Testicular Cancer

IARC SUPPLEMENT 7

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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

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[1,9]. 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].

Another study in which 12 280 users of metronidazole were followed up for two and one-half years gave a relative risk of 0.9 (95% confidence interval, 0.5-1.9) for all cancers[6].

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

Metronidazole has been tested for carcinogenicity by oral administration to mice and rats. It significantly increased the incidences of lung tumours in mice of each sex, of lymphomas in female mice[7,8] and of mammary, pituitary, testicular and liver tumours in rats[7,9,10]. It increased the incidence of colonic tumours induced in rats by subcutaneous administration of 1,2-dimethylhydrazine[11,12].

C. Other relevant data

Studies on bone-marrow cells and lymphocytes from a series of patients treated with metronidazole showed no increase in the incidence of chromosomal damage. Metronidazole was active in body fluid assays using sweat, faeces and urine from humans exposed *in vivo* and urine from rodents exposed *in vivo*[13].

Metronidazole did not induce micronuclei in bone-marrow cells of mice or rats, sister chromatid exchanges in bone-marrow cells of Chinese hamsters or unscheduled DNA synthesis in germ cells of male rabbits treated *in vivo*. Human cells exposed to metronidazole *in vitro* did not show increased incidences of chromosomal aberrations, whereas results with respect to sister chromatid exchanges were inconclusive. Metronidazole did not induce sister chromatid exchanges in cultured hamster cells; conflicting results were reported for the induction of mutation and DNA damage in rodent cells *in vitro*. It did not induce sex-linked recessive lethal mutations in *Drosophila* or recombination in yeast. It induced mutation in fungi and bacteria and induced prophage in bacteria[13].

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year of first employment; the incidence of lung cancer (82 cases; relative risk, 3.7) gave no indication of a consistent decrease during the period 1916-1959. A slight, statistically nonsignificant excess of laryngeal cancer (5 cases observed, 2.4 expected) was also reported[8,9].

Reports of an increased occurrence of lung cancer among nickel smelting workers have also come from New Caledonia, Slovakia and the USSR[10-16].

There have been three case reports of cancers of the respiratory tract in workers who were involved in nickel plating and grinding operations[1].

Three investigations that examined the possible cancer risk associated with exposure to nickel and nickel compounds in nickel alloy plants showed no significant increase in mortality from cancer[17-19]. In one of these, excess mortality from lung cancer was noted in maintenance workers; however, it was unclear whether the risk was directly associated with nickel exposures[18]. Workers at a gaseous diffusion plant who were exposed to high-purity metallic nickel powder did not exhibit any increase in mortality from respiratory-tract cancers[20,21]. An incidence study at a hydrometallurgical nickel refining plant in Canada did not indicate an increased risk of cancer. Exposure was to metallic nickel and nickel concentrate dust[22].

Other investigations have addressed more complex and mixed exposure conditions and thus provide little evidence to evaluate the specific role of nickel and nickel compounds[23-30].

The association of specific types of cancer with nickel exposure has also been examined by means of case-control investigations. One study of cancer of the larynx supported an association with nickel exposure[31], but another did not[32]. Studies of sinonasal cancer and lung cancer yielded contradictory results; all suffered from inadequate description of the exposure to nickel[33-36]. In one of these[35], the risk was high in welders with nickel exposure (relative risk, 3.3, 95% confidence interval, 1.2-9.2); however, exposure to nickel compounds was so highly correlated with the presence of chromium that the observed exposure to nickel could have reflected a confounding effect of chromium (see p. 165). A study at an aircraft-engine factory showed no association between lung cancer deaths and exposure to nickel oxides, sulphate, chloride or alloys[37].

It is still not possible to state with certainty which specific nickel compounds are human carcinogens, and which are not. A large amount of evidence has accrued that nickel refining carries a carcinogenic risk to workers. The risk is particularly high in those exposed during certain processes, mainly entailing exposure to nickel (sub)sulphides and oxides. The lung and nasal sinuses are the most clearly established target organs.

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

Nickel subsulphide produced malignant tumours in rats after its inhalation[1] or intramuscular[1,38,39], intrarenal[40,41], intratesticular[42] or intraocular[43] administration and after its insertion into heterotransplanted tracheas[44]; it also produced local sarcomas in mice and rabbits after intramuscular administration[1,45-47]. Nickel powder, nickel oxide, hydroxide and carbonate, nickelocene and nickel-iron sulphide matte produced local sarcomas in mice, rats, hamsters and rabbits when given intramuscularly[1,38,48]. Intravenous

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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

(ii) *Testicular cancer*

Mills *et al.* (1984) studied 347 hospital patients with histologically confirmed germ-cell tumour of the testis in the USA and matched them by age, sex, race and residence with 347 hospital controls, most of whom had tumours other than cancer of the testis. The ascertainment period was from 1 January 1977 to 31 August 1980. Occupational histories were extracted from medical records; when the type of industry was not apparent in the record, this was ascertained from the employer. An excess risk for testicular cancer was observed among petroleum and natural gas extraction workers (odds ratio, 2.3; 95% CI, 1.0–5.1). [The Working Group noted that information was obtained only on current occupation.]

Sewell *et al.* (1986) conducted a population-based study in New Mexico, USA, in which cases were identified at the New Mexico Tumor Registry. In order to be included in the study, the cases had to have had histologically confirmed testicular cancer registered in 1966–84, to have been 15 years old or more at the time of diagnosis and to have died of the disease. Controls consisted of persons who had died from other cancers, matched by age, year of diagnosis, race and sex. A total of 81 cases and 311 controls was identified. The source of occupational data was either death certificates (99%) or information on file at the tumour registry (1%). No excess risk for testicular cancer was observed among petroleum and gas workers (odds ratio, 0.57; 95% CI, 0.16–2.0). The authors noted the limited power of the study, that an association might have been obscured by the restriction to fatal cases and that information on exposure was limited.

(iii) *Multiple sites*

In a large case-control study of cancer at many sites conducted in Montreal, Canada, which is described in detail in the monograph on gasoline, p. 185, an association was seen between exposure to crude oil and rectal cancer (five cases; adjusted odds ratio 3.7; 90% CI, 1.3–10.6) and squamous-cell lung cancer (seven cases; adjusted odds ratio, 3.5; 90% CI, 1.5–8.2) (Siemiatycki *et al.*, 1987). It was indicated, however, that these associations might only be apparent since they are based on very small numbers. The authors suggested that one of the main groups exposed to crude oil, namely seamen, would probably have had life styles very different from those of the rest of the study population.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Crude oil, which may be broadly characterized as paraffinic or naphthenic, is a complex mixture of alkanes, cycloalkanes and aromatic hydrocarbons containing low percentages of sulfur, nitrogen and oxygen compounds and trace quantities of many other elements. Worldwide, about 500 000 workers are employed in crude oil exploration and production. Occupational exposures during drilling, pumping and transportation of crude oil, including maintenance of equipment used for these processes, may involve inhalation of volatile

Another part of the US National Bladder Cancer Study was based in New Jersey in 1978 (Schoenberg *et al.*, 1984). The design was similar to that of the study described above and included 658 male incident cases and 1258 population controls. Home interviews with the study subjects provided information on a variety of personal and environmental risk factors. In a logistic regression analysis with adjustment for age and cigarette smoking, the odds ratio was 2.4 (95% CI, 1.5–3.8) for garage and/or service station workers. For motor vehicle mechanics, the odds ratio was 1.3 (0.87–1.8). There was no clear trend in risk in relation to latency since first exposure or duration among the garage and/or gasoline station workers.

A study based partly in New Jersey also used data from the US National Bladder Cancer Study during 1977–78 (Smith *et al.*, 1985). An analysis of some occupational groups among 2108 male bladder cancer cases and 4046 controls frequency matched on age and sex revealed odds ratios for automobile and truck mechanics of 1.3 (95% CI, 0.77–2.3) and 1.2 (0.90-1.6) for nonsmokers and smokers, respectively. The corresponding odds ratios for 'chemically-related exposures' were 1.5 (1.1–2.1) and 0.99 (0.81–1.2). This occupational group included electrical and petroleum engineers, repairmen, mechanics and drivers, as well as garage and service station attendants.

[The Working Group noted that it was not possible to determine the degree of overlap of the two studies carried out in New Jersey.]

(iii) Other sites

Job titles and information on occupational exposure to motor fuels were recorded for all 50 male patients with acute nonlymphocytic leukaemia seen at a department of the University Hospital of Lund, Sweden, from 1969 to 1977 (Brandt *et al.*, 1978). Three clinical groups served as controls: 100 outpatients treated for nonmalignant disorders, 100 treated for allergic diseases and 31 men treated for other types of leukaemias. Eighteen acute nonlymphocytic leukaemia patients, and ten, ten and three patients in the three control groups, respectively, had been occupationally exposed to petroleum products (e.g., as service station attendants and as bus or truck drivers). [The Working Group estimated an unadjusted odds ratio of 5.1 (95% CI, 2.6–9.8).] The authors suggested that benzene present in gasoline was a possible etiological factor, but detailed exposure data were not given. [The Working Group noted the inadequate description of the methodology used in this study.]

Case-control studies on some rare malignant neoplasms, including testicular cancer and cancer of the pancreas, were conducted in five metropolitan areas in the USA between 1972 and 1975 (Lin & Kessler, 1979, 1981). Eligible patients were identified from hospital records, and an equal number of controls was selected from among contemporary admissions to the participating hospitals for nonmalignant diseases and matched to the cases on age, sex, race and marital status. Occupational histories were obtained by interview. The 205 cases of testicular cancer were reported to be 'significantly more likely to be employed as truck drivers, gasoline station attendants, garage workers, firemen, smelter workers and metal heaters or to hold other jobs involving heat exposure'. No quantitative data were given. There seemed to be a positive association between occupational exposure to dry cleaning or

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IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 98

Painting, Firefighting, and Shiftwork

LYON, FRANCE
2010

1.2 Composition of fire smoke

1.2.1 *Fire chemistry*

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

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

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

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

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

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

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

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

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

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

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

1.2.2 *Modern versus pre-modern fires*

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

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

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

1.2.3 *Carcinogens found in smoke at fires*

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

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

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

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Aronson *et al.* (1994), Ontario, Canada	5373 firefighters employed 1950–89	Employment records	Overall	3	**SMR** 2.5 (0.5–7.4)	Age, calendar year	
			Duration of employment				
			<15 years	3	3.7 (0.8–10.7)		
			15–29 years	0	0.0 (0.0–14.2)		
			30+ years	0	0.0 (0.0–36.9)		
Bates *et al.* (2001), New Zealand	All firefighters employed at least 1 yr, 1977–95	Employment registry	Overall	11	**SIR** 1.6 (0.8–2.8)	Age, calendar year	Only results for men were presented
			Duration of employment				
	Testicular		0–10 years	3	1.6 (0.3–4.5)		
			11–20 years	4	3.5 (1.0–9.0)		
			>20 years	2	4.1 (0.5–14.9)		
Ma *et al.* (2006), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Men	54	**SIR** 1.6 (1.2–2.1)	Age, calendar year	
Brain / CNS							
Musk *et al.* (1978), Massachusetts, USA	5655 male firefighters employed 1915–75	Death certificates		8	**SMR** 1.0		Confidence interval not provided, not calculated

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

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

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

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

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

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

2.2 Case–control studies

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

Table 2.3 (contd)

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
Stang *et al.* (2003) Bremen, Essen, Hamburg, Saarbrücken, and Saarland, Germany, 1995–97	Testicular or extragonadal germ cell tumours	269 cases from an active reporting system of clinical and pathological departments; aged 15–69 years; 78% response rate; histologically confirmed. 4 cases (1.5%) were firefighters	797 controls selected randomly from mandatory registries of residence; 57% response rate; matched by age and region of residence 3 controls (0.4%) were fireghters	In-person and telephone interviews conducted by trained interviewers	Worked as a firefighter Ever ≥10 years of duration Work began ≥5 years before diagnosis	4 2 3	4.3 (0.7–30.5) 3.0 (0.2–45.5) 3.1 (0.4–24.4)	History of cryptorchidism	Number of firefighter case and controls too low for precise effect but trend is strong

2.4 Case reports

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

2.5 Meta-analyses

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

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

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

5. Summary of Data Reported

5.1 Exposure data

Several types of firefighters exist, including municipal, wildland, industrial, aviation, and military firefighters. Municipal firefighters may be assigned to combat firefighting units only or to unexposed activities such as fire prevention or technical support. Firefighters may also be fire-scene investigators who are exposed during fires or shortly following a fire. Many firefighters work in shifts (see the monograph in this Volume).

Both municipal and wildland firefighting involve two phases: in an initial phase (knockdown and attack, respectively), the fire is extinguished; in a second phase (overhaul and mop-up, respectively), small fires and hot-spots are extinguished.

All fires generate an enormous number of toxic combustion products, including known and possible carcinogens, long-lived free radicals, and particulate matter. Smoke particles may serve as vehicles for adsorbed volatile organic compounds. Peak exposures to some carcinogens may be very high, notably for benzene, 1,3-butadiene, and formaldehyde. The concentrations of respirable particulate matter to which firefighters may be exposed during overhaul can reach 50 mg/m^3, or up to 1000 mg/m^3, and above in the case of coarser particles. Exposures of firefighters to volatile organic vapours have generally been in the low parts-per-million range.

Firefighters may be exposed at different levels depending on crew assignment, tasks and/or the time spent at fires. Wildland firefighters appear to spend more time at fires during a fire season than municipal firefighters spend during an entire year. In municipal firefighting, overhaul also involves pulling down ceilings and walls, which may entail exposures to substances other than combustion products. Both municipal and wildland firefighters engage in heavy work levels when combating fires, and the increased respiration rate results in an increase in absorbed dose. In recent decades, very effective respiratory protection equipment has been made available to municipal firefighters. In most jurisdictions, wildland firefighters generally do not use respiratory protection.

5.2 Human carcinogenicity data

The Working Group reviewed 42 studies of cancer in firefighters that included 19 cohorts, 11 case–control studies, and 14 studies that used other designs. The studies that were most relevant to the assessment of the risk for cancer among firefighters were the larger historical cohort studies.

Elevated relative risks for cancer at many different sites were identified by one or more studies, but few were observed consistently. A recent meta-analysis evaluated 32 studies and found that the risk for cancer in firefighters was significantly elevated for ten sites, four of which showed the strongest evidence of an association. Since that analysis, two more large epidemiological studies of cancer in firefighters have been

reported. Therefore, another meta-analysis that included these two studies was performed by the Working Group for the four primary cancer sites. Three types of cancer showed significant summary risk estimates: the incidence of testicular cancer was ~50% in excess based on six studies and approximately 150 cases, that of prostatic cancer was ~30% in excess based on 17 studies and approximately 1800 cases, and that of non-Hodgkin lymphoma was ~20% in excess based on seven studies and more than 300 cases.

Four cohort studies that investigated testicular cancer in firefighters yielded risk estimates that ranged from 1.2 to 2.5 and one case–control study gave odds ratios that ranged from 1.5 to 4.3. One of three studies found a positive trend between duration of exposure and the increased risk for testicular cancer.

Of 20 studies of prostatic cancer, 17 reported elevated risk estimates that ranged from 1.1 to 3.3; however, only two reached statistical significance and only one study showed a trend with duration of employment.

The studies that investigated non-Hodgkin lymphoma in firefighters used different definitions of this tumour. Five cohort and one case–control studies that evaluated non-Hodgkin lymphoma reported risk estimates that ranged from 0.9 to 2.0. Only one study evaluated exposure–response with duration and did not find a positive relationship.

Although firefighters are exposed concurrently to a multitude of chemical compounds that include numerous carcinogens, human epidemiological studies at best used indirect (poor) measurements of exposure to such agents. Also, exposures of firefighters vary considerably depending on their job activities, and only crude measures of exposure, such as duration of employment and number of runs, have been used in these studies. Despite these limitations, increased risks for some cancers were found for firefighters in the meta-analysis.

5.3 Animal carcinogenicity data

No data were available to the Working Group.

5.4 Other relevant data

Smoke is a complex mixture of suspended particulate matter, gas, and vapour. The lack of data on toxicokinetics and toxicity of the adsorption of chemical components onto particles prevents a full understanding of the effects of smoke on firefighters. The toxicokinetics of chemical mixtures are not well understood but are probably of significant importance because of the multiplicity of chemicals in smoke. For individual smoke components, inhalation was considered to be the major source of exposure; however, dermal absorption is also an important route of exposure for polycyclic aromatic hydrocarbons and polychlorinated biphenyls.

There are insufficient studies to evaluate genotoxic effects in firefighters.

There is clear evidence of chronic and acute inflammatory respiratory effects in firefighters, which provides a potential mechanism for carcinogenesis, although the major effect would be expected in the respiratory system.

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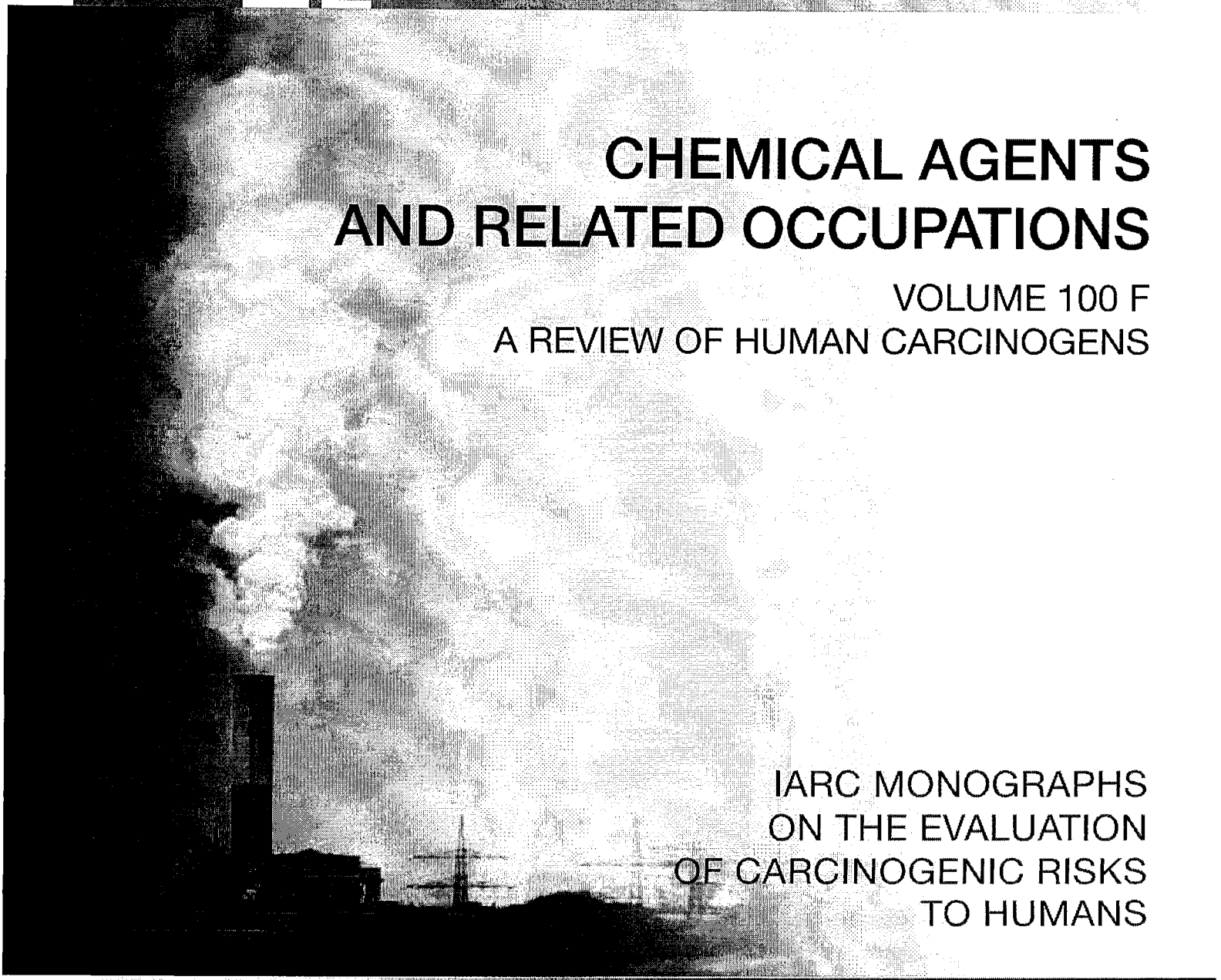

CHEMICAL AGENTS AND RELATED OCCUPATIONS

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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/m^3], and in multiple organs in mice at exposure concentrations ranging from 6.25 to 1250 ppm [13.8–2760 mg/m^3]. 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/m^3] (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).

2.1.4 Soap manufacture

The only study of soap-manufacturing workers exposed to sulfuric acid vapours in the hydrolysis and saponification areas, found increased risks – not statistically significant – for laryngeal cancer incidence and mortality through 1983 (Forastiere *et al.*, 1987).

2.1.5 Manufacture of phosphate and nitrate fertilizer

Sulfuric acid is used to convert phosphate rock to phosphoric acid and superphosphate; nitric acid is the precursor of nitrate fertilizers. Many fertilizer plants manufacture these two acids on site (Al-Dabbagh *et al.*, 1986; Rafnsson & Gunnarsdóttir, 1990; Hagmar *et al.*, 1991; Fandrem *et al.*, 1993; Checkoway *et al.*, 1996). Several research groups studied phosphate-fertilizer manufacturing in the USA (Stayner *et al.*, 1985; Block *et al.*, 1988; Checkoway *et al.*, 1996). All found elevated lung cancer mortality, with higher rates for those who had been employed longer. Nitrate-fertilizer manufacture has been studied in Iceland, Norway, the Russian Federation, Sweden, and the United Kingdom (Al-Dabbagh *et al.*, 1986; Rafnsson & Gunnarsdóttir, 1990; Hagmar *et al.*, 1991; Fandrem *et al.*, 1993; Zandjani *et al.*, 1994; Bulbulyan *et al.*, 1996). None of these studies found statistically significantly elevated risks among workers potentially exposed to nitric acid mists except the study from Sweden (Zandjani *et al.*, 1994), which showed a standardized incidence ratio (SIR) for stomach cancer of 1.50 ($P < 0.05$) for 27 men hired before 1960, and an SIR for testicular cancer of 3.33 ($P < 0.05$) for 5 men hired during or after 1960. In a factory complex where both phosphate and nitrate fertilizers were manufactured, Bulbulyan *et al.* (1996) reported a statistically significant increase in stomach-cancer mortality for men in the sulfuric acid tower department (11 deaths, SMR 2.04, 95%CI: 1.02–3.66) (see Table 2.1, on-line).

2.1.6 Battery manufacture

Mortality for all cancers combined and for various separate respiratory cancers has been reported from four cohort studies of battery-manufacturing workers (one including cohorts from steel works as well) in the United Kingdom and the USA (Malcolm & Barnett, 1982; Cooper et. al., 1985; Coggon *et al.*, 1996; Sorahan & Esmen, 2004; see Table 2.1, on-line). In two studies, excesses of laryngeal cancer were found (Cooper *et al.*, 1985; Sorahan & Esmen, 2004). Within the United Kingdom cohort, a nested case–control analysis was carried out in two battery-manufacturing plants and two steel works, with respect to exposure to acid mists. The study included 15 cases with upper aerodigestive cancers (ICD-9 140–141, 143–149, 160–161) and 75 controls. The odds of cancer among those with high exposure to acids, or among those with five or more years of high exposure were increased compared with those with no exposure to acids, but this was not statistically significant (Coggon *et al.*, 1996).

2.1.7 Other industries

Two nested case–control studies, one in the Norwegian nickel-refining industry (Grimsrud *et al.*, 2005) and one in the chemical industry in the USA (Bond *et al.*, 1986; 1991) were reviewed. In the first study, a job-exposure matrix for sulfuric acid mist was developed, the second study developed a job-exposure matrix for hydrochloric acid; neither found an association between acid mist exposure and lung cancer.

2.2 Case–control studies

Case–control studies of cancer of the upper respiratory tract, larynx, lung, stomach, and other sites have evaluated whether exposure to acid mists affected the cancer risk (see Table 2.2, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-28-Table2.2.pdf).