Pancreatic Cancer

IARC MONOGRAPH'S

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1,3 Butadiene

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

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[7]*IARC Monographs, Suppl. 6*, 57–59, 1987

ALUMINIUM PRODUCTION (Group 1)

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

The lung has been the most common site identified for which there is an excess cancer risk in populations of aluminium production workers. Overall, early studies showed a borderline excess in relative risk, with some studies showing a doubling of risk and some showing no excess. Smoking histories were not given in any of these studies. In one study in which populations in the industry were compared on the basis of their exposures to pitch volatiles, there was a relationship between incidence of lung cancer and length of exposure, and there was a significant excess of cancer among workers who had worked for 21 years or more[1].

In three studies in the same aluminium-producing area, an increased risk of bladder cancer was associated with work in aluminium production in plants where primarily the Söderberg process was used. In one study in which smoking was controlled for, while there was a borderline excess in risk for nonsmokers, the risk for smokers was markedly increased[1].

Excess mortality from lymphosarcoma/reticulosarcoma was noted in two cohort studies, which covered partially the same population[1].

Statistically significant excess risks for pancreatic cancer and for leukaemia were noted as isolated findings in two studies and in one study, respectively[1].

Some of these studies have been updated. In Canada, the mortality of a large group of men employed in aluminium production using the Söderberg process was examined between 1950 and 1977, and compared with the pertinent rates for the Province of Quebec. Workers 'ever' exposed to condensed pitch volatiles ('tar') exhibited significantly increased mortality from all cancers (304 observed, 246.6 expected), and from oesophageal and stomach cancer (50 observed, 32.8 expected), lung cancer (101 observed, 70.7 expected) and other malignancies (60 observed, 45.3 expected). Analysis of lung cancer mortality by increasing years of exposure, tar-years of exposure and years since first exposure to tar revealed a steady, statistically significant, increasing trend. No similarly clear-cut pattern was noted for cancers of the oesophagus or stomach. Deaths from cancer of the urinary organs (20 observed, 13.7 expected) and bladder (12 observed, 7.5 expected) were more numerous than expected, but not significantly so. Nonetheless, when mortality from cancer at each of these sites was analysed according to tar-years of exposure, significantly increasing trends were noted. Among workers 'never' exposed to tar, mortality was not elevated above expectancy for any cancer site[2].

Using a case-control approach for these cases of prostatic cancer and for those in two other UK cohorts (of cadmium-nickel battery and cadmium-copper alloy workers), 39 cases were reported to have an odds ratio for cadmium exposure of 1.6 for 'ever medium' compared to 'always low' exposure levels and 1.4 for 'ever high' compared to 'always low' exposures; a similar approach for nine renal cancer patients revealed no elevation of odds ratio[6]. In a cohort of 522 male Swedish cadmium workers, eight cases of lung cancer were reported, resulting in a statistically nonsignificantly elevated standardized mortality ratio (SMR) for five years' exposure and ten or more years' latency. For prostatic cancer, four cases resulted in a statistically nonsignificant excess for the same exposure and latent periods[7].

In the USA, a follow-up study of 602 white male cadmium smelter workers with at least six months of production work between 1940 and 1969 was extended to 1978. The SMR (95% confidence interval) for respiratory cancer deaths was 165 (101-254), based on 20 deaths, and that for lung cancer, 157 (93-249), based on 18 deaths. Concomitant exposure to arsenic was especially high up to 1925. Reanalysis of lung cancer mortality for workers employed before or after 1 January 1926 revealed SMRs of 714 (195-1829) for the pre-1926 group (four cases) and 229 (131-371) for the post-1926 group with two or more years employment (16 deaths). For the post-1926 group (576 workers), a significant trend was noted for cumulative cadmium exposure and lung cancer mortality. Although the data on smoking are inadequate, and arsenic exposure continued after 1926, albeit at a lower level, the authors contend that these factors do not account for the excess lung cancer rates noted in the study. The number of prostatic cancers was unchanged from the earlier study (3 observed, 2.2 expected)[8]. Further reports of a UK population of 3025 (2559 male and 466 female) cadmium-nickel battery workers showed an excess of lung cancer in groups exposed for 18 years or more[9]. The excess mortality from prostatic cancer was accounted for by the original four cases described in 1967[1].

Potential confounding factors in these studies, such as smoking and exposure to nickel and arsenic, do not appear to account for the excess of lung cancer deaths. For prostatic cancer, the risk appears to be debatable, especially when the four hypothesis-generating UK cases from 1967 are removed from the analysis.

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

Cadmium chloride, oxide, sulphate and sulphide produced local sarcomas in rats after their subcutaneous injection, and cadmium powder and cadmium sulphide produced local sarcomas in rats following their intramuscular administration. Cadmium chloride and cadmium sulphate produced testicular tumours in mice and rats after their subcutaneous administration[1,10]. In one experiment, cadmium chloride administered subcutaneously to rats produced local sarcomas, testicular tumours and a significant increase in the incidence of pancreatic islet-cell tumours[11]. Cadmium chloride produced a dose-dependent increase in the incidence of lung carcinomas in rats after exposure by inhalation[12,13] and a low incidence (5/100) of prostatic carcinomas after injection into the ventral prostate[14]. Administration of up to 50 mg/kg (ppm) cadmium chloride in the diet to rats did not increase the incidence of tumours[15]. Cadmium acetate was not carcinogenic in a mouse-lung adenoma assay[16].

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[7]*IARC Monographs, Suppl. 6*, 178-181, 1987

CLOFIBRATE (Group 3)

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

Results of a further four years of follow-up to the clofibrate trial of the World Health Organization[1] have become available[2]. On average, the total follow-up period was 13.2 years, 5.3 of which were during the actual treatment phase (range, four to eight years) and 7.9 thereafter. Three groups of men, divided according to their cholesterol levels, were studied, comprising 208 000 man-years of observation. The first two groups included subjects in the upper third of the serum cholesterol distribution, randomly allocated either to treatment by clofibrate (1.6 g daily) or an olive-oil placebo. The third group was composed of half of the men in the lowest third of the distribution, who received an olive-oil placebo. At the conclusion of follow-up, the age-standardized death rates from malignant neoplasms per 1000 per annum were 2.4, 2.4 and 2.3, respectively (based on 206, 197 and 173 deaths from neoplasms). However, the age-standardized death rates for malignant neoplasms during the treatment phase had been 1.9 (42 deaths), 1.2 (25 deaths) and 1.7 (30 deaths), respectively.

Reports of two of four other clofibrate trials did not include information on the occurrence of cancer[1]. Of those which did, one showed no excess of cancer in treated groups over the six-year period of the trial (eight cancer deaths in all)[3], and, in the other, covering a follow-up period of five to 8.5 years, the death rates for all cancers were 0.9% for the group receiving clofibrate, 0.8% for a group receiving niacin and 0.9% for the placebo group[4]. Two further trials of clofibrate showed no excess of cancer in treated groups[2].

In a single case report, a man who received clofibrate (among other drugs) for 15 years developed a jejunal adenocarcinoma[2].

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

Clofibrate was tested in two studies by oral administration to male rats; it produced hepatocellular carcinomas, and a few pancreatic exocrine acinar adenomas and carcinomas were observed[1]. Clofibrate decreased the incidence of 7,12-dimethylbenz[*a*]anthracene-induced mammary carcinomas in rats, but did not affect the carcinogenic action of

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)   Reference P. 399-401
                                                      IARC 98

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.

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Crude Oil and Major Petroleum Fuels**

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Table 11 (contd)

Reference	Study subjects[a]	Comparison population	Period of follow-up	Occupation/exposure	Cancer site (cause of death)	Number of deaths observed	SMR[b]	Comments
Thomas et al. (1980)	1722 white male OCAW members in TX	US men	1947–77	Petroleum refinery chemical plant workers	All cancer	394	1.3*	Proportionate mortality study including deaths only among active Union members
					Digestive tract	111	1.2*	
					Respiratory tract	134	1.3*	
					Skin	14	1.9*	
					Brain	25	1.8*	
Thomas et al. (1982a,b)	2509 male OCAW members employed by 3 TX oil refineries	US men	1943–79		All cancer	553	1.2*	Proportionate mortality study including deaths among active and retired Union members
					Stomach	48	1.5*	
					Pancreas	37	1.4*	
					Lung	157	1.1	
					Skin	13	1.8*	
					Prostate	46	1.4*	
					Kidney	15	1.4	
					Brain	28	2.2*	
					Leukaemia	33	1.8*	
					Multiple myeloma	9	2.0	
Thomas et al. (1984)	Male OCAW members employed by 3 TX oil refineries	Internal comparison	1943–79	Intraplant pumping and transport of bulk liquids	Brain	7	2.8	Odds ratios from nested case-control study (Thomas et al., 1982a,b)
				Lubricating oil	Stomach	19	1.7	
				Maintenance work	Stomach	47	4.5	
				Treating	Leukaemia	6	1.6	
				Boiler makers	Leukaemia	5	1.5	
Divine et al. (1985)	19 077 white men employed 5+ years by Texaco	US white men	1947–77	Refinery, petro-chemical, research	All causes	4024	0.75**	[Includes workers from refinery A (Thomas et al., 1980, 1982a,b, 1984)] Significant deficits of cancers of the stomach, large intestine, lung and bladder
					All cancer	767	0.75**	
					Pancreas	62	1.1	
					Brain	31	1.1	
					Leukaemia	48	1.2	
					Other lymphatic cancer	25	1.2	
					Benign neoplasms	20	1.5	

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,

(Wigle, 1977). An equal number of controls who had died from other causes were matched on city, calendar period of death and age. Fifty-seven study subjects were residents of Sarnia, where 28% of the male work force was employed in petroleum refining or the chemical industry; while 291 were from London, where 1% of the men were so employed. Five cases and 12 controls were employed in petroleum refining [odds ratio calculated by the Working Group, 0.42; 95% CI, 0.2—1.0]. [The Working Group noted that no information was available on smoking habits.]

Usual occupation and type of industry listed on the death certificates of residents of 19 southern Louisiana, USA, parishes were obtained for all lung cancer deaths (3327) that occurred between 1960 and 1975 and for an identical number of adults who had died from causes other than cancer, matched on sex, race, age and parish of usual residence (Gottlieb et al., 1979). A logistic model was used to calculate odds ratios (adjusted for age, marital status, year of death, birthplace and parish of residence) by sex and race to estimate the risk for lung cancer of specific occupational and industrial categories. Among men who had been employed in petroleum refining, the race-adjusted odds ratio for lung cancer was 1.3 (95% CI, 0.93—1.9). The sex-adjusted odds ratio for lung cancer among whites who had been employed in petroleum refining was 1.3 (95% CI, 0.88—1.8) and that among blacks was 2.2 (95% CI, 0.59—7.9). Odds ratios for lung cancer among subjects whose usual residence had been in a town in which there was a petroleum refinery were elevated in each sex-race group (white men: 306 cases; odds ratio, 1.2 (95% CI, 0.97—1.4); black men: 28 cases; odds ratio, 1.9 (0.99—3.6); white women: 58 cases; odds ratio, 1.3 (0.86—2.0); black women: ten cases; odds ratio, 1.7 (0.60—4.6)). However, none of the results was significant. Further analyses of specific occupations within the petroleum industry indicated a significantly elevated odds ratio for lung cancer among men who had been employed in skilled maintenance trades or operator jobs in petroleum refining and who had died at age 60 or older (25 cases; odds ratio, 2.4; 95% CI, 1.0—5.9; Gottlieb, 1980). When the study group was restricted to subjects whose length of residence at the location listed on the death certificate could be verified from public records, subjects who had lived within a mile of a petroleum industry work site for at least ten years had an elevated lung cancer risk (work site with <100 employees: 11 cases; odds ratio, 1.5; work sites with ≥100 employees: 32 cases; odds ratio, 1.7). Among subjects who had lived near a petroleum industry work site and whose usual occupation had been in the petroleum industry, there was a significantly elevated risk for lung cancer (36 cases; odds ratio, 2.3), controlling for year of death, age, race, years of residence and industry size (Gottlieb et al., 1982). [No information on smoking habits or on exposure to asbestos was available.]

(iii) Other sites

[A preliminary study of risk factors for pancreatic cancer in the same Louisiana parishes included 876 case-control pairs identified from death certificates for the years 1960—75, using the same methods as for the studies on bladder and lung cancer (Pickle & Gottlieb, 1980). There was a two-fold excess risk for pancreatic cancer among white men whose usual industry of employment had been petroleum refining (15 cases; odds ratio, 2.1; 95% CI, 0.86—5.2), but this was not significant. Pancreatic cancer risk was elevated among white men

(40 cases; odds ratio, 1.2), white women (36 cases; odds ratio, 1.2) and black women (three cases, odds ratio, 1.4) whose usual residence had been near a petroleum refinery, but not among black men (three cases; odds ratio, 1.0).

Usual industry and occupation on the death certificates of 718 white men aged 30 and over who had died from malignancies or unspecified tumours of the brain were compared with those of 738 white men who had died of other causes, excluding epilepsy and stroke, and were frequency matched for age and study area (Thomas *et al.*, 1986). All study subjects were residents of three geographical areas of the USA with a heavy concentration of petroleum and chemical industries (southern New Jersey, Philadelphia area and Gulf Coast of Louisiana), who had died between 1979 and 1981, and for whom a death certificate was found (99.7%). Risk for brain tumours in each usual occupation and industry listed was estimated by calculating a maximum likelihood estimate of the odds ratio, adjusting for age, marital status and occupation status (blue-collar, white-collar). The odds ratio for petroleum refining was 1.2 (95% CI, 0.6–2.6).

In a further analysis, lifetime occupational histories were obtained through interviews with next-of-kin (Thomas *et al.*, 1987); 483 cases and 386 controls agreed to be interviewed. The analysis was performed on 300 white men who had had confirmed astrocytic tumour of the brain (astrocytoma, glioblastoma multiforme or mixed glioma with astrocytic cells). Astrocytic tumour risk associated with ever having been employed in specific industries was estimated by maximum likelihood techniques. Among men who had ever been employed in petroleum refining, the odds ratio for astrocytic tumours was 1.5 (18 cases; 95% CI, 0.7–3.2). The elevated risk among men ever employed in petroleum refining was limited to those who had worked in production and maintenance jobs (15 cases; odds ratio, 1.7; 95% CI, 0.7–4.2); however, among those whose duration of employment was known, risk decreased with increasing duration of employment in the industry (<5 years: five cases, odds ratio, 6.7; 5–9 years: two cases, odds ratio, 1.3; ≥20 years: four cases, odds ratio, 0.8). [The Working Group calculated that this trend was statistically significant.]

A death certificate-based case-control study was conducted in the counties of Cleveland, Humberside and Cheshire and the Wirral district of Merseyside in the UK to examine the relationship between occupation and risk for five cancers — of the oesophagus, pancreas, kidney and brain and melanoma (Magnani *et al.*, 1987). Cases had been male residents of the study areas who had died from one of the five cancers between the ages of 18 and 54 during the periods 1959–63 and 1965–79 (data for 1964 were not available). One set of controls who had died from other causes was matched to each case on county of residence and another set on 'local authority area' of residence; both sets were matched on sex and age at death. Occupation and industry listed on the death certificates were used to classify subjects into occupational and exposure categories. There were 244 cases of oesophageal cancer with 935 controls, 343 of pancreatic cancer with 1315 controls, 99 of melanoma with 361 controls, 147 of kidney cancer with 556 controls, and 432 of brain cancer with 1603 controls. Significantly elevated odds ratios were not reported for oesophageal, pancreatic or kidney cancer in association with petroleum refining occupations; there were significantly elevated odds ratios for melanoma (odds ratio, 8.0; 95% CI, 1.5–43.7) and brain cancer (odds ratio, 3.5; 1.5–8.1) associated with occupational exposure to coal and petroleum products. Both

Mortality from leukaemia was significantly elevated in two refinery cohorts; in one of these, mortality increased with duration employed and also with time since first employment. Nonsignificant excess mortality from leukaemia was reported among two additional cohorts; in one of these, the excess was significant for boiler makers and pipe fitters. Elevated mortality from unspecified lymphatic leukaemia, unspecified myeloid leukaemia and acute monocytic leukaemia, but not other cell types, was reported in a subset of workers in the British cohort whose exposures included benzene. A significantly elevated incidence of lymphocytic leukaemia was reported in a large cohort study which included many of the refineries in the USA. Excess mortality from 'cancer of other lymphatic tissues' (multiple myeloma, polycythaemia vera and non-Hodgkin's lymphoma, excluding lympho-sarcoma and reticulum-cell sarcoma), which was not significant, was reported in five refinery cohorts. One report indicated significant excess mortality from leukaemia and 'cancer of other lymphatic tissues' combined.

Mortality from malignant neoplasms of the brain was elevated in six of the refinery cohorts, but this was significant in only one of the studies and only for workers with short duration of employment. The elevated mortality was seen in operators and in maintenance and laboratory workers. A case-control study of astrocytic brain tumours showed a decreasing trend in risk with duration employed among men who had ever worked in petroleum refining during their lifetime. Another case-control study showed a significantly elevated risk for malignant neoplasms of the brain among men employed in petroleum refining.

Stomach cancer mortality was elevated among six refinery cohorts, significantly so in only one, among labourers, riggers and fire and safety workers; it was associated with lubricating oil production in one refinery and with solvent dewaxing in another. Mortality increased with increasing duration of employment in one of the studies.

Kidney cancer mortality was elevated, but not significantly so, among three petroleum refinery cohorts, particularly among operators, labourers and maintenance workers. Kidney and bladder cancer mortality combined was elevated in one refinery cohort. Five case-control studies of bladder cancer showed excess risk associated with employment in petroleum refining; the results were significant in two of these.

Pancreatic cancer mortality was reported to be elevated in four petroleum refining cohorts, and was associated with employment in the petroleum refining industry in one case-control study; however, none of these results was significant.

Excess mortality from cancer of the prostate, which increased with duration of employment, was reported in two refinery cohorts, and an overall excess was reported in two others. The only result that attained significance was found for men employed for 20 years or more in one of the refineries.

Lung cancer mortality was elevated in two refinery cohorts but not significantly so. There was a significant excess of lung cancer among workers with daily exposure to petroleum and its products in one of these cohorts. In five cohort studies, significant deficits in mortality from lung cancer were seen. In a case-control study, refinery maintenance workers and operators had a significantly elevated risk for lung cancer.

control group of 616 women who had no contact with chemicals was also studied. The majority (78.9%) of exposed women were aged 20—40 years and 60.8% had been employed for three years or more. A higher percentage of exposed women (16.8% *versus* 8.4% of controls) had toxaemia of pregnancy and short gestation period (11.2% *versus* 4.2%), and perinatal mortality was reported to be increased (Mukhametova & Vozovaya, 1972). [The Working Group noted the complex exposure of the women in the rubber plant and the lack of control for potential confounding factors.]

Genetic and related effects

A group of 16 tank cleaners were studied for cytogenetic changes; a subgroup of four men who had cleaned gasoline tanks over the preceding ten months was also included. Micronuclei in bone-marrow cells and chromosomal aberrations in peripheral blood lymphocytes were reported to be significantly more prevalent in the whole group than in the control group (Högstedt *et al.*, 1981). [The Working Group noted that the results were not reported separately for the different subgroups of cleaners and that the workers would have been subjected to mixed exposures.]

3.3 Epidemiological and case report studies of carcinogenicity to humans

The studies considered in this section generally involved mixed exposures. In particular, exposure was often to both gasoline and diesel fuels, and it is not possible from the data to separate the effects of the two types of fuel. In the selection of papers for consideration, emphasis was placed on those which discussed exposure to the fuels themselves and not on those which concerned their combustion products, which are covered in Volume 46 of the *Monographs* series (IARC, 1989).

(a) Cohort studies

An analysis of the mortality of 23 306 men employed for at least one year between 1950 and 1975 at petroleum distribution centres in the UK was performed by Rushton and Alderson (1983). The dominant job titles were drivers (43%) and operators (20%), according to company records. No detailed exposure data were given. Only 0.2% of the men were not traced in a follow-up of the cohort until 1975. Causes of death (3926) were obtained from central registers; in comparison with male mortality rates for England and Wales, a significant ($p < 0.0001$) deficit in overall mortality (standardized mortality ratio (SMR), 0.85) was observed in the cohort, which was consistent for most malignant and nonmalignant causes of death. Mortality from neoplasms of the lymphatic and haemato-poietic tissues was slightly increased overall (77 deaths; SMR, 1.1; $p = 0.3$), reaching significance for myelofibrosis only (SMR, 2.8; $p = 0.04$). Mortality was increased in some subgroups of the population defined primarily by company and job, but no consistent pattern emerged, suggesting that these were chance findings.

In a study of the risks for pancreatic cancer in various occupations, a record linkage was performed between the 1960 Swedish census and the Swedish cancer registry for 1961—79 (Norell *et al.*, 1986). Information on branch of industry was obtained from the census for

about two million male employees aged 20—64 years, and the observed number of pancreatic cancer cases in certain occupational groups was compared with corresponding expected numbers based on cumulative incidence in the total cohort. Particular attention was paid to employment in the wood and paper industry, and to occupations involving potential exposure to metals or petroleum products. The observed number of cases was similar to those expected for the occupational groups studied, although a moderate excess in the incidence of pancreatic cancer was noted among gasoline station workers (SMR, 1.6; 90% confidence interval (CI), 1.1—2.3).

[The Working Group noted the lack of detailed exposure data and lack of control of potentially important confounding factors, which render the interpretation of these studies difficult.]

Information on occupation and cause of death from death records of a total of 429 926 men in Washington State, USA, from 1950—79 were used in a proportionate mortality ratio (PMR) analysis standardized for age and year of death (Milham, 1983). Three occupational groups in which exposure to gasoline may occur were studied: service station and garage owners and attendants; fuel oil dealers/workers and motor vehicle mechanics/repairmen. Considering all age groups during the total observation period, increased PMRs ($p < 0.05$) were found for cancer of the oesophagus, bronchus and lung and for non-Hodgkin's lymphomas in motor vehicle mechanics/repairmen. When specific decades were considered, elevated PMRs were also found for lymphatic leukaemia in motor vehicle mechanics/repairmen (1960—69; 8 cases; PMR, 2.8) and bladder cancer in service station and garage owners and attendants (1950—59; 9 cases; PMR, 2.2; and 1960—69; 11 cases; PMR, 1.9).

A PMR analysis was conducted of all white male deaths (37 426) occurring in the state of New Hampshire, USA, between 1975 and 1985 (Schwartz, 1987). Information on occupation, industry and cause of death was abstracted from death certificates, and expected numbers were calculated from the US general population. Total numbers of 453 and 134 deaths were recorded among motor vehicle mechanics and workers in the gasoline service industry, respectively. No significantly elevated PMR was noted for malignant neoplasms among motor vehicle mechanics, although there was a slight increase for leukaemias and aleukaemias (PMR, 1.8). For workers in service stations, the increase in PMR for leukaemia and aleukaemia was significant (PMR, 3.3; $p < 0.05$). Among nine cases of leukaemia observed, five were myeloid, two were lymphoid and two were unspecified.

[The Working Group noted the limitations inherent in PMR analysis. Furthermore, crude exposure information and lack of control for potentially important confounding factors weaken the possibility of causal interpretations.]

(b) Case-control studies

(i) Kidney

In a population-based case-control study, risk factors for renal-cell carcinoma, including occupational exposures, were investigated (McLaughlin et al., 1984). A total of 506 cases diagnosed between 1974 and 1979 were identified from hospitals in the

suggested an elevated risk for workers exposed to unspecified petroleum, tar or pitch products.

A Swedish study, similar in design to a case-control study, indicated an increased risk for acute nonlymphocytic leukaemia in men with occupational exposure to petroleum products. One hospital-based case-control study in the USA revealed an increased risk for testicular cancer in service station attendants and garage workers; another showed an increased risk for pancreatic cancer in men with occupational exposure to dry cleaning agents or gasoline. Another US case-control study demonstrated an increased risk for liver cancer in service station attendants, particularly for hepatocellular carcinoma. A case-control study of cancer at many sites in Canada revealed an elevated risk only for stomach cancer among men exposed to automotive gasoline.

Nine case-control studies from four countries provide data on paternal occupations involving exposure to hydrocarbons and the risk for cancer in children. There was no consistent association between father's occupation and risk for childhood cancer, although significant results appeared in a few of the studies. Only one study gave detailed data on maternal occupations involving exposure to hydrocarbons during pregnancy; this suggested an increased risk for leukaemia in their children. No study specifically assessed exposure to gasoline, but paternal occupations such as motor vehicle mechanic and service station attendant were not consistently associated with an increase in risk.

4.4 Other relevant data

Urinary thioether excretion was increased in samples taken from service station attendants after work. The half-life of antipyrine was reduced in such workers.

No report specifically designed to study genetic and related effects in humans following exposures to gasoline was available to the Working Group.

Male, but not female, rats developed nephropathy after exposure to unleaded gasoline, with hyaline droplet accumulation, necrosis and degeneration of proximal convoluted tubules. The extent and severity of hyaline droplet accumulation paralleled the extent and localization of renal tubular cell proliferation.

Two samples of unleaded gasoline (one described as PS-6, the other as having a boiling range of 31–192°C) were tested in a series of assays for genetic and related effects. Neither sample induced chromosomal aberrations in the bone marrow of rats treated *in vivo*. The PS-6 sample induced unscheduled DNA synthesis *in vivo* in male and female mouse hepatocytes, but not in male rat hepatocytes or in male or female rat kidney cells, nor did it induce sister chromatid exchange or mutation in cultured human lymphocytes. Neither sample induced mutation in cultured mammalian cells; however, an extract of and the residue from the evaporation of the PS-6 sample did induce mutation in cultured mammalian cells. The PS-6 sample induced unscheduled DNA synthesis *in vitro* in mouse, rat and human hepatocytes but not in rat kidney cells. A leaded gasoline induced somatic mutation in insects. The other sample of unleaded gasoline, an extract of the PS-6 sample and the residue from the evaporation of the PS-6 sample did not induce mutation in bacteria (see Appendix 1).

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incident cancers of the lung (SIR, 1.5; 95% CI: 1.2–1.9, 87 cases), of the small intestine (SIR, 2.6; 95% CI: 1.0–5.4, seven cases), of the colon (SIR, 1.3; 95% CI: 1.0–1.7, 52 cases), of the pancreas (SIR, 1.7; 95% CI: 1.1–2.4, 30 cases), and non-lymphocytic leukaemia (SIR, 2.1; 95% CI: 1.1–3.6, 13 cases). [The relevance of these findings for paint-manufacturing workers specifically is difficult to judge as they are combined with lacquer-manufacturing workers, who may have had different exposures].

2.2 Case–control studies

2.2.1 Cancer of the lung (Table 2.2)

In 1989 (Monograph 47), nine case–control studies of lung cancer and two multisite case–control studies, which included lung cancer, were evaluated. These studies are summarized in Table 24 of Monograph 47 (IARC, 1989).

(a) Europe

Jahn et al. (1999) carried out a pooled analysis of the two case–control studies on lung cancer conducted in Germany: the Bremen Institute for Prevention Research and Social Medicine (BIPS) study in the Bremen and Frankfurt/Main areas, during 1988–1993, and the GSF-National Research Center for Environment and Health (GSF) study in Nordrhein-Westfalen, Rheinland-Pfalz and Bayern, Saarland, Thuringen, and Sachsen, during 1990–1996. The results from the BIPS study had been reported earlier by Jöckel et al. (1992, 1998) for both sexes combined. The Jahn et al. (1999) analysis was restricted to women, and included 686 cases aged 75 or less at diagnosis, of German nationality, residing in the study regions. All cases were confirmed by histology or cytology. Population controls, 712 individuals, were randomly selected from population registries or by random digit dialling, and were individually (BIPS study) or frequency- (GSF study) matched to cases by age, and region. A standardized questionnaire, with full occupational history and supplementary job-specific modules, was administered during face-to-face interviews. The response rate was 73% among cases, and 45% in controls. An odds ratio (OR) of 3.00 (95% CI: 0.73–12.33) was found after adjustment for smoking and asbestos exposure (age and region of residence were strata-defining variables in the conditional logistic regression models) for the occupation of 'ever' painter. [A major strength of this study was exposure definitions, based on complete and accurate occupational histories, and expert-based quantitative exposure assessment for a series of carcinogens. However, the low response rate among controls might have led to selection bias].

Brüske-Hohlfeld et al. (2000) also carried out a pooled analysis of the two case-control studies described above (the BIPS and GSF studies). The results from the BIPS study had been reported earlier by Jöckel et al. (1992, 1998) for both sexes combined. This analysis was restricted to men, and included 3498 cases aged 76 or less at diagnosis who lived in Germany for at least 25 years and resided in the study regions. All cases were confirmed by histology or cytology. Population controls, 3541 individuals, were randomly selected from population registries or by random digit dialling, and were individually (BIPS study) or

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:

$$CH_4 + 2O_2 + \text{Energy of activation} \rightarrow CO_2 + 2H_2O + \text{Heat of combustion} + \text{Light}$$
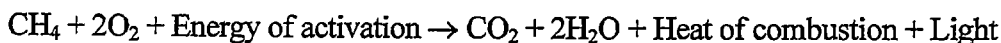
Given the appropriate ratio of fuel (wood, solvent, plastic, rubber), oxygen, and combustion temperature, the products of combustion should be only water and carbon dioxide (CO_2).

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:

$$CH_4 \rightarrow CH_3^{\bullet} + H^{\bullet}$$
$$H^{\bullet} + O_2 \rightarrow OH^{\bullet} + O^{\bullet}$$
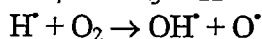
The free radicals formed during combustion are very reactive and side reactions are propagated to yield hundreds of chemical products, and smoke.

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	

years of service weighted by exposure opportunity. The study attained 96% follow-up of vital status and over 64 983 person–years of observation; 370 deaths were recorded. Excesses were observed for all malignant neoplasms (SMR, 1.3; 95% CI: 1.0–1.6), and for cancers of the lung (SMR, 1.4; 95% CI: 0.9–2.1), bladder (SMR, 3.2; 95% CI: 0.9–8.1), kidney and ureter (SMR, 4.1; 95% CI: 1.7–8.5), colon and rectum (SMR, 1.6; 95% CI: 0.9–2.7), pancreas (SMR, 1.6; 95% CI: 0.5–3.6), and leukaemia, lymphoma and myeloma (SMR, 1.3; 95% CI: 0.6–2.3). The lung cancer excess was confined to Edmonton; there was no consistent association with duration of employment, exposure opportunity, or decade of entry into the cohort (before or after the 1950s) except that the highest risk was observed among Edmonton firefighters with over 35 weighted years of service. Urinary tract cancer excess was observed mostly among firefighters entering service after 1950, and appeared to increase with the length of service and exposure opportunity, and was observed in both cities.

Aronson et al. (1994) conducted a retrospective cohort mortality study of all male employees of the six fire departments within metropolitan Toronto, Ontario, Canada (n = 5995). The study population consisted of all male firefighters who had worked for at least 6 full months in metropolitan Toronto at any time during 1950–1989. Mortality was ascertained through computerized record linkage and compared to that of the male Ontario population specific to cause, age, and calendar period during 1950–1989. The cohort accrued 114 008 person–years and the average duration of follow-up was 21 years. Mortality was examined by duration of exposure. The SMR for all malignant neoplasms was 105 (95% CI: 91–120), for brain tumours, 201 (95% CI: 110–337), and for "other" malignant neoplasms, 238 (95% CI: 145–367). Non-significant increases in risk were observed for some other sites, in particular rectum (SMR, 171), larynx (SMR, 140), and testis (SMR, 252).

Tornling et al. (1994) conducted a cohort mortality study of all male fire fighters employed for at least 1 year in the City of Stockholm, Sweden during 1931–1983 (n = 1116). The population was identified from annual employment records. Follow-up for mortality was from 1951 until 1986, and for cancer incidence from 1958 to 1986. Except for four persons who had emigrated from Sweden, follow-up was 100% complete. To assess the occupational exposure as a firefighter, an index of participation in number of fires was calculated for each individual based on the number of reports on all fires in Stockholm that had been maintained since the beginning of the twentieth century. The all-site cancer mortality in 1958–1986 was equal to the expected (SMR, 100; 95% CI: 83–119). An excess of stomach cancer incidence (SIR, 192; 95% CI: 114–304; 18 observed versus 9.37 expected) was observed. There was also a tendency for higher incidence and mortality in stomach and brain cancers with increasing number of fires. Four brain cancer cases were observed compared to 0.8 expected (SIR, 496; 95% CI: 135–1270) in the highest exposure category.

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.

Table 2.7 (contd)

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR/SMR/MO R (95% CI)	Adjustment for potential confounders	Comments
Ma et al. (1998), 24 states, USA	Analysis of 1984–1993 death certificate data, 6607 firefighters identified	Usual occupation on death certificate		Overall, caucasian males		**MOR**	Age, year of death	
			All		1817	1.1 (1.1–1.2)		
			Lip		3	5.9 (1.9–18.3)		
			Colon		149	1.0 (0.9–1.2)		
			Rectum		27	1.1 (0.8–1.6)		
			Pancreas		88	1.2 (1.0–1.5)		
			Lung		633	1.1 (1.0–1.2)		
			Prostate		189	1.2 (1.0–1.3)		
			Bladder		48	1.2 (0.9–1.6)		
			Kidney & pelvis		49	1.3 (1.0–1.7)		
			Brain & CNS		41	1.0 (0.8–1.4)		
			non-Hodgkin lymphoma		76	1.4 (1.1–1.7)		
			Multiple Myeloma		28	1.1 (0.8–1.6)		
			Leukaemia		60	1.1 (0.8–1.4)		
			Soft tissue sarcoma		14	1.6 (1.0–2.7)		
				Overall, black males				
			All		66	1.2 (0.9–1.5)		
			Nasopharynx		1	7.6 (1.3–46.4)		
			Colon		9	2.1 (1.1–4.0)		
			Pancreas		5	2.0 (0.9–4.6)		
			Lung		15	0.8 (0.5–1.3)		
			Prostate		16	1.9 (1.2–3.2)		
			Brain & CNS		5	6.9 (3.0–16.0)		

* specify P value if no confidence interval indicated; MOR, mortality odds ratio; NJ, New Jersey; NR, not reported; n.s, not significant; PMR, proportionate mortality ratio; SMR, standardized mortality ratio

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.]

CHEMICAL AGENTS
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vol100F/100F-14-Table2.1.pdf). Case series indicative of an increased risk for scrotal cancer continue to be published based on historical exposures. Pressmen working in a wax-manufacturing department in an oil refinery in the USA had a marked excess of scrotal cancer based on 11 cases in men working >10 years during the period 1937–56, which corresponds to a crude rate of 806 per 100,000 relative to a general population rate estimated at 0.15 per 100,000 (Hendricks et al., 1959). Tool setters and tool fitters in the West Midlands area of England showed notably elevated risk for scrotal cancer over the period 1936–1976 (Waldron et al., 1984).

Several epidemiological studies were able to detect the expected increased risk for skin cancer in general, or scrotal cancer in particular, but since these cancers are rarely fatal, studies based on cancer mortality were of limited use to address the question. Roush et al. (1982) studied squamous-cell carcinoma of the scrotum in a case–control study in Connecticut, USA, among men diagnosed between 1935 and 1973 (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.2.pdf). Occupations associated with exposure to cutting oils, including tool or machine setters, screw-machine operators, machinists, and machine operators, were examined and showed an odds ratio of 10.5 (95%CI: 4.0–36.9).

2.3 Other cancers

The more rigorous epidemiological studies pertain to the occupations in which mineral oils are used in various formulations and in different degrees, including metal workers, machinists, jute workers, and others. Given the time period and setting, the mineral oils studied were likely to be highly treated. At the time of the previous *IARC Monograph* there were several studies of workers in these industries, mostly based solely on job title and industry of employment and limited in detail regarding exposure (IARC, 1984). Exposure to mineral oil was inferred based solely on job title or self-reported exposure. Whereas dermal exposure is the primary route of exposure for skin/scrotal cancer, for other sites and under improved hygienic conditions, aerosols are of equal or greater concern.

Focusing on studies that made attempts to address exposure to mineral oil directly, there has been sporadic and inconsistent support for an association with bladder cancer (Ugnat et al., 2004; Friesen et al., 2009; see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.3.pdf and Table 2.4 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.4.pdf), stomach cancer (Zhao et al., 2005; see Table 2.5 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.5.pdf and Table 2.6 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.6.pdf), rectal cancer (Gerhardsson de Verdier et al., 1992; Eisen et al., 2001; see Table 2.7 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.7.pdf and Table 2.8 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.8.pdf), pancreatic cancer (Yassi et al., 2003), sinonasal cancers (Roush et al., 1980), laryngeal cancer (Ahrens et al., 1991; Eisen et al., 1992), and lung cancer (Rønneberg et al., 1988; Acquavella et al., 1993; see Table 2.9, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.9.pdf and Table 2.10 at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-14-Table2.10.pdf). Individual studies have suggested that mineral oil may be related to a range of other cancers, including those of the larynx and pancreas, based on studies of metal-workers and related manufacturing occupations. For each of these, however, there are studies of equal or higher quality that do not show associations, and in many cases there are inconsistent results within the same study across exposure indices. There have been varyious interpretations of the strength of the

The epidemiological evidence for an association with specific subtypes of haematolymphatic malignancies is weaker, mainly since numbers are lower, giving imprecise risk estimates. However, when malignant lymphomas and leukaemias are distinguished, the evidence is strongest for leukaemia.

3. Cancer in Experimental Animals

3.1 1,3-Butadiene

Studies on the carcinogenesis of 1,3-butadiene in rats and mice have been reviewed in previous IARC Monographs (IARC, 1999, 2008) and by Grosse et al. (2007). The results of adequately conducted carcinogenicity studies are summarized in Table 3.1. There were no additional studies reported in the published literature since IARC Monograph Volume 97 (IARC, 2008).

1,3-Butadiene was tested for carcinogenicity by inhalation exposure in one study in rats and four studies in mice.

Inhalation of 1,3-butadiene induced tumours in rats at exposure concentrations ranging from 1000 to 8000 ppm [2200–17650 mg/m³], and in multiple organs in mice at exposure concentrations ranging from 6.25 to 1250 ppm [13.8–2760 mg/m³]. In rats, 1,3-butadiene caused a significantly increased incidence of carcinomas of the Zymbal gland, sarcomas of the uterus, adenomas and carcinomas (combined) of the mammary gland, and follicular cell adenomas of the thyroid gland in females. In males, it caused malignant gliomas and adenomas of the pancreas and testes in males (Owen et al., 1987; Owen & Glaister, 1990; Melnick et al., 1993; Melnick & Huff, 1993). In mice of both sexes, 1,3-butadiene caused a significantly increased incidence of Harderian gland adenomas and carcinomas, heart haemangiosarcomas, lymphoid tissue neoplasms (lymphoma, histiocytic sarcoma), lung adenomas and carcinomas, hepatocellular

adenomas and carcinomas, and fore-stomach papillomas and carcinomas. It caused mammary gland cancers, benign tumours and carcinomas of the ovary, and skin sarcomas in females. It also caused preputial gland carcinomas and kidney tubule adenomas in males (NTP, 1984, 1993; Huff et al., 1985; Miller et al., 1989; Melnick et al., 1990a, b, 1993; Melnick & Huff, 1993; Hong et al., 2000; Melnick & Sills, 2001; Kim et al., 2005). No increased incidence of tumours was observed in one study in mice exposed once to 1,3-butadiene at concentrations up to 10 000 ppm [22000 mg/m³] (Bucher et al., 1993).

3.2 Diepoxybutane

Diepoxybutane, a metabolite of 1,3-butadiene, was tested for carcinogenicity by inhalation in one study in rats and one study in mice, by four skin-application studies in mice, by one subcutaneous injection study in rats and two such studies in mice, and by one gavage and one intraperitoneal injection study in mice (Tables 3.1, 3.2, 3.3, 3.4).

Diepoxybutane increased the incidence of adenomas of the Harderian gland in female mice, and of squamous cell carcinoma of the nose in female rats after inhalation exposure (Henderson et al., 1999, 2000). Subcutaneous injection resulted in an increased incidence of fibrosarcomas in female rats and female mice. The gavage study in mice did not produce any tumours (Van Duuren et al., 1966). Intra-peritoneal injection led to an increased incidence of lung tumours in strain A/J mice (Shimkin et al., 1966). Two skin-application studies in mice resulted in an increased incidence of dermoid carcinomas (Van Duuren et al., 1963, 1965).

Table 3.1 Carcinogenicity studies in experimental animals exposed to 1,3-butadiene and diepoxybutane by inhalation

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
1,3-Butadiene				
Rat, Sprague-Dawley (M, F) killed at 52 wk, remainder killed when survival was approximately 20% (105 wk for F, 111 wk for M) Owen & Glaister (1990), Melnick et al. (1993), Melnick & Huff (1993)	0, 1 000, 8 000 ppm, 6 h/d, 5 d/wk 110/group	Pancreas (exocrine adenomas): 3/100, 1/100, 10/100 (M); 2/100, 0/100, 0/100 (F)	$P \leq 0.001$ (high-dose M) $P \leq 0.001$ (trend M)	99.2% pure 16 deaths occurred during the first yr. During the second yr mortality increased with increasing dosage. Increased mortality in females was due to mammary tumours and in males due to renal lesions. The incidence of uterine sarcomas and Zymbal-gland tumours were similar to the historical laboratory control. Zymbal-gland tumours were noted between 76 and 90 wk.
		Uterus (sarcomas): 1/100, 4/100, 5/100 (F)	$P \leq 0.005$ (trend F)	
		Zymbal gland (adenomas): 1/100, 1/100, 1/100(M); 0/100, 0/100, 0/100 (F)	Carcinoma: $P \leq 0.05$ (trend F)	
		Zymbal gland (carcinomas): 0/100, 0/100, 1/100 (M); 0/100, 0/100, 4/100 (F)		
		Mammary gland (benign): 0/100, 2/100, 0/100 (M); 32/100, 64/100, 55/100 (F)	NS	
		Mammary gland (malignant): 1/100, 0/100, 0/100 (M); 18/100, 15/100, 26/100 (F)	NS	
		Mammary gland (total combined benign and malignant mammary tumours): 1/100, 2/100, 0/100 (M); 50/100, 79/100, 81/100 (F)	$P \leq 0.001$ (trend F)	
		Thyroid (follicular cell adenomas): 3/100, 5/100, 1/100 (M); 0/100, 2/100, 10/100 (F)	$P \leq 0.01$ (trend F)	
		Thyroid (carcinomas): 1/100, 0/100, 0/100 (M); 0/100, 2/100, 1/100 (F)	NS	
		Testis (leydig cell tumours): 0/100, 3/100, 8/100 (M)	$P \leq 0.001$ (trend M)	
		Brain (glial cell tumours (malignant)): 1/100, 4/100, 5/100 (M)	$P \leq 0.05$ (trend M)	

Composition of Fire Smoke:

Smoke from fires comprises suspended liquid and solid particulate matter, gases, and vapors that result from the combustion or pyrolysis of material.

- **ALL** types of fire release toxic and carcinogenic substances.

Overall Evaluation: The agent is described according to the wording of one of the following categories, and the designated group is given. This categorization of an agent is a matter of scientific judgment that reflects the strength of evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1	Carcinogenic to humans
Group 2A	Probably carcinogenic to humans
Group 2B	Possibly carcinogenic to humans
Group 3	Not classifiable as to its carcinogenicity to humans
Group 4	Probably not carcinogenic to humans

Carcinogens Found in Smoke at Fires	
Chemicals measured in fires	Classification
1,3-Butadiene	1
2,3,7,8-tetrachloro dibenzo-*para*-dioxin	1
Arsenic	1
Asbestos	1
Benzene	1
Benzo[*a*]pyrene	1
Cadmium	1
Formaldehyde	1
Polychlorinated biphenyls	1
Radioactivity (γ activity)	1
Radionuclides (α-particle-emitting)	1
Radionuclides (β-particle-emitting)	1
Silica (crystalline)	1
Trichloroethylene	1
Dibenz[*a,h*]anthracene	2A
Dichloromethane (methylene chloride)	2A
Lead compounds, inorganic	2A
Tetrachloroethylene (perchloroethylene)	2A
Acetaldehyde	2B

Carcinogens Found in Smoke at Fires	
Chemicals measured in fires	Classification
2-Nitroanisole	2B
Benz[*a*]anthracene	2B
Benzo[*b*]fluoranthene	2B
Benzo[*k*]fluoranthene	2B
Benzofuran	2B
Carbon black	2B
Chrysene	2B
Ethylbenzene	2B
Furan	2B
Indeno-1,2,3-[*cd*]pyrene	2B
Isoprene	2B
Lead	2B
Naphthalene	2B
Polychlorophenols	2B
Styrene	2B
Toluene diisocyanates	2B
Trichloromethane (chloroform)	2B
Lead compounds, organic	3
Silica (amorphous)	3
Triphenylene	3

Several studies have been conducted with the purpose of identifying the chemicals and known carcinogens found **during the overhaul phase of a structure fire.** 🖎

- o *Characterization of Firefighter Exposures During Fire Overhaul* (Phoenix FD and the University of Arizona Prevention Center and Arizona State University).
- o *A Study on Chemicals found in the Overhaul Phase of Structure Fires using Advanced Portable Air Monitoring available for Chemical Speciation* (Tualatin Valley Fire & Rescue – Oregon)

Chemicals measured in overhaul environment	IARC Classification
1,3 Butadiene	1
Arsenic	1
Asbestos	1
Benzene	1
Benzo(a)pyrene	1
Coal Tar Pitch	1
Diesel Exhaust	1
Formaldehyde	1
Vinyl Chloride	1
Dibenz(a,h)anthracene	2A
N-Nitrodimethylamine	2A
1,2 Dichloroethane	2B
Acetaldehyde	2B
Benz(a) anthracene	2B
Benzo(b)fluoranthene	2B
Benzo(k)fluoranthene	2B
Benzofuran	2B
Ethyl benzene	2B
Furan	2B
Indeno(1,2,3-cd)pyrene	2B
Lead	2B
Napthalene	2B
Styrene	2B
Mercury	3
Hydrochloric Acid	3
Toluene	3
Acrolein	3
Furfural	3
Acenaphthene	3
Anthracene	3
Benzo(ghi)perylene	3
Fluoranthene	3
Fluorene	3
Phenanthrene	3
Pyrene	3

Diesel Engine Exhaust:

On June 12, 2012, the International Agency for Research on Cancer (IARC), part of the World Health Organization and the authority on cancer, classified diesel engine exhaust as a Group 1 Carcinogen, meaning that it causes cancer in humans.

Diesel engine exhaust in fire stations has been and continues to be a serious health problem for firefighters. This exhaust is generated whenever a fire apparatus leaves or returns to the station. If not properly captured and removed, it will remain in the apparatus bay as well as enter the firefighters' living quarters. As a result, firefighters can be exposed to diesel engine exhaust for a considerable portion of their shift.

Diesel exhaust contains multiple cancer-causing chemicals such as (Source IARC Monograph 105):

Metals	IARC Classification
Antimony Compounds	2B
Arsenic and inorganic arsenic compounds	1
Beryllium and beryllium compounds	1
Cadmium and cadmium compounds	1
Chromium (VI)	1
Cobalt and cobalt compounds	2B
Lead compounds (inorganic/organic0	2A/3
Nickel (metallic/compounds)	2B/1
Organic Chemicals	**IARC Classification**
1,3-Butadiene	1
Acetaldehyde	2B
Benzene	1
Bis(ethylhexyl)phthalate	2B
Ethylbenzene	2B
Formaldehyde	1
Propylene oxide	2B
Halogenated and other chemicals	**IARC Classification**
Dioxin/dibenzofurans	1
Polycyclic aromatic hydrocarbons	**IARC Classification**
Benz(a) anthracene	2B
Benzo(b)fluoranthene	2B
Benzo(k)fluoranthene	2B
Benzo(a)pyrene	1
Chrysene	2B
Dibenz(a,h)anthracene	2A
3,7-Dinitrofluoranthene	2B
3,9-Dinitrofluoranthene	2B
1,3-Dinitropyrene	2B
1,6-Dinitropyrene	2B
1,8-Dinitropyrene	2B
Indeno(1,2,3-_cd_)pyrene	2B
Napthalene	2B
3-Nitrobenzanthrone	2B
6-Nitrochrysene	2A
2-Nitrofluorene	2B
1-Nitropyrene	2A
4-Nitropyrene	2B
Styrene	2B

Soot:

Soot is a byproduct of the incomplete burning of organic (carbon-containing) materials, such as wood, fuel oil, plastics, and household refuse.

Soot particles absorb many hazardous chemical vapors that are released during fires, holding them in place on surfaces including firefighter's personal protective equipment (PPE), clothing and skin.

As firefighters work, their body temperature rises and they begin to sweat. Skin becomes more permeable and soot particles are more easily absorbed into the body.
- For every 5°increase in skin temperature, absorption increases by 400%.

The International Agency for Research on Cancer, part of the World Health Organization, lists soot in the Group 1 category meaning that the agent is ***"Carcinogenic in Humans."***

In their *13th Report on Carcinogens* which was released on October 2, 2014, the U.S. Department of Health and Human Services continues to list **soots** as a substance under the category of ***"Known To Be Human Carcinogens."***