KIDNEY/RENAL CANCER

IARC SUPPLEMENT 7

PAGES 85, 177 AND 230

IARC 45

PAGES 94, 104, 184, 185 1ND 186

IARC 98

PAGES 304, 305, 399, 400, 401, 403, 489, 491 AND 492

IARC 100F

PAGES 55, 146, 211, 480, 481, AND 607

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

for the first six years of observation (SMR, 438; 180-870). An increase in mortality from respiratory cancer in the exposed group was also evident (SMR, 253; 100-500)[16].

A few case reports of cancer other than hepatocellular in aflatoxin-exposed workers have been published[1,17-19].

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

Aflatoxins produce liver tumours in mice, rats, fish, ducks, marmosets, tree shrews and monkeys after administration by several routes, including the mouth. In rats, cancers of the colon and kidney were also seen[1]. Recent studies have extended these findings. In hamsters, aflatoxin B_1 produced cholangiocellular but not hepatocellular tumours[20]. In mice, aflatoxin B_1 administered orally or intraperitoneally resulted in an increased incidence of lung adenomas[1,21]. All rats fed 5 mg/kg of diet aflatoxin B_1 for six weeks developed hepatocellular carcinomas[22]; neoplastic hepatic nodules were produced in rats by oral administration of a single dose of 5 mg/kg bw aflatoxin B_1[23]; rats fed peanut oil containing 5-7 μg/kg aflatoxin B_1 developed parenchymal liver damage but no liver-cell tumour[24]. Aflatoxin B_1 can induce liver tumours in monkeys[25,26]; osteogenic sarcoma, adenocarcinoma of the gall-bladder or bile duct and carcinomas of the pancreas were also observed[26]. Aflatoxin B_1 also induced liver tumours in the subhuman primate tree shrew, *Tupaia glis*[27]. Intraperitoneal administration of aflatoxin B_1 to pregnant rats induced liver and other tumours in the mothers and in the progeny[28]. Aflatoxin M_1, a hydroxy metabolite of aflatoxin B_1, produced fewer hepatocellular carcinomas following its oral administration to rats than aflatoxin B_1 given at the same dose level and by the same route[29].

C. Other relevant data

In one study, aflatoxin B_1-DNA adducts were excreted in human urine. No data were available on the genetic and related effects of aflatoxins B_2, G_1, G_2 or M_1 in humans[30].

Aflatoxin B_1 has been tested extensively for genetic effects in a wide variety of tests *in vivo* and *in vitro*, giving consistently positive results. It induced chromosomal aberrations, micronuclei, sister chromatid exchanges, unscheduled DNA synthesis and DNA strand breaks, and bound covalently to DNA in cells of rodents treated *in vivo*; it was reported to be weakly active in a dominant-lethal mutation assay in mice. In human cells *in vitro*, it induced chromosomal aberrations, micronuclei, sister chromatid exchanges and unscheduled DNA synthesis and bound covalently to DNA. It induced cell transformation in several test systems, and induced chromosomal aberrations, sister chromatid exchanges, mutation, unscheduled DNA synthesis and DNA strand breaks in rodent cells *in vitro*. It induced sex-linked recessive lethal mutations and somatic mutation and recombination in *Drosophila*. In fungi, aflatoxin B_1 was mutagenic and induced gene conversion and mitotic recombination. It was mutagenic and induced DNA damage in bacteria and bound covalently to isolated DNA[30].

Aflatoxin B_2 bound covalently to DNA in hepatocytes of rats treated *in vivo*. It transformed Syrian hamster embryo cells and induced sister chromatid exchanges in Chinese hamster cells *in vitro* and induced unscheduled DNA synthesis in rat hepatocytes,

Excess risk of kidney cancer has been repeatedly associated with work in coke plants. In one study in the USA, a seven-fold increase in risk was seen for workers employed for five years or more at coke ovens. In single studies, excess risks were reported for cancers of the large intestine and pancreas[1].

The largest study was conducted on a cohort of some 59 000 steel workers in the Pittsburgh area (USA)[1]. The study has recently been extended up to 1975 and the dose-response analysis of exposure to coal-tar pitch volatiles and lung cancer reviewed. Coke-oven workers (both white and nonwhite) exhibited a large, statistically significant increase in lung cancer mortality that was strongly associated with duration of exposure to coke-oven fumes and intensity of exposure, as documented by comparing topside- with side-oven experience. Significantly elevated mortality from prostatic and kidney cancer was also noted, but without clear evidence of an exposure-response relationship. Non-oven workers had no excess of lung cancer but a significantly increased mortality from cancer of the large intestine and pancreas. Cumulative exposure indices of exposure to coal-tar pitch volatiles were calculated and increasing lung cancer risk with increasing estimated exposure was found[2,3]. A possible causative agent is coal-tar fumes.

B. Other relevant data

An increase in the incidence of sister chromatid exchanges was observed in cultured peripheral blood lymphocytes from 12 nonsmoking coke-oven workers in a steel plant, when they were compared to a group of age-matched controls. Urine samples from nonsmoking coke-plant workers were mutagenic to Salmonella typhimurium in the presence of an exogenous metabolic system. In a second study of coke-plant workers, the mutagenic activity in S. typhimurium of extracts of urine samples collected after work was not statistically different from that of samples taken before work. Antigenicity against benzo[a]pyrene diol epoxide-DNA adducts has been demonstrated in peripheral blood lymphocytes of coke-oven workers[4].

References

[1]IARC Monographs, 34, 101-131, 1984

[2]Redmond, C.K. (1983) Cancer mortality among coke oven workers. Environ. Health Perspect., 52, 67-73

[3]Rockette, H.E. & Redmond, C.K. (1985) Selection, follow-up, and analysis in the coke oven study. Natl Cancer Inst. Monogr., 67, 89-94

[4]IARC Monographs, Suppl. 6, 187, 1987

CREOSOTES (Group 2A)

A. Evidence for carcinogenicity to humans (limited)

In a number of case reports, the development of skin cancer in workers exposed to creosotes is described. One study involved a review of 3753 cases of cutaneous epithelioma

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

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

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

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

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

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

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

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

results were due to clusters of workers employed in petroleum refining. The four melanoma cases so employed had the following occupations reported on their death certificates: process worker/blender, engineer, security officer and clerk of works. The odds ratio for brain cancer was significantly elevated among men employed in petroleum refining (odds ratio, 2.9; 95% CI, 1.2–7.0), and four of the seven cases had worked as process operators.

Several studies on parental occupation involving exposure to hydrocarbons and cancer risks in children are reviewed in the monograph on gasoline. One of the studies, described more fully in that monograph, looked specifically at petrochemical occupations and industries and included 499 Texas children who had died from intracranial and spinal cord tumours and 998 controls (Johnson et al., 1987). On the basis of information on paternal occupation extracted from the birth certificate, an odds ratio of 2.0 (95% CI, 0.6–6.2) for children of petroleum refinery workers was observed.

(c) Correlation studies

A survey by county of the average annual age-adjusted lung cancer mortality rates for the years 1950–69 among white men in the USA indicated higher than expected lung cancer rates (1.32 per 100 000), when compared with total US rates, in counties where at least 1% of the population was employed in the petroleum industry (Blot & Fraumeni, 1976). A second survey examined cancer mortality rates in 39 US counties where at least 100 persons were employed in the petroleum industry and the estimated number of workers comprised at least 1% of the county population (Blot et al., 1977). White male residents of the petroleum industry counties had significantly higher average age-adjusted mortality rates for cancers of the lung (rate ratio, 1.15), nasal cavity and sinuses (rate ratio, 1.48), stomach (rate ratio, 1.09), rectum (rate ratio, 1.07), testis (rate ratio, 1.10) and skin (rate ratio, 1.10) than those of control counties with similar demographic characteristics.

Average annual age-adjusted cancer incidence rates for the period 1971–77 among Kaiser Health Foundation plan members living near petroleum and chemical plants in the San Francisco Bay area of the USA were compared with those among other San Francisco Bay area residents who did not live near the plants (Hearey et al., 1980). Site-specific rates for cancer were not elevated for members living near the petroleum and chemical plants.

Average annual age-adjusted cancer incidence rates for the period 1969–77 in Contra Costa County, CA, USA, were examined to determine whether there was any correlation with levels of air emissions from petroleum and chemical plants (Kaldor et al., 1984). The county was divided into four exposure areas, from low to high, based on air levels of sulfur dioxide, hydrocarbons and nitrogen oxides. Among men, significantly increasing incidence rates by level of exposure were found for cancers of the buccal cavity and pharynx, of the stomach, trachea, bronchus and lung, of the prostate and of the kidney. For all cancer sites combined, rates increased by exposure level, and the trend was significant. Among women, significantly increasing trends were noted only for cancers of the buccal cavity and pharynx.

Average annual age-adjusted mortality rates for multiple myeloma by state economic area in the USA were calculated for the period 1950-75 for each sex and race (Blattner et al., 1981). A multiple regression model was used to examine the relationship between the

pattern of increasing mortality was seen by time since first employment or duration of employment for brain tumours among laboratory workers or leukaemia among pipe fitters and boiler makers.

In a cohort study at the Gulf Port Arthur, TX, refinery, all 15 095 men employed for more than one day between 1 January 1937 and 1 January 1978 were followed for vital status on 1 January 1978. Of these, 972 (6.4%) were lost to follow-up; death certificates were not available for 277 (6.5%) of the 4269 male decedents. The average follow-up was 24.7 years. Expected mortality was determined from rates in the US general population, adjusted for age, race and calendar period. Excesses were seen for cancers of the bone, skin, kidney, Hodgkin's disease, leukaemia and cancer of 'other lymphatic tissue'. Only the result for cancer of the bone was significant. When white, blue-collar employees were evaluated separately, SMRs greater than 1 were observed for cancers of the pancreas, lung, bone, skin, prostate, eye and kidney, and for Hodgkin's disease and leukaemia; however, only the SMR for cancer of the bone was significant (Wen et al., 1983). [The Working Group noted that the ICD8 code cited to describe the category 'cancer of other lymphatic tissue' is probably in error and should have been reported as 202–203, 208.]

SMRs for kidney cancer were examined in a separate publication by time since first employment and duration employed; no trend was observed (Wen et al., 1984a).

A separate analysis with regard to employment status (retired, terminated before retirement age, actively employed) was performed on the white men in this cohort. The number of such employees was 12 526; 730 (5.8%) were lost to follow-up, 724 of whom were in the terminated group in which 88% were followed-up successfully (Wen et al., 1984b). Among those who had been actively employed, nonsignificant excess mortality was observed for cancers of bone and kidney and for leukaemia. Among white men who had terminated their employment at the refinery prior to retirement, there was excess mortality from cancers of the lung, bone, skin (ICD8 172, 173) and prostate and from Hodgkin's disease. Mortality among retired men was elevated for cancers of the lung, bone, skin (ICD8 172, 173), prostate, kidney and brain, leukaemia and cancer of 'other lymphatic tissues' (ICD8 202–203, 208). None of the results was significant. Data were not shown by duration of employment, but retirees were assumed to have worked a minimum of 15 years.

In an interim report on 15 698 male and 1823 female workers employed on 15 June 1935 and followed until 31 December 1979 (4766 deaths; 87% follow-up), nonsignificant excess mortality from brain tumours (malignant, benign and unspecified combined) was observed among men who had been employed for 20 or more years (Wen et al., 1982). No variation in SMR was reported for specific cancer sites by calendar period of employment (Wen et al., 1986). [The Working Group noted that the 882 employees at refinery B in the study of Thomas et al. (1980, 1982a,b, 1984) who had died between 1947 and 1977 were included in the studies of Wen et al.]

Mortality among 1008 men who had worked at any time between 15 June 1935 and 1 January 1978 in the lubricating oil department at the Gulf Port Arthur, TX, refinery was examined separately (Wen et al., 1985). In this department, lubricating oil was manufactured, and wax was separated from the product using a solvent dewaxing process. A mixture

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

Minneapolis/St Paul area of Minnesota, USA. An age- and sex-stratified sample of 714 population controls was taken from the same area. In addition, 495 deceased controls were frequency-matched on age at death and year of death to cases who were either deceased (237) or too ill to be interviewed directly (14). Information on smoking, diet and drug use as well as on medical, occupational and residential history was obtained from interviews of study subjects or next of kin. The response rate was 98%. Positive dose-response relationships were noted for smoking and some other exposures. In men, an elevated odds ratio adjusted for age and smoking was associated with occupational exposure to 'petroleum, tar, and pitch products' (1.7; 95% CI, 1.0—2.9). In a subsequent, more detailed analysis of this material (McLaughlin *et al.*, 1985), no clear association with petroleum-related occupations or with employment as a service station attendant was found, although a nonsignificant upward trend in risk with duration of employment was seen in the latter category.

A study was carried out of 92 white men, aged 30—89, with histologically confirmed renal-cell carcinoma and 1588 controls selected from among patients admitted to the same hospital in Buffalo, NY, USA, from 1957 to 1965 (Domiano *et al.*, 1985). Patients with neoplastic disease or with circulatory, respiratory, mental or urogenital disorders were excluded from the control group. Information on smoking habits, diet, occupational history and other variables had been obtained by interview at the time of admission. The age-adjusted odds ratio for the group exposed to gasoline was 0.53, based on four cases. The age-adjusted odds ratio associated with employment in service stations among men with over 20 pack-years of smoking was 1.6 [95% CI, 0.48—5.3].

A case-control study of cancer at many sites was performed in Montréal, Canada, to generate hypotheses on potential occupational carcinogens (Siemiatycki *et al.*, 1987a,b). Each cancer type constituted a case series. About 20 types of cancer were included and, for each cancer site analysed, controls were selected from among cases with cancer at other sites. Job histories and information on possible confounders were obtained by interview from 3726 men aged 35—70 years with cancer diagnosed at one of 19 participating hospitals between 1979 and 1985. The response rate was 82%. Each job was translated into a series of potential exposures by a team of chemists and hygienists using a check-list of 300 of the most common occupational exposures in Montréal. A separate analysis of risks associated with exposure to different petroleum-derived liquids was performed. Cumulative indices of exposure were estimated for a number of occupational exposures. Exposure below the median was considered to be 'nonsubstantial' and that above the median to be 'substantial'. Among men exposed to aviation gasoline, an increased risk was seen for kidney cancer only (adjusted odds ratio, 3.1; 90% CI, 1.5—6.5). Among subjects classified as having substantial exposure, the odds ratio was 3.9 (1.7—8.8) using a logistic regression analysis taking confounding factors detected in a preliminary analysis into consideration. There was overlap between groups exposed to aviation gasoline and groups exposed to jet fuel resulting from combined exposures (see also monograph on jet fuel).

(ii) *Lower urinary tract*

All residents, aged 20—89 years, of an area in eastern Massachusetts, USA, with newly diagnosed, histologically confirmed transitional- or squamous-cell malignancy of the lower

urinary tract, including the renal pelvis, ureter, bladder or urethra, were ascertained for an 18-month period (Cole *et al.*, 1972). Occupational risk factors were investigated for 461 of the patients with neoplasms and for 485 population controls living in the same area. Of the cases, 94% had a bladder tumour. Data on smoking and occupational histories were obtained by interview. Among men, an age- and smoking-adjusted odds ratio of 1.0 (95% CI, 0.75—1.3) was associated with employment in occupations with suspected exposure to 'petroleum products'; 81% of controls in this exposure category were 'machinists and mechanics'. Specific data on occupations with exposure to gasoline were not provided.

A Danish case-control study of bladder cancer and occupational risk factors consisted of 212 patients (165 men and 47 women), diagnosed in 1977—79 for men and 1979—80 for women at a hospital department serving a predominantly rural area, and 259 population controls (Mommsen *et al.*, 1982, 1983; Mommsen & Aagaard, 1984). Controls were individually matched to cases (men, 1:1; women, 2:1) for sex, age, geographic area and degree of urbanization. Occupational histories were obtained by hospital interviews for cases and by telephone or by mailed questionnaire for controls. The authors compiled a list of occupations thought to involve exposure to oil or gasoline. An odds ratio of 2.7 (95% CI, 1.2—6.2), restricted to men, associated with 'oil or gasoline' work was estimated by logistic regression analysis, without adjustment for potential confounders. Among the exposed men, there were five mechanics, four 'semiskilled workers', three blacksmiths, two printers, two engineers and four workers in other occupations. [An odds ratio of 1.8 was estimated by the Working Group for work as a blacksmith or mechanic, adjusting for smoking habits, nocturia and previous venereal disease. The Working Group noted that information on exposure was obtained differently for cases and controls.]

In a population-based case-control study investigating risk factors for cancers of the renal pelvis, including occupational exposures, a total of 74 cases diagnosed between 1974 and 1979 were identified from hospitals in the Minneapolis/St Paul area of Minnesota, USA (McLaughlin *et al.*, 1983). An age- and sex-stratified sample of 697 population controls was taken from the same area. Information on smoking, diet, drug use and occupational and residential history was obtained by interview with study subjects or next of kin. An age- and smoking-adjusted odds ratio of 2.4 (95% CI, 0.9—6.1) was associated with occupational exposure to 'petroleum, tar, or pitch products'. No further specification was given about exposures or occupations in this group.

As part of the US National Bladder Cancer Study, a population-based case-control study was carried out on occupation and cancer of the lower urinary tract in men in Detroit, MI, USA (Silverman *et al.*, 1983). The cases were diagnosed in 1977—78, and 95% had urinary bladder specified as the primary site. Controls were selected from the general population of the study area in such a way that the age distribution corresponded to that of the case series. Following exclusion of non-whites, of subjects who had never held jobs during at least six months and of refusals, a total of 303 cases and 296 controls remained for analysis. Information on smoking, diet, occupation, residence and other items was obtained by home interviews. Workers in the gasoline service industry had a crude odds ratio of 1.6 (95% CI, 0.8—3.5); after adjustment for smoking, the odds ratio was 1.3. Mechanics and repairmen had an odds ratio of 1.0 (0.6—1.4).

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 98

Painting, Firefighting, and Shiftwork

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

CI: 0.4–7.4; five cases). Employment in these occupations by duration of employment were 1.0 (95% CI: 0.2–4.9; three cases) for 5 or more years, and 1.4 (95% CI: 0.3–6.2; four cases) for 10 or more years.

Shu et al. (1989) conducted a population-based case–control study of ovarian cancer in Shanghai. Cases (n = 229) were identified from the Shanghai Cancer Registry during 1984–1986. Controls were selected from the Shanghai general population and matched to cases by age. Participants were interviewed to obtain information on demographic characteristics, reproductive history, medical history, familial cancer history, personal habits, diet and occupation. ORs were adjusted for education, reproductive history, ovarian cysts, and age at menarche. ORs for occupational exposure to paint was 2.2 (95% CI: 0.8–5.9; 18 cases) for epithelial ovarian cancer, and 3.7 (95% CI: 0.4–34.2; four cases) for non-epithelial ovarian cancer.

Brownson et al. (1988) evaluated occupational risks for cancer of the prostate in cases (n = 1239) selected from the Missouri Cancer Registry during 1984–1986.. Age-matched controls were selected from other cancer cases (n = 3717). Information on smoking and alcohol use as well as occupation (occupation held for the longest period of time) were available from registry files. ORs were calculated using two control groups: all-controls and all-controls except for lung and bladder cancer. The OR among persons employed in the manufacture of paints and varnishes using all-controls was 5.7 (95% CI: 1.4–24.3; five cases). No controls in the second control group were employed in this industry.

Sharpe et al. (2001) reported on occupational exposures and prostate cancer in a case–control study among men from Montreal. Cases (n = 400) were identified during 1979–1985. Population controls (n = 476) were selected from electoral lists or by random-digit dialling. Subjects were interviewed at home or in the hospital. Information on a variety of risk factors and a detailed history on occupations and occupational exposures as well as non-occupational exposures was gathered. Specific occupational exposures were assessed by chemists and industrial hygienists. ORs were adjusted for age, ethnicity, respondent status, income, BMI, and tobacco and alcohol consumption. The OR among individuals reporting painting, stripping or varnishing furniture often during leisure time was 2.1 (95% CI: 0.7–6.7; ten cases). The OR for self-reported exposure to paints, lacquers, or stains was 1.0 (95% CI: 0.6–1.5; 50 cases).

Asal et al. (1988) evaluated occupational risk factors renal cell cancer in case–control study (cases, n = 315) recorded during 1981–1984 from 29 hospitals in Oklahoma, USA. Hospital (n = 313) controls were matched to cases on age, sex, race, hospital and date of admission. Population controls (n = 336) selected by random digit dialling were matched to cases by age and sex. Information gathered was analysed to identify occupations held for longet than 1 or more years. The OR for men employed in painting or paint manufacturing was 1.3 (95% CI: 0.7–2.6; 22 cases).

Delahunt et al. (1995) conducted a case–control study of occupational risk factors for renal cell carcinoma within the New Zealand Cancer Registry (NZCR) during 1978–1986. The NZCR captures and codes the current and most recent occupation at the time of registration. A total of 914 cases (710 men, 204 women) with an active occupation coded

were identified as well as 12 756 male controls with non-urinary tract tumours. Women were excluded from the analysis due to a low representation of female cases with "at-risk" occupations. Among painters, the OR for renal cell carcinoma was 1.59 (95% CI: 1.00–2.43) when adjusted for age only, and 1.79 (95% CI: 1.31–3.44) when stratified by age and smoking history.

Pesch *et al.* (2000b) conducted a population-based case–control study of renal cell carcinoma in Germany. Cases (570 men and 365 women) were recorded during 1991–1995 from five regions (West Berlin, Bremen, Leverkusen, Halle, and Jena). Population controls (2650 men and 1648 women) were selected from local residency registries and matched to cases by region, age, and sex. Occupational histories covered all occupations held for at least one year. Job exposure matrices (JEMs) developed in Germany and Great Britain were used to assess specific exposures. Conditional logistic regression was used to calculate ORs, adjusting for smoking as a potential confounder. The ORs for painters, tanners, dyers, and related occupations were 1.9 (95% CI: 1.1–3.3; 19 cases) for men, and 0.6 (95% CI: 0.1–5.2; one case) for women. The ORs for male painters and dyers by duration of employment were 1.6 (95% CI: 0.8–3.0; 12 cases) for the 30th percentile, 1.4 (95% CI: 0.7–2.8; ten cases) for the 31st to 60th percentile, and 2.3 (95% CI: 0.8–6.8; five cases) for the 60th percentile or greater. [It is not clear if the "painters/dyers" for the duration analyses were the same as the "painters, tanners, dyers, and related occupations" for the ever/never analyses. Also, in the duration analysis, the sum of exposed cases for "painters/dyers" was 26, while the number for the ever/never analysis was 19.] ORs from the British JEMs on paints were for "paints and pigments" (0.9, 1.1, and 1.6 for medium, high, and substantial exposure among men, and 1.8, 1.1, and not calculable for the same categories among women). The German JEM for paints produced ORs of 1.1, 1.3, and 1.1 for medium, high and substantial exposure to paints among men, and 1.2, 1.2, and 0.6 for the same categories among women.

Mattioli *et al.* (2002) evaluated risk for renal cell cancer in a hospital-based case–control study in northern Italy. A total of 324 cases were identified at the University Hospital of Bologna during 1987–1994. Controls (*n* = 324) were individuals admitted to the hospital for anything other than renal cell cancer and residing in the same geographic area. Controls were matched to cases by age, gender, place of birth, same urban area, same cluster of small towns, and plains or hills. The OR for male painters was 0.31 (95% CI: 0.06–1.56; five cases). ORs were calculated by matched analysis and additionally adjusted for BMI, smoking, alcohol consumption, use of phenacetin and diuretics, meat consumption, coffee consumption, occupation titles and related exposures.

Brüning *et al.* (2003) conducted a case–control study of renal cell carcinoma in Arnsberg and surroundings, Germany. Interviews were completed with 134 cases identified during 1992–2000. Controls (*n* = 401) without dementia and with no diagnosis of cancer were selected from the same hospitals and matched to cases by age and sex. Information was obtained on all occupations held for longer than 1 year. A British JEM was used to classify jobs by exposure. Conditional regression was used to calculate ORs, adjusted for gender, age, and smoking. The OR for individuals potentially exposed to paints/pigments at

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:

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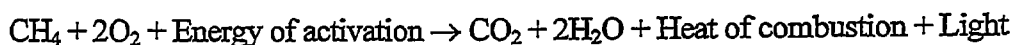
Given the appropriate ratio of fuel (wood, solvent, plastic, rubber), oxygen, and combustion temperature, the products of combustion should be only water and carbon dioxide (CO_2).

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:

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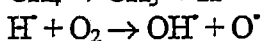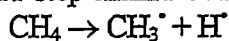
The free radicals formed during combustion are very reactive and side reactions are propagated to yield hundreds of chemical products, and smoke.

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

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

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

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

1.2.2   Modern versus pre-modern fires

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

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

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

1.2.3   Carcinogens found in smoke at fires

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

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

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

Table 1.1 (contd)

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

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

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

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

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

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.

Table 2.3. Case–control studies of the urogenital system

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratio (95% CI)	Adjustment for potential confounders	Comments
Delahunt et al. (1995) New Zealand, 1978–86	Renal cell (189.0)	Total number of renal cell carcinomas for all occupations ~710 men (Cancer Registry); coverage of 95% incident cases including pathology coding. Occupational code for 86.2%; 5 categories of service workers including firefighters; in which, 52 cases with an unknown number of firefighters	Random sample drawn from all cancer cases except renal cell carcinoma aged over 20 years, having primary tumours from sites other than the urinary tract. 12 756 (all men, Cancer Registry); matched by age, and registration period. 737 controls for category of service workers	Occupation code used to identify employment	Firefighters unadjusted Firefighters age- and smoking-adjusted	NR NR	3.51 (2.09–5.92) 4.69 (2.47–8.93)	Age, smoking	Firefighters likely represented ~10 cases although exact numbers not reported

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
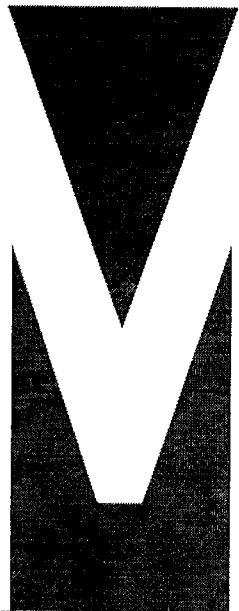
synthesis gas (Shadle et al., 2002; Crelling et al., 2005).

The moving-bed gasifiers produce tars, oils, phenols and heavy hydrocarbons, and the concentrations in the gas product are controlled by quenching and water scrubbing. Fluidized-bed gasifiers produce significantly smaller amounts of these compounds because of higher operating temperatures. Entrained-flow gasifiers that operate at even higher temperatures (in excess of 1650 °C) can achieve carbon conversions of more than 99.5%, while generating essentially no organic compounds heavier than methane (Shadle et al., 2002).

In addition to PAHs, workers in coal gasification may be exposed to many compounds, including asbestos, silica, amines, arsenic, cadmium, lead, nickel, vanadium, hydrocarbons, sulfur dioxide, sulfuric acid and aldehydes (IARC, 1984).

2. Cancer in Humans

2.1 Cohort studies of coal-gasification workers

[Occupational exposure during coal gasification was evaluated in *IARC Monograph* Volume 92 (IARC, 2010). There was *sufficient evidence* in epidemiological studies for the carcinogenicity of occupational exposure during coal gasification. The main body of evidence came from two cohort studies of coal-gasification workers in the United Kingdom (Doll et al., 1972) and Germany (Berger & Manz, 1992), and a case–control study nested within a cohort of French gas- and electricity-production workers (Martin et al., 2000; see Table 2.1, available at http://monographs. iarc.fr/ENG/Monographs/vol100F/100F-10-Table2.1.pdf). In all studies an excess of lung cancer in association with coal gasification was found, which was not likely to be explained by

confounding from tobacco smoking. There was evidence supporting a lung-cancer excess in a historical record-linkage study from the United Kingdom (Kennaway & Kennaway, 1947), in two smaller cohorts (Kawai et al., 1967; Hansen et al., 1986), and a large but inadequately reported Chinese study (Wu, 1988).

[In addition to lung cancer, the study from the United Kingdom (Doll et al., 1972) showed an excess of bladder cancer, and the German study (Berger & Manz, 1992) showed an excess of cancers of the stomach and colon-rectum.]

No epidemiological studies of coal-gasification workers have been published since the previous evaluation (IARC, 2010).

2.2 Synthesis

In three large studies, a consistent excess of lung cancer was found in association with occupational exposure during coal gasification. This excess was not likely to be explained by tobacco smoking.

3. Cancer in Experimental Animals

Coal-tars from gas works were previously evaluated in *IARC Monograph* Volume 34 (IARC, 1984). As early as 1923 and in subsequent decades, crude coal-tars from gas-works were tested for carcinogenicity by skin application in six studies in mice and two studies in rabbits. These tars induced a high number of skin papillomas and carcinomas in all studies in mice (Deelman, 1923; Kennaway, 1925; Hieger, 1929; Woglom & Herly, 1929; Berenblum & Schoental, 1947; Grigorev, 1960) and in both studies in rabbits (Berenblum & Schoental, 1947; Grigorev, 1960). No new studies have been published since the previous evaluation.

Manufactured gas plant residues (MGP) were previously evaluated in *IARC Monograph*

sweeps: the 1-hydroxypyrene concentrations were in the same wide range as those reported for the chimney sweeps in Germany and Poland (Letzel et al., 1999).

Increased concentrations of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzo-furans were found in blood lipids of 227 chimney sweeps from Bavaria (Wrbitzky et al., 2001).

2. Cancer in Humans

In *IARC Monograph* Volume 92 (IARC, 2010), epidemiological studies of cancer in humans were considered to provide *sufficient evidence* for the carcinogenicity of occupational exposure as a chimney sweep. The evidence partly came from a large series of reports on cases of scrotal skin cancer in this occupational group. Soot was first noted as a cause of scrotal cancer in humans by Pott (1775). Many case reports of scrotal and other skin cancers among chimney sweeps appeared subsequently in several different countries (e.g. Earle, 1808; Butlin, 1892; Henry & Irvine, 1936; Henry, 1937, 1946, 1947). A total of 1487 cases of scrotal cancer were reported to the Registrar General for England and Wales from 1911–1935 (Henry, 1937). Of these, 6.9% had occurred in chimney sweeps; the estimated proportion of chimney sweeps in England and Wales in 1921 and 1931 was about 0.06% of all adult males, indicating a large excess of scrotal cancer among workers in this profession.

Evanoff et al. (1993) conducted large cohort study of Swedish chimney sweeps and found an excess of cancer of the lung, bladder, oesophagus and haematolymphatic organs; a study from Finland corroborated these findings (Pukkala, 1995). These studies did not include individual adjustments for tobacco smoking, but in the Swedish study an adjustment was made for smoking at the group level, whereas in the Finnish study adjustment was for social class. Both

analyses indicated that confounding from tobacco smoking did not explain the findings regarding lung cancer. In two Danish cohort studies an excess of total cancer was found, but the studies were too small to evaluate individual cancer sites (Hansen et al., 1982; Hansen, 1983; see Table 2.1, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-16-Table2.1.pdf).

Pukkala et al. (2009) reported on a record-linkage study from the Nordic countries encompassing 15 million people aged 30–64 identified from the censuses in 1960, 1970, 1980/81, and 1990, and followed for cancer in the national cancer registries until 2005. A total of 5498 male chimney sweeps from Denmark, Finland, Norway and Sweden were identified in the cohort. Statistically significant excesses of cancers of the lung, oesophagus, pharynx, bladder, and colon were found. There was no excess of non-melanoma skin cancer. There was not a large heterogeneity in risk between countries, and no adjustment for smoking was made.

The above-mentioned study by Pukkala et al. (2009) – which included information from the earlier study (Pukkala, 1995) – adds to the previous evidence of an excess of cancer of the lung, bladder and oesophagus among chimney sweeps. Despite the classical risk for scrotal cancer in chimney sweeps, studies of this occupational group under modern working conditions show no such excesses.

Overall, considering a consistently observed increased lung-cancer risk in several studies, and on the basis of a large cohort study that demonstrated an internal dose–response after group-level adjustment for smoking, there is evidence from human epidemiological studies that lung cancer is causally associated with occupational exposure during work as a chimney sweep. No internal dose–response was observed for bladder cancer in the large Swedish study, and the evidence for an excess bladder cancer among chimney sweeps must be considered as

reported to contain trace amounts of benzidine (< 5 to 270 ng/g) (Lancaster & Lawrence, 1999).

2. Cancer in Humans

In a previous *IARC Monograph* (IARC, 2010) it was concluded that there is *sufficient evidence* in humans for the carcinogenicity of benzidine in the human bladder. Numerous case reports from different countries have been published (IARC, 1972, 1982, 1987, 2010). In one extreme instance, all five of a group of workers permanently employed in the manufacture of benzidine for 15 years or more developed bladder cancer (IARC, 1982). Vigliani & Barsotti (1962) reported on 20 workers with tumours of the urinary bladder between 1931 and 1948 among 83 Italian dyestuff workers involved in benzidine production and use. Case et al. (1954) found 10 bladder-cancer deaths among dyestuff workers exposed only to benzidine (standardized mortality ratio (SMR) 13.9 [95%CI: 6.7–25.5]). In benzidine-exposed workers in the chemical dye industry in China, the morbidity from bladder cancer increased with increasing duration of exposure (p for trend < 0.01) (Sun & Deng, 1980), while in a cohort of benzidine manufacturers in the USA, risks were significantly elevated for those with ≥2 years exposure to benzidine (SMR 13.0 [95%CI: 4.8–28.4]) (Meigs et al., 1986). In a cohort of dyestuff workers in Torino, Italy, the SMR was 100.8 [95%CI: 60.8–167.2] during exposure and 14.8 [95%CI: 71–31.0] at 20 or more years after exposure ceased (Piolatto et al., 1991). In a study of workers from a chemical manufacturing plant in Shanghai, China, an interaction was found between benzidine exposure and cigarette smoking in the development of bladder cancer (Wu, 1988). Relative to those who did not smoke and had no exposure to benzidine, the risks (RR) for bladder cancer were 6.2 (*P* = 0.05) for smokers who were not exposed to benzidine;

63.4 (*P* < 0.05) for non-smokers exposed to benzidine; and 152.3 (*P* < 0.01) for smokers exposed to benzidine. In another study of Chinese workers in benzidine production and use facilities, the odds ratios (OR) for bladder cancer were 1.0, 2.7 (1.1–6.3) and 4.4 (1.8–10.8) for low, medium and high cumulative exposure to benzidine, respectively, after adjustment for life-time cigarette smoking (Carreón et al., 2006b) In a case–control study in Canada, excesses of renal cell cancer in relation to duration of exposure to benzidine (*P* < 0.004) were noted, but other consistently supporting data were not found (Hu et al., 2002).

Overall, case reports and epidemiological investigations from several countries show strong and consistent associations between benzidine exposure and risk for bladder cancer.

3. Cancer in Experimental Animals

Studies on the carcinogenicity of benzidine in the mouse, rat, hamster, rabbit, dog, and frog by oral, subcutaneous injection, intraperitoneal injection, or inhalation routes of exposure have been reviewed by previous IARC Working Groups (IARC, 1972, 1982, 1987, 2010). There have been no additional carcinogenicity studies in animals reported since the most recent evaluation (IARC, 2010). Results of adequately conducted carcinogenicity studies are summarized in Table 3.1.

Benzidine and its dihydrochloride were adequately tested for carcinogenicity by oral administration (feed, drinking-water or gavage) in eight experiments in mice and one experiment in rats; by subcutaneous injection in one experiment in rats and one experiment in frogs; and in rats in one experiment by intraperitoneal injection.

Following oral administration to male and female mice, newborn and adult, of different strains, benzidine significantly increased the

55

From the National Occupational Exposure Survey (1981–83) it was estimated that approximately 4.7 million workers (including approximately 2.1 million women) in the United States of America (USA) were potentially exposed to isopropanol (NIOSH, 1990). No specific information on the numbers of workers exposed during isopropanol production was provided.

Although no data were available on exposure measurements at the workplace during isopropanol production, potential exposures from the indirect-hydration process include propylene, sulfuric acid, isopropanol, diisopropyl and isopropyl hydrogen sulfates, diisopropyl ether, propanal, acetone, sulfur oxides, polymeric oils and residues. In the past, benzene was used as an azeotroping agent to remove water from 'wet isopropanol', but nowadays diisopropyl ether or cyclohexane are preferentially used for this purpose (IARC, 1992; Papa, 2000; Logsdon & Loke, 2001).

2. Cancer in Humans

In *IARC Monographs* Supplement 7 it was concluded that there was *sufficient evidence* in humans for the carcinogenicity of work in the manufacture of isopropyl alcohol by the strong-acid process and *inadequate evidence* for the carcinogenicity of exposure to isopropyl alcohol and isopropyl oils (IARC, 1987). The carcinogenic hazards to humans of work in the manufacture of isopropyl alcohol by other methods, and of exposure to diisopropyl sulfate were not evaluated. The evaluation was based on an increased incidence of cancer of the paranasal sinuses observed in workers at factories where isopropyl alcohol was manufactured by the strong-acid process. The risk for laryngeal cancer may also have been elevated in these workers.

In *IARC Monograph* Volume 54 (IARC, 1992) an evaluation was made of exposure to mists

from strong inorganic acids. The epidemiological data on isopropanol production in that *Monograph* are updated and reviewed elsewhere in the present volume, and partly overlap with the information given below.

2.1 Cohort studies

See also Section 2.1.3 in the *Monograph* on Mists from Strong Inorganic Acids in this volume.

Two cases of nasal sinus cancer and two cases of laryngeal cancer had occurred among an unspecified number of workers at a Baton Rouge, Louisiana, USA, isopropyl alcohol-production plant by about 1950 (Eckardt, 1974; Hueper, 1966). Subsequent analyses considered isopropyl alcohol workers in combination with employees in ethanol production and other production units (Lynch *et al.*, 1979; Hanis *et al.*, 1982; see Table 2.1, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-27-Table2.1.pdf). At this plant, a nested case–control study of workers in isopropyl alcohol manufacturing and others ascertained 50 cases of upper respiratory tract cancer among employees and former employees who had worked during at least 10–15 years. The study made use of an unidentified non-company tumour registry (see Table 2.1, on-line). Cases and controls were assessed for exposure to sulfuric acid and other agents; those with high exposure to sulfuric acid had a significantly elevated odds ratio (OR) of 5.2 (95%CI: 1.2–22.1) for pharyngeal, nasal sinus, or laryngeal cancer (Soskolne *et al.*, 1984).

Six cases of cancer occurred in the 1970s at an isopropyl alcohol-production unit in the USA, which began operation in 1943 and had employed 600 workers through 1976 (Fishbein, 1976). Mortality through 1978 was studied among 433 isopropyl alcohol-manufacturing workers in this facility (see Table 2.1, on-line): two buccal cavity/pharyngeal cancer deaths were reported (Enterline, 1982). Subsequent studies of workers

at this plant did not include data on the mortality experience of isopropyl alcohol-manufacturing workers (Enterline et al., 1990; Marsh et al., 1991).

Among 182 workers employed 1928–50 in another isopropyl alcohol-production unit in the USA, a statistically significant excess of sinus cancer occurred (four cases) (Hueper, 1966; Weil et al., 1952). Subsequently, a case–control study that used reported lymphohaematopoetic cancer deaths as the cases was conducted. Workers ever having had exposure to alkyl sulfates, including diisopropyl sulfate, were at elevated risk for non-Hodgkin lymphoma (8 deaths; OR, 5.1; $P < 0.05$) (Ott et al., 1989). A later mortality study analysed isopropyl alcohol-manufacturing workers together with ethyl alcohol-manufacturing workers at the same and another facility ($n = 1031$) (Teta et al., 1992). Excesses of cancers of the larynx, buccal cavity and pharynx were observed, but based on very small numbers. There was one death due to sinus cancer (see Table 2.1, on-line).

Among 262 men employed in an isopropyl alcohol-manufacturing unit in the United Kingdom, nine cancer deaths had occurred by 1980, including one from nasal sinus cancer, corresponding to a 50-fold increased risk (see Table 2.1, on-line; Alderson & Rattan, 1980)

No further cancer mortality or incidence studies specifically updating any of these cohorts in isopropyl alcohol manufacture have been conducted, and no studies of other isopropyl alcohol-manufacturing plants have appeared in the scientific literature.

2.2 Case–Control Studies

Hu et al. (2002) conducted a study of carcinoma of the kidney (renal cell) in eight Canadian provinces. From cases and population-based cancer-free controls, data were collected on exposures during one year or more to 17 substances, including isopropyl oil. The OR – adjusted for age, province of residence, education, body-mass index, pack-years of cigarettes smoked, alcohol, and meat consumption – was 1.6 for men (95%CI: 1.0–2.6) and 1.2 for women (95%CI: 0.4–3.5) (see Table 2.2, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-27-Table2.2.pdf).

Pan et al. (2005) conducted a similar study of cancer of the brain in eight Canadian provinces. Likewise, from cases and population-based cancer-free controls, data were collected on occupational exposures during one year or more to 18 substances, including isopropyl oil. Exposure to this type of oil was associated with an elevated but not significantly increased risk for brain cancer (see Table 2.2, on-line).

Overall, there is evidence from epidemiological studies that exposure of humans during the manufacture of isopropyl alcohol by the strong-acid process causes cancer of the nasal sinuses, based on three cohort studies. The evidence is inadequate to draw conclusions on other cancer sites.

3. Cancer in Experimental Animals

No data were available to the Working Group.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

The kinetics of the toxic effects of inhaled acid mists on the respiratory tract depend on several interrelated factors, which include whether exposure occurs to a gas or an aerosol; the particle size, with small particles being more able to penetrate deeply into the lung (Martonen et al., 1985; Jarabek et al., 1989; US EPA, 1989); the solubility in water, with agents of higher solubility

481

evaluated grossly and histologically for tumours. A group of 18 males and 18 females were fed the basal diet alone and served as controls. Four females in the treated group developed mammary gland tumours (44%) and one fibroadenoma was observed in a control female (1 out of 18). Most 2-nitrofluorene-treated rats developed multiple papillomas or squamous cell carcinomas in the forestomach (5 out of 7 males and 2 out of 2 females examined) (Miller et al., 1955).

To confirm these findings, groups of 10 and 20 male Holtzman rats [age unspecified] were fed a basal diet containing 0 and 1.62 mmol/kg of 2-nitrofluorene [purity unspecified] for 12 months. In the treated group, 17 out of 18 (94%; $P < 0.05$) survivors had squamous cell carcinomas of the forestomach, 13 out of 18 (72%) had liver tumours ($P < 0.05$) [type not specified], 4 out of 18 (22%) had tumours of the ear duct, 2 out of 18 (11%) had tumours in the epithelium of the small intestine and 1 out of 18 (5%) had a tumour of the mammary gland. No tumours were observed in the control group (Miller et al., 1955).

Groups of 18–20 male Wistar rats [age unspecified] were fed 0, 0.24, 0.95 or 2.37 mmol/kg of 2-nitrofluorene (purity, > 98%) in the diet for 11 months, and were then placed on a basal diet for an additional 13 months before gross or histological evaluation. The incidence of tumours was: hepatocellular carcinoma – 2 out of 18 (11%) low-dose, 15 out of 19 (79%; $P < 0.01$) mid-dose and 20 out of 20 (100%; $P < 0.01$) high-dose rats; forestomach squamous cell carcinoma – 10 out of 18 (5%) low-dose, 16 out of 19 (84%) mid-dose and 11 out of 20 (55%) high-dose rats; and cortical kidney [renal cell] carcinoma – 1 out of 18 (5%) low-dose, 15 out of 19 (79%; $P < 0.01$) mid-dose and 10 out of 20 (50%; $P < 0.05$) high-dose rats. No tumours were observed in the control animals (Cui et al., 1995). [The Working Group noted that the high-dose animals died within 10–13 months.]

3.2.2 Skin application

Seven male and three female Minnesota rats [age unspecified] received a single topical application of 69 mg of 2-nitrofluorene [purity unspecified] and were then maintained on a basal diet and analysed grossly and histologically for tumours at approximately 300 days (approximate average life-span of the group). An untreated group of three males and three females served as controls. No tumours were observed in females or in the controls. In the males, 1 out of 7 (14%) had mammary gland carcinoma, 3 out of 7 (43%) had adrenal gland carcinoma, 2 out of 7 (28%) had lung lymphosarcoma, 1 out of 7 (14%) had subcutaneous fibroma and 1 out of 7 (14%) had anaplastic carcinoma of the salivary glands. The incidence of these tumours was not statistically significant compared with controls (Morris et al., 1950). [The Working Group noted that the small number of animals hampered an evaluation of the study.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, excretion

The metabolism of 2-nitrofluorene in vivo has been reviewed extensively (Möller, 1988, 1994).

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

(a) In-vivo studies

In Sprague-Dawley rats treated with a single oral dose of 1 mg/kg body weight (bw) of 2-nitro[9-^{14}C]fluorene, 2-nitrofluorene was excreted rapidly in the urine and faeces; 60%