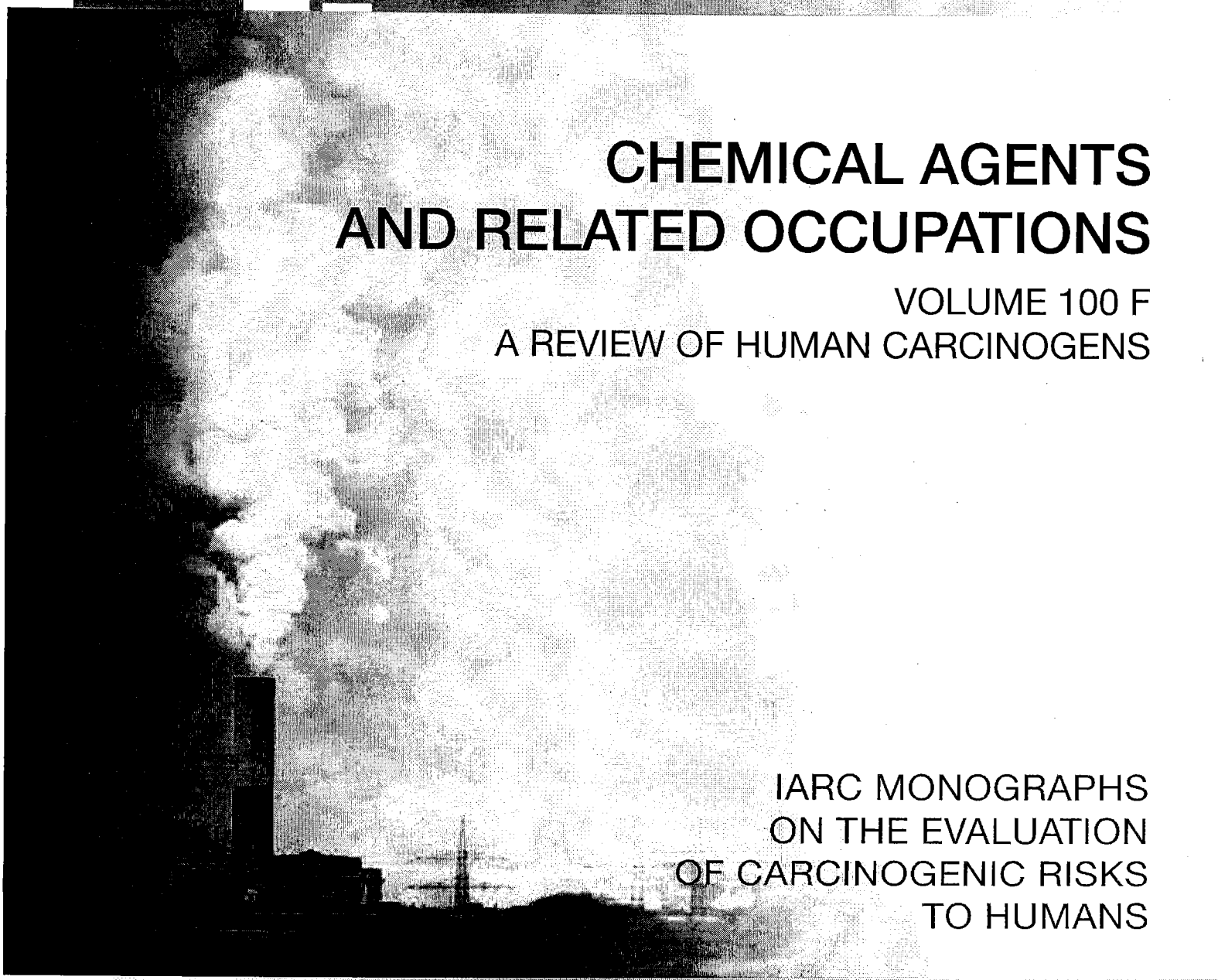
4.1.1 *Particles*

Particle deposition depends on the size and shape of the particle. Smoke from combustion of products such as wood tends to produce small particles that can easily reach the alveolar region of the lung, with a mode size distribution of 0.1–0.2 μm diameter (Kleeman *et al.*, 1999). Particles not cleared by phagocytosis and transferred to the mucociliary escalator may be translocated to the interstitial tissue and to lung-associated lymph nodes (International Commission on Radiological Protection, 1994). This local

Table 4.1 (contd)

Chemical	Absorption	Distribution	Metabolism	Excretion	Mechanism	Cancer	Note/Reference
Formaldehyde	Inhalation (100%) Dermal (3.4% in rats)	Predominantly local before metabolism	Metabolism in all tissues to carbon dioxide, formate, other one-carbon molecules	Plasma half-life 1 min (rat)	DNA–protein crosslinking, chromosomal abberations, and cell proliferation. Gene mutations Sister chromatid exchange	Nasopharyngeal and sinonasal cancer, leukaemia	IARC (2006); Egle 1972); Bartnik *et al.* (1985); Heck *et al.* (1982, 1983)
PAHs	Dermal (20% for pyrene) > inhalation	Following dermal exposure, highest concentrations in liver, kidney, fat, and lung	Metabolism in all tissues. 1-hydroxy-pyrene used as proxy for overall exposure	Elimination half-life (dermal exposure) 30 h for benzo[*a*]pyrene	Metabolites PAH oxides and diol epoxides form stable DNA adducts and induce mutations. Other mechanisms also postulated	Lung, bladder, skin, possibly prostate	IARC (2010a); Van Rooij *et al.* (1993); Withey *et al.* (1993); ATSDR (2007); Sanders *et al.* (1986); Rybicki *et al.* (2006); Seidler *et al.* (1998)

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.

IARC 105 Chem. List Overhaul & 2004

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.

sidestream cigarette smoke have been reported to range from 52 to 95 ng/cigarette — more than three times the concentration in mainstream smoke. Major sources of PAHs in ambient air (both outdoors and indoors) include residential and commercial heating with wood, coal or other biomasses (oil and gas heating produce much lower quantities of PAH), other indoor sources such as cooking and tobacco smoke, and outdoor sources like motor-vehicle exhaust (especially from diesel engines), industrial emissions and forest fires. Average concentrations of individual PAHs in the ambient air in urban areas typically range from 1 to 30 ng/m^3; however, concentrations up to several tens of nanograms per cubic metre have been reported in road tunnels, or in large cities that make extensive use of coal or other biomass as residential heating fuel. Estimates of PAH intake from food vary widely, ranging from a few nanograms to a few micrograms per person per day. Sources of PAHs in the diet include barbecued/grilled/broiled and smoke-cured meats; roasted, baked and fried foods (high-temperature processing); bread, cereals and grains (at least in part from gas/flame-drying of grains); and vegetables grown in contaminated soils, or in areas with surface contamination from atmospheric PAH fall-out (IARC, 2010).

1.2.2 Occupational exposure

Occupational exposure to PAHs occurs primarily through inhalation and via skin contact. Monitoring by means of ambient air-sampling or personal air-sampling at the workplace, to determine individual PAHs, sets of PAHs or surrogates (e.g. coal-tar pitch volatiles) has been used to characterize exposure via inhalation; more recently, biological monitoring methods have been applied to characterize the uptake of certain specific PAHs (e.g. benzo[*a*]pyrene) to be used as biomarkers of total exposure (IARC, 2010).

Industries where occupational exposure to benzo[*a*]pyrene has been measured and reported include: coal liquefaction, coal gasification, coke production and coke ovens, coal-tar distillation, roofing and paving (involving coal-tar pitch), wood impregnation/preservation with creosote, aluminium production (including anode manufacture), carbon-electrode manufacture, chimney sweeping, and power plants. Highest levels of exposure to PAHs are observed in aluminium production (Söderberg process) with values up to 100 μg/m^3. Mid-range levels are observed in roofing and paving (e.g. 10–20 μg/m^3) and the lowest concentrations (i.e. at or below 1μg/m^3) are observed in coal liquefaction, coal-tar distillation, wood impregnation, chimney sweeping and power plants (IARC, 2010).

2. Cancer in Humans

No epidemiological data on benzo[*a*]pyrene alone were available to the Working Group.

3. Cancer in Experimental Animals

Benzo[*a*]pyrene was considered by three previous Working Groups (IARC, 1973, 1983, 2010).

In *IARC Monograph* Volume 3 (IARC, 1973) it was concluded that benzo[*a*]pyrene produced tumours in all species tested (mouse, rat, hamster, guinea-pig, rabbit, duck, newt, monkey) for which data were reported following exposure by many different routes (oral, dermal, inhalation, intratracheal, intrabronchial, subcutaneous, intraperitoneal, intravenous). Benzo[*a*]pyrene had both a local and a systemic carcinogenic effect, was an initiator of skin carcinogenesis in mice, and was carcinogenic in single-dose studies and following prenatal and transplacental exposures.

IARC-Chemical List 105 (Found in Firesmoke, Overhaul & Diesel Exhaust)

Benzo[a]pyrene

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).

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.

effects were reported of a similar treatment of psoriasis patients on the levels of benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adducts in peripheral blood lymphocytes (Pavanello & Levis, 1994). In a study of 111 Korean painters using coal-tar-based paint, the levels of aromatic DNA adducts measured by ^{32}P-postlabelling analysis were slightly higher compared with 17 on-site control workers (Lee *et al.*, 2003).

In lymphocytes of 49 coal-tar workers a significant increase of chromosomal aberrations, sister chromatid exchange, and satellite associations was observed, compared with values in non-exposed controls (Yadav & Seth, 1998).

Increased levels of p53 peotein were found in skin biopsies of atopic eczema patients treated topically with coal-tar; a correlation was observed between p53 and aromatic DNA-adduct levels measured in the same tissue by ^{32}P-postlabelling analysis (Godschalk *et al.*, 2001).

4.2 Synthesis

In experimental systems, coal tars were mutagenic in bacteria and mammalian cells, and induced sister chromatid exchange and morphological cell transformation in cultured mammalian cells. Coal tar was also mutagenic *in vivo*, in transgenic mice. Mouse-lung tumours induced by coal-tar treatment had mutations in the K-*ras* proto-oncogene.

Epidemiological studies in humans and studies in experimental animals were consistent with respect to coal-tar exposures being carcinogenic to the lung. Coal tars produced lung and skin tumours in mice and rats after exposure by inhalation, lung tumours in rats after dermal treatment, and skin tumours in mice after dermal treatment. Coal tar was a mouse skin-tumour initiator (see Section 3).

Indications on the role of PAH in the mechanism of action of exposure to coal tar are based on the detection of DNA adducts of several PAHs, e.g. benzo[*ghi*]perylene, benzo[*b*]fluoranthene, *7H*-benzo[*c*]fluorene and benzo[*a*]pyrene in *in vitro* studies, with DNA adducts of benzo[*b*]fluoranthene, benzo[*c*]fluorene and benzo[*a*]pyrene being detected in lung tissues of exposed animals. The benzo[*a*]pyrene DNA adduct was identified as an *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-deoxyguanosine-adduct.

In studies in humans, the urine from patients undergoing coal-tar treatments was mutagenic in bacteria. Peripheral blood lymphocytes of workers occupationally exposed to coal tars had increased chromosomal damage. Measurements of PAH-DNA adducts in human studies are based exclusively on detection of benzo[*a*]pyrene-DNA adducts, in particular *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-deoxyguanosine.

In conclusion, studies in experimental systems and in surrogate tissues of humans provide strong evidence for a genotoxic/mutagenic mechanism underlying the effects of occupational exposures during coal-tar distillation.

5. Evaluation

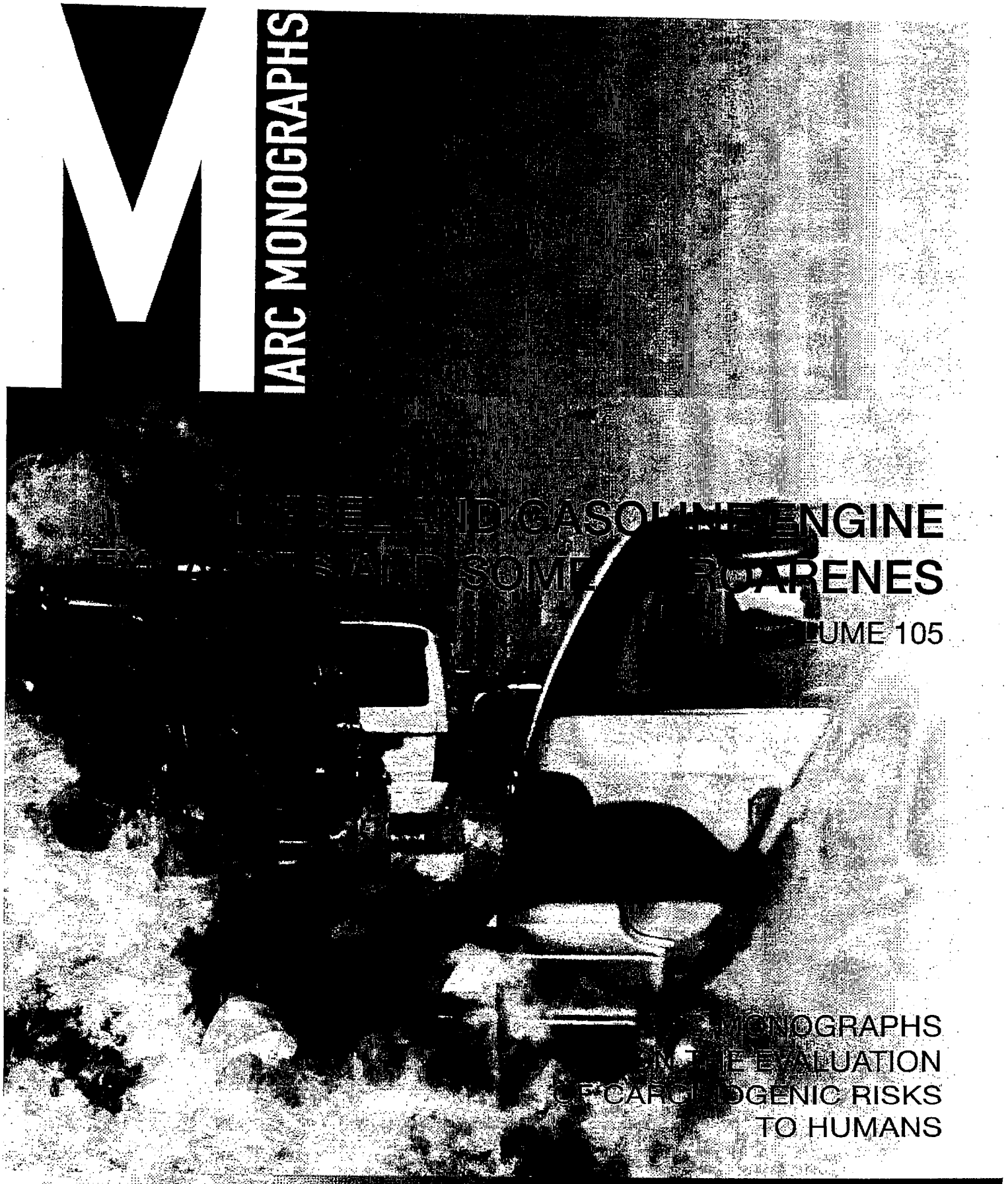
There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures during coal-tar distillation. Occupational exposures during coal-tar distillation cause cancer of the skin (including, but not limited to, cancer of the scrotum).

There is *sufficient evidence* in experimental animals for the carcinogenicity of coal tars.

Studies in experimental systems and in tissues of humans provide strong evidence for a genotoxic mechanism underlying the effects of occupational exposures during coal-tar distillation in humans. The detection of *anti*-benzo[*a*]pyrene-7,8-diol-9,10-epoxide-DNA adducts in the peripheral blood lymphocytes of exposed humans suggests the participation of benzo[*a*]pyrene in the genotoxic mechanism of this exposure in humans.

Occupational exposures during coal-tar distillation are *carcinogenic to humans (Group 1)*.

IARC MONOGRAPHS



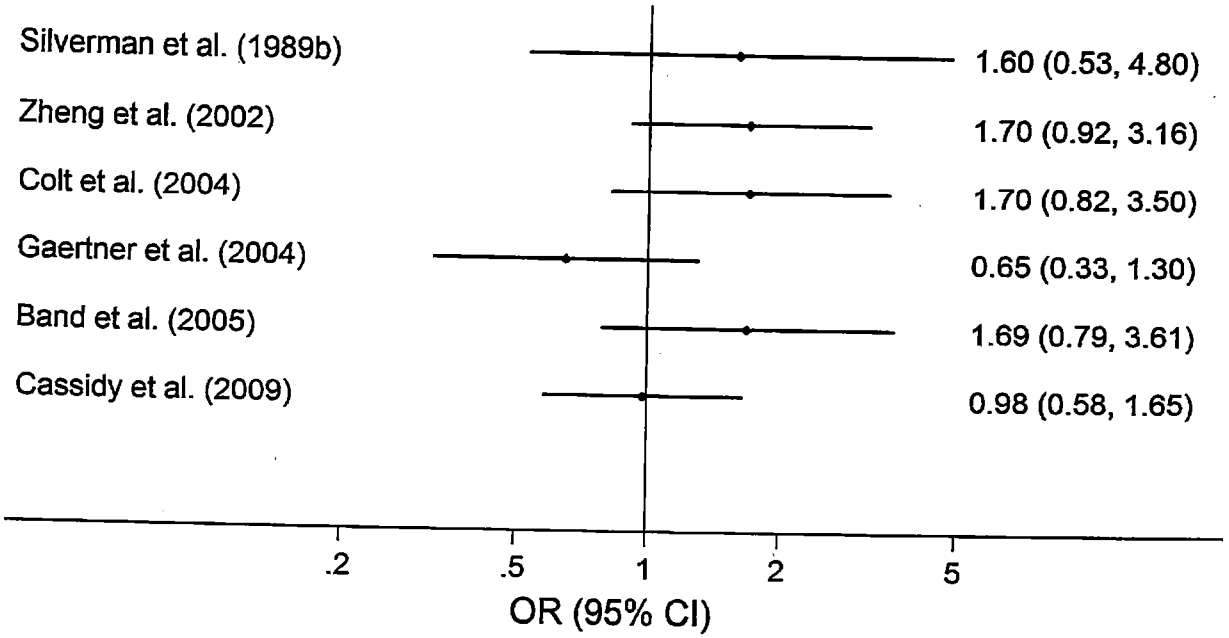
ENGINE
RENES

UME 105

ONOGRAPHS
E EVALUATION
OGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

Fig. 2.7 Case–control studies of urinary bladder cancer that reported risk estimates for ever or usual exposure as a garage worker



CI, confidence interval; OR, odds ratio

Zheng *et al.* (2002) found elevated risks for employment as a transport or material-moving supervisor (OR, 6.5; 95% CI, 1.4–29.9), which they stated were occupations associated with exposure to diesel exhaust (see Table 2.4). No elevated risk for urinary bladder cancer was found for ever employment as a warehouse materials handler in the American Health Foundation study, which was also an occupation that the authors stated was associated with exposure to diesel exhaust (Wynder *et al.*, 1985).

2.3.3 Cancer at other and multiple sites

See Table 2.5

A study by Decouflé *et al.* (1977) of cancer and occupation included cancer cases and hospital controls admitted to a large hospital in Buffalo, NY, USA, from 1956 to 1965. Ever employment in an occupation and duration of employment of at least 5 years were analysed on the basis of personal interviews. A large number of different occupations and cancer sites were evaluated, using clerical occupations as an unexposed comparison group. For employment as an HGV or tractor driver, relative risks [CI not provided] of 1.53 (29 exposed cases; $P > 0.05$) for laryngeal cancer, 0.60 (24 exposed cases; $P = 0.04$) for colon/rectal cancer and 0.63 (23 exposed cases; $P > 0.05$) for lymphoma were reported. For cancers at other sites, numbers were generally low and the risks were close to unity. [The Working Group noted that the report included many comparisons, lacked detailed descriptions of occupations and information on confounders, and was of limited value for the evaluation of exposure to exhaust.]

In a large population-based case–control study in Canada (Siemiatycki *et al.*, 1988), the associations between 10 types of engine exhaust and combustion products and cancers at 12 sites

(oesophagus, stomach, colon, 'rectosigmoid', rectum, pancreas, lung, prostate, bladder, kidney, skin melanoma and non-Hodgkin lymphoma) were evaluated for 3726 male cancer patients, aged 35–70 years, diagnosed in any of the 19 participating hospitals in Montreal and interviewed (response rate, 82%). For each cancer site, patients with cancers at other sites comprised the control group. The interview elicited a detailed job history, and a team of chemists and industrial hygienists translated each job into a list of potential exposures (Gérin *et al.*, 1985). The probability of exposure ('possible', 'probable' and 'definite'), the frequency of exposure (< 5, 5–30 and > 30% working time) and the level of exposure (low, medium and high) were estimated. After stratifying for age, socioeconomic status, ethnic group, cigarette smoking and blue-/white-collar job history, elevated odds ratios were seen for exposure to diesel engine exhaust and colon cancer (OR, 1.3; 90% CI, 1.1–1.6 for any exposure; OR, 1.7; 90% CI, 1.2–2.5 for long-term, high-level exposure), for long-term high-level exposure to gasoline engine exhaust and cancer of the rectum (OR, 1.6; 90% CI, 1.1–2.3) and kidney cancer (OR, 1.4; 90% CI, 1.0–2.0) and for bus, HGV and taxi drivers and rectal cancer (90% CI, 1.5; 1.0–2.2). [The Working Group noted that the study included numerous comparisons and used 90% confidence intervals; at the 95% level, most of the intervals would have included unity. Thus, this study was considered to give weak evidence of an association between cancers of the colon, rectum and kidney with exposure to engine exhaust.]

In the framework of the previous Canadian multisite population-based case–control study of occupational exposures and risks for various cancers (Siemiatycki *et al.*, 1988), Goldberg *et al.* (2001) assessed the associations of colon cancer with diesel engine emissions, and many other occupational exposures, in 497 male case patients compared with 1514 other cancer patients (excluding lung and peritoneal cancer, and cancers possibly associated with known risk factors for colon cancer and other cancers of the digestive tract) and 533 population controls. Exposures were assessed as described above (Siemiatycki *et al.*, 1988). The results differed according to the control group: when the pooled group of cancer and population controls was used, the odds ratio for substantial exposure to diesel engine exhaust was 1.6 (95% CI, 1.0–2.5), whereas the risk increased to 2.1 (95% CI, 1.1–3.7) when only the population-based controls were used. [The Working Group noted that the reasons for these differences were not discussed, but the use of cancer controls was a potential source of bias. Multivariate models were adjusted for an extended list of risk factors including socioeconomic status, tobacco smoking and body mass index, but no detailed dietary factors or physical activity.]

Another Canadian study obtained information on lifetime occupational history through a questionnaire from male cancer patients, aged 20 years and over, registered by the British Columbia Cancer Registry between 1983 and 1990. A case–control study was conducted on 1155 cases of colon cancer and 7752 cases of other cancers matched on age and year of diagnosis as controls (Fang *et al.*, 2011). Occupations and industries were coded according to Canadian and international standard classifications. Having ever/never been employed in a specific occupation or industry, as well as the usual occupation or industry of employment, were analysed for all of the 597 occupational titles and 1104 industry titles used in Canada, but results were only reported for those that concerned at least five cases. The analyses showed elevated risks for colon cancer (OR, 1.54; 95% CI, 1.01–2.25) for ever employment as a taxi driver/chauffeur, while other occupational titles, including bus drivers, HGV drivers and locomotive operators, showed no association. [The Working Group noted that no specific assessment of exposure to diesel or gasoline exhaust was carried out. The large number of

HGV and light goods vehicle drivers (OR, 3.46; 95% CI, 1.01–11.83). For male cases in the highest tertile of exposure to diesel engine exhaust, the odds ratio was 1.88 (95% CI, 0.72–4.90), calculated from a multivariate model with adjustment for confounding by age, sex, hospital province, alcohol consumption, tobacco smoking and educational status. The corresponding odds ratio for exposure to gasoline engine exhaust was 1.85 (95% CI, 0.71–4.80). [The Working Group noted that the study had a high proportion of direct interviews with case patients. Some known risk factors for pancreatic cancer, such as diabetes and obesity, were not controlled for in the analyses. The sample size and number of exposed cases were small, and multiple comparisons were made, which hampered the interpretation of the positive findings.]

A case–control study of laryngeal cancer included 183 male patients from 56 hospitals on the Texas Gulf Coast (USA), diagnosed between 1975 and 1980, and 250 controls frequency-matched for age group, vital status, ethnicity (all white) and area of residence, recruited through various population sources and records (Brown *et al.*, 1988). Information on employers, job titles and duties was collected by interview. Exposure data were categorized into industrial and occupational categories and potential exposure to specific agents was coded by an industrial hygienist. In the agent-specific analyses, results were given for potential exposure to diesel/gasoline fumes. The risks for laryngeal cancer were non-significantly elevated for the occupational category of drivers. [The Working Group noted that it was unclear whether the target exposure was fumes of diesel fuel or diesel exhaust, and the study was therefore regarded as uninformative with regard to engine exhausts.]

The risk from occupational exposure to diesel fumes and exhaust was investigated in a hospital-based case–control study of 235 male cases of laryngeal cancer and 205 control patients frequency-matched for age, hospital and year of interview (Muscat & Wynder, 1995). Control patients had malignancies such as prostate cancer and lymphoma or various non-malignant diseases. The response rate was 90% for the eligible study subjects who were approached. Detailed data were collected on tobacco smoking, alcohol consumption, lifetime occupational history and self-reported exposure to occupational agents, including diesel exhaust and fumes. Jobs with known substantial exposure to diesel exhaust (HGV drivers, mine workers, fire-fighters and railroad workers) were analysed jointly and yielded a smoking-adjusted odds ratio of 0.96 (95% CI, 0.5–1.8). Self-reported exposure to diesel exhaust had no significant association with laryngeal cancer (OR, 1.47; 95% CI, 0.5–4.1), with an exposure prevalence of 5.5% for cases and 4.4% for controls. Work as an automobile mechanic yielded an odds ratio of 1.3 (95% 0.4–4.1) for laryngeal cancer. [The Working Group noted that the exposure assessment in this study was crude and, overall, the level of detail was limited; the interpretation of the results was hampered by low numbers, and residual confounding from tobacco smoking and alcohol consumption was possible.]

A larger hospital-based case–control study included 940 male cases of laryngeal cancer and 1519 controls from a referral hospital in Istanbul, Turkey (Elci *et al.*, 2003). Controls were patients with other cancers, including Hodgkin lymphoma, soft tissue sarcoma and non-melanoma skin cancer, and several non-cancer diseases. Based on a standardized personal interview, occupations and industries were coded using standard classification schemes, and exposure intensity and probabilities for diesel exhaust, gasoline exhaust and other agents were assigned by an industrial hygienist. Analyses were adjusted for age and ever consumption of alcohol and tobacco. For ever exposure to diesel exhaust, the odds ratio was 1.5 (95% CI, 1.3–1.9). Analyses that used exposure intensity and those that used exposure probability both