Colon Cancer

IARC MONOGRAPH'S

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WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF THE CARCINOGENIC

RISKS TO HUMANS

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

SUPPLEMENT 7

LYON, FRANCE

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

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

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

[Epidemiological studies in areas with different frequencies of black-foot disease and where drinking-water contained 0.35-1.14 mg/l arsenic revealed elevated risks for cancers of the bladder, kidney, skin, lung, liver and colon in both men and women[16,17].]   *Group 1. Product of Combustion*

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

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

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

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

Laryngeal cancer has been considered in two case-control studies, resulting in risk ratios of 2.4 and 2.3 that relate to shipyard work and unspecified exposure, respectively[40,58]. A cohort study of insulation workers showed a relative risk of 1.9, based on nine cases[57]. A case series indicated a high frequency of exposure to asbestos, especially in low-grade smokers[59]. A risk ratio of 3.2 for laryngeal cancer was reported among chrysotile miners in an area with generally high incidence[60], but no increased risk was seen in a cohort of workers with exposure to crocidolite[61]. Two correlation studies have also indicated a relationship between laryngeal cancer and exposure to asbestos[39,62].

Mesotheliomas related to shipyard work and other exposures, including household contact with asbestos workers, have also been subject to epidemiological studies[36,63-67], resulting in risk ratios of about 3-15 in comparison with background rates not clearly referable to asbestos exposure.

Some studies have specifically considered environmental exposures with reference to mesotheliomas[66,67]. Three correlation studies and one case-control study considering exposure to piped drinking-water[68-71] did not show consistently increased risks for any type of cancer, whereas another study[72] considering chrysotile contamination mainly from natural sources gave some indication of an increase in the incidence of peritoneal and stomach cancers in persons of each sex, although no other cancer site was consistent in this respect.

Exposure to crocidolite has been studied with regard to risk of lung cancer[61,73-76], and risk ratios of about 2-3 have been reported. Three lung cancers and two mesotheliomas occurred in 20 individuals after one year of high exposure to crocidolite; at least 17 of the cases had asbestos-induced lung changes on X-ray films[77].

One study[78] of histological types of lung cancers showed that among persons exposed to crocidolite 45.7% of cases were squamous-cell carcinomas, as compared to 35.2% among unexposed persons. In the context of unspecified and complex exposures, small-cell carcinoma was found to be relatively more prevalent than other forms[50].

Exposure to chrysotile was found in some studies to result in virtually no increase in risk ratio[60,79-81], or a slightly elevated relative risk of lung cancer[82-86]. Somewhat higher risk ratios, up to 2.5, 3.5 and 2, respectively, were obtained in one study of chrysotile miners[87] and in two independent studies from one asbestos [chrysotile] textile plant[88,89], the latter being the more comprehensive. With regard to mesotheliomas, one study suggested a particularly high risk of combined exposure to chrysotile and amphiboles (risk ratio, 61), thus almost multiplying the risk ratios (6 and 12, respectively) of exposures to chrysotile and to amphiboles alone[90]. Another study showed no mesothelioma among a large worker population with exposure to chrysotile only[91].

A slight excess of lung cancer and some mesotheliomas appeared in some groups with mixed exposures involving amosite, chrysotile and crocidolite[92-94]. Exposure predominantly to amosite, but also to chrysotile, was reported to be the probable cause of at least four of five mesotheliomas (one peritoneal) observed in a UK insulation-board factory[95]. One cohort with exposure to cummingtonite-grunerite, which is closely related to amosite, had no clear excess of lung cancer, although one case of mesothelioma was observed[96].

Exposure to tremolite and actinolite has been the subject of a few studies in investigations of vermiculite mining and milling[97,98] and environmental exposure[99]. The studies of miners indicated a risk ratio for lung cancer of up to approximately six fold. Deaths from mesothelioma were found in the occupational studies, whereas the study of environmental exposure showed no increased risk, although pleural plaques were reported. Publication of one case report of a mesothelioma after environmental exposure suggests that tremolite was of etiological importance[31].

Cancers other than of the lung or mesothelioma have been considered in many studies[1,17,35,39,41-44,48,51,55,60-62,68-70,72-74,76,83,87,89,92,93,96,97,99-108]. Some indicated an approximately two-fold risk with regard to gastrointestinal cancer in connection with shipyard work[41,43], and some increased risk was also seen in association with exposure to both chrysotile and crocidolite[103], to crocidolite[61,74] or to chrysotile[87]. Cancer of the colon and rectum was associated with asbestos exposure during chrysotile production, with an approximately two-fold risk[87]; a similar excess was found for unspecified asbestos exposure[104]. Some excess of ovarian cancer has been reported in two studies[73,76] but not in another[92]; exposure to crocidolite was probably more predominant in the studies that showed excesses. Bile-duct cancer appeared in excess in one study based on record-linking[105], and large-cell lymphomas of the gastrointestinal tract and oral cavity appeared to be strongly related to asbestos exposure in one small study covering 28 cases and 28 controls, giving a risk ratio of 8; however, ten cases and one control also had a history of malaria[106]. An excess of lymphopoietic and haematopoietic malignancies has been reported in plumbers, pipe-fitters, sheet-metal workers and others with asbestos exposure[17,54,107,108].

Group 1
Product of
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The relationship between asbestos exposure and smoking indicates a synergistic effect of smoking with regard to lung cancer[1]. Further evaluations indicate that this synergistic effect is close to a multiplicative model[52,109]. As noted previously[1], the risk of mesothelioma appears to be independent of smoking[47,66], and a significantly decreasing trend in risk was observed with the amount smoked in one study[65].

The studies of the carcinogenic effect of asbestos exposure, including evidence reviewed earlier[1], show that occupational exposure to chrysotile, amosite and anthophyllite asbestos and to mixtures containing crocidolite results in an increased risk of lung cancer, as does exposure to minerals containing tremolite and actinolite and to tremolitic material mixed with anthophyllite and small amounts of chrysotile. Mesotheliomas have been observed after occupational exposure to crocidolite, amosite, tremolitic material and chrysotile asbestos. Gastrointestinal cancers occurred at an increased incidence in groups occupationally exposed to crocidolite, amosite, chrysotile or mixed fibres containing crocidolite, although not all studies are consistent in this respect. An excess of laryngeal cancer has also been observed in some groups of exposed workers. No clear excess of cancer has been associated with the presence of asbestos fibres in drinking-water. Mesotheliomas have occurred in individuals living in the neighbourhood of asbestos factories and mines and in people living with asbestos workers.

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

C. Other relevant data

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

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

References

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

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

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

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

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

FORMALDEHYDE (Group 2A)

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

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

In the study of US producers and users of formaldehyde, 11% of the subjects were not exposed, 12% had an estimated time-weighted average (TWA) exposure of <0.1 ppm (<0.12 mg/m³), 34% a TWA of 0.1-<0.5 ppm (0.12-<0.6 mg/m³), 40% a TWA of 0.5-<2 ppm

Slight excesses in the occurrence of lung cancer have been noted in several studies[2,4,7,12,18,19]. These excesses have shown no consistent pattern with increasing level or duration of exposure to formaldehyde. A statistically significant excess (SMR, 132) was reported among wage workers 20 or more years after first exposure. The risk of lung cancer did not increase among this, or any other group, with either level or duration of exposure[4]. In the UK, the risk of lung cancer rose with level of exposure in one factory from an SMR of 58 among those with low exposure to an SMR of 118 among those with high exposure[6]. No such pattern was seen, however, for the other factories[6], nor was risk associated with cumulative exposure[20]. In a case–control study of respiratory cancer among Finnish plywood and particle-board workers, an odds ratio of 1.6 (adjusted for smoking) was found after ten years of latency. RRs, however, decreased with level and duration of exposure to formaldehyde[7]. In a cohort mortality study of 1332 workers in a formaldehyde-resin plant in Italy, there was an overall excess of lung cancer (SMR, 186). The excess occurred among those not exposed to formaldehyde (SMR, 148) as well as among those exposed (SMR, 136), with the greatest excess among those with uncertain exposure (SMR, 358). Lung cancer mortality was not clearly associated with duration of exposure[19].

Studies of professional groups have shown rather consistent deficits of lung cancer. None of these studies, however, included information on smoking, and the lower prevalence of tobacco use in these groups would probably lead to such deficits. No excess occurrence of lung cancer was noted among Danish physicians[21] or among persons exposed to formaldehyde at a US chemical production facility[22].

Mortality from leukaemia and/or cancer of the brain has been found consistently to be elevated in studies of professional groups[1,12,13,16,23,24]. Except for a very slight excess of leukaemia reported in one study[5] (which was not statistically significant), excesses of these tumours have not been found among industrial workers exposed to formaldehyde. Among professionals, gliomas were the predominant cell type of brain cancer, and the leukaemias were predominantly of the myeloid type. The absence of excesses for these cancers among industrial workers, however, argues against a role of formaldehyde.

Mortality from prostatic cancer has been found to be elevated among professionals[13] and among industrial workers[4,5], but the excess was statistically significant only among embalmers[13]. This tumour has shown a dose-response gradient in both studies of industrial workers, although the test for trend in the study of Blair[4] was not statistically significant.

Slight excesses of mortality from bladder cancer have been reported among professionals[13,23] and among industrial workers[5]. No such excess occurred, however, in the other large industrial cohorts, and none of the excesses was statistically significant. Significant Group 1 excesses of colon cancer were noted among professionals[12,13] and among industrial workers[2]; nonsignificant elevations have also been reported[11,16]. A significant excess mortality from cancer of the skin was reported among New York embalmers (proportionate mortality ratio, 221)[12], and a slight excess was noted among industrial workers (based on two deaths)[11]. Excesses of Hodgkin's disease were seen among white industrial workers in

died during the study period; among the 237 'nonroutinely' exposed, two deaths were observed, with 6.4 expected, one of which was due to cancer of the large intestine[1].

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

The carcinogenicity of a commercial preparation of polybrominated biphenyls (FireMaster FF-1, various lots), composed primarily of hexabromobiphenyl with smaller amounts of penta- and heptabrominated isomers, was tested by oral administration in mice and rats. In mice, it produced malignant liver tumours. In five studies in rats, it produced benign and malignant hepatic tumours, including cholangiocarcinomas, depending on the exposure conditions. Oral administration of polybrominated biphenyls enhanced the incidence of liver nodules induced by *N*-nitrosodiethylamine[2], but cutaneous application did not increase the incidence of skin tumours induced by 2-acetylaminofluorene[1].

C. Other relevant data

No data were available on the genetic and related effects of polybrominated biphenyls in humans.

Polybrominated biphenyls did not induce chromosomal aberrations in bone-marrow cells of rats or mice nor in rat spermatogonia and did not induce micronuclei in mice treated *in vivo*. They did not induce mutation in human or rodent cells *in vitro* or unscheduled DNA synthesis in rodent hepatocytes *in vitro*. Polybrominated biphenyls were not mutagenic to bacteria *in vitro* or in a host-mediated assay[3].

2,4,5,2′,4′,5′-Hexabromobiphenyl, 2,3,4,5,2′,4′,5′-heptabromobiphenyl and 2,3,4,5,2′,3′,4′,5′-octabromobiphenyl inhibited intercellular communication in Chinese hamster V79 cells; other congeners tested were only weakly active or were inactive[3].

References

[1]*IARC Monographs, 41*, 261-292, 1986

[2]Jensen, R.K. & Sleight, S.D. (1986) Sequential study on the synergistic effects of 2,2′,4,4′,5,5′-hexabromobiphenyl and 3,3′,4,4′,5,5′-hexabromobiphenyl on hepatic tumour promotion. *Carcinogenesis, 7*, 1771-1774

[3]*IARC Monographs, Suppl. 6*, 466-468, 1987

POLYCHLORINATED BIPHENYLS (Group 2A)

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

Information on the possible carcinogenic risk of human exposure to polychlorinated biphenyls (PCBs) comes from studies of occupational populations and of populations

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

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

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

patients, two adenocarcinomas of the liver were found, with no indication of a direct association with exposure to PCBs[9]. Ultrasonic and tumour marker examination of two series of 79 and 125 patients with 'Yusho' disease in 1983 and 1984, respectively, did not reveal any case of hepatic-cell carcinoma[10]. Two studies of the PCB content of fat tissues and cancer occurrence were available. [An association was suggested between PCB concentrations in subcutaneous abdominal adipose tissue and the occurrence of cancers of the stomach, colon, pancreas, ovaries and prostate[11].] No indication emerged of a relationship between PCB content in extractable breast fat tissue and the occurrence of breast cancer[12].

*Group 1
Product of
Combustion*

The available studies suggest an association between cancer and exposure to PCBs. The increased risk from hepatobiliary cancer emerged consistently in different studies. Since, however, the numbers were small, dose-response relationships could not be evaluated, and the role of compounds other than PCBs could not be excluded, the evidence was considered to be limited.

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

Certain PCBs (particularly with greater than 50% chlorination) produced benign and malignant liver neoplasms in mice and rats after their oral administration[1,13,14]. Oral administration of Aroclor 1254 to rats yielded hepatocellular adenomas and carcinomas as well as intestinal metaplasia and a low, statistically nonsignificant incidence of stomach adenocarcinomas[15]. PCBs were inadequately tested in mice for induction of skin tumours[16,17]. In several studies, oral or intraperitoneal administration of PCBs enhanced the incidences of preneoplastic lesions[18-20] and of neoplasms[21,22] of the liver induced in rats by *N*-nitrosodiethylamine or 2-acetylaminofluorene. In one study, intragastric administration of PCBs to mice increased the incidence of lung tumours induced by intraperitoneal administration of *N*-nitrosodimethylamine[23].

C. Other relevant data

No data were available on the genetic and related effects of PCBs in humans.

Dominant lethal effects were not induced in rats administered PCBs orally, but were produced in rats nursed by females that had received PCBs orally. PCBs did not induce chromosomal aberrations in bone-marrow cells or spermatagonia of rats treated *in vivo*; micronuclei were not induced in bone-marrow cells of mice in one study, while equivocal results were obtained in a second study in which the PCBs were administered in corn oil. They did not transform Syrian hamster embryo cells *in vitro*. PCBs induced DNA strand breaks and unscheduled DNA synthesis in rat hepatocytes *in vitro*. Neither chromosomal breakage nor aneuploidy was induced in *Drosophila*. PCB mixtures did not induce SOS repair and were not mutagenic to bacteria[24].

2,2',5,5'-Tetrachlorobiphenyl induced DNA strand breaks in mouse cells *in vitro*. 2,4,5,2',4',5'-Hexachlorobiphenyl but not 3,4,5,3',4',5'-hexachlorobiphenyl inhibited intercellular communication in Chinese hamster V79 cells. Purified 2,4,2',4'-, 2,5,2',5'- and

C. Other relevant data

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

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

References

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

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

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

TETRACHLOROETHYLENE (Group 2B)

Group 2A
Product of
Combustion

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

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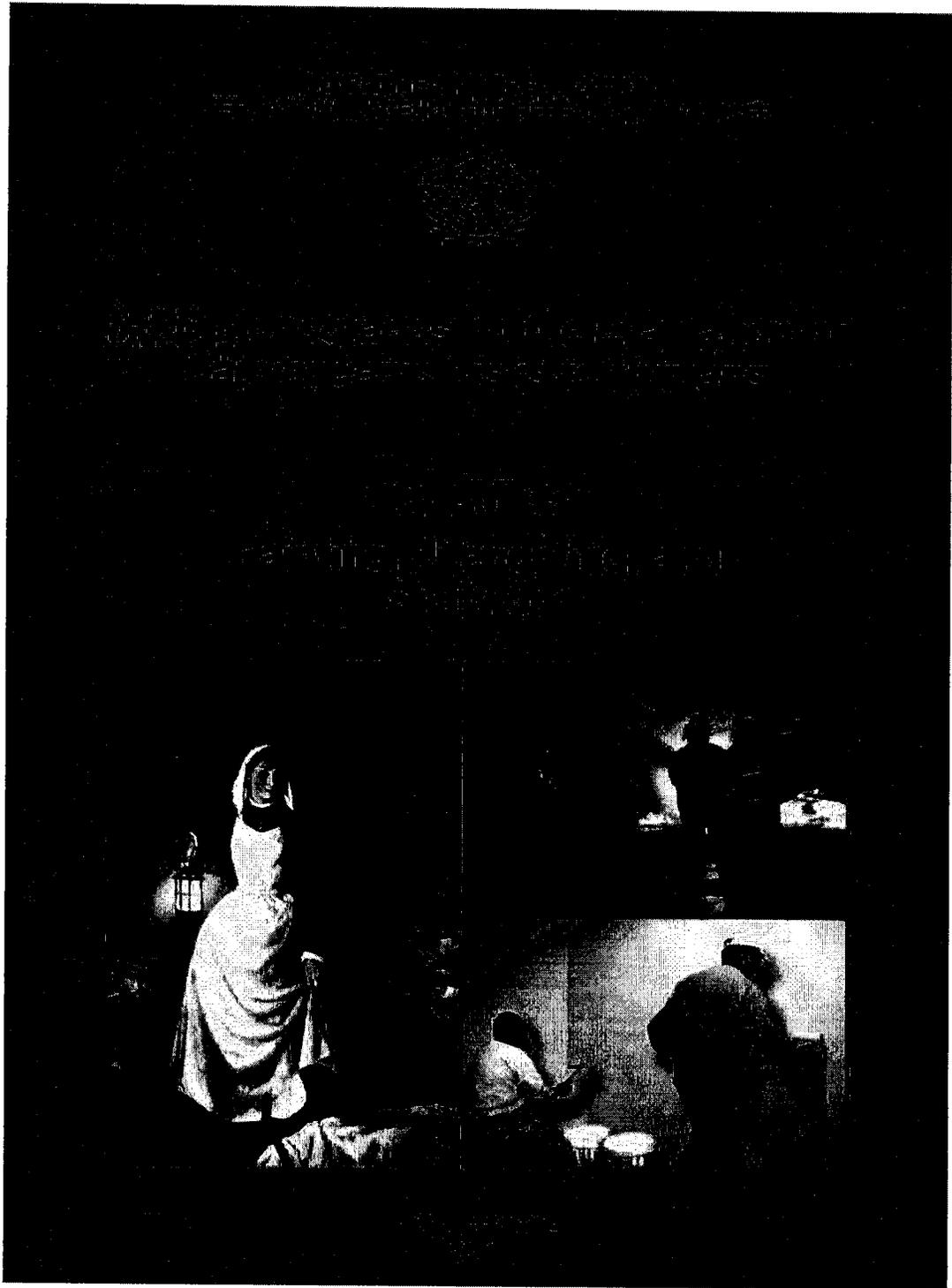
1.2   Composition of fire smoke

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:

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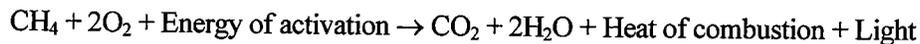
Given the appropriate ratio of fuel (wood, solvent, plastic, rubber), oxygen, and combustion temperature, the products of combustion should be only water and carbon dioxide (CO_2).

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:

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

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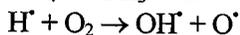
The free radicals formed during combustion are very reactive and side reactions are propagated to yield hundreds of chemical products, and smoke.

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.

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

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

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

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

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

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

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

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

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

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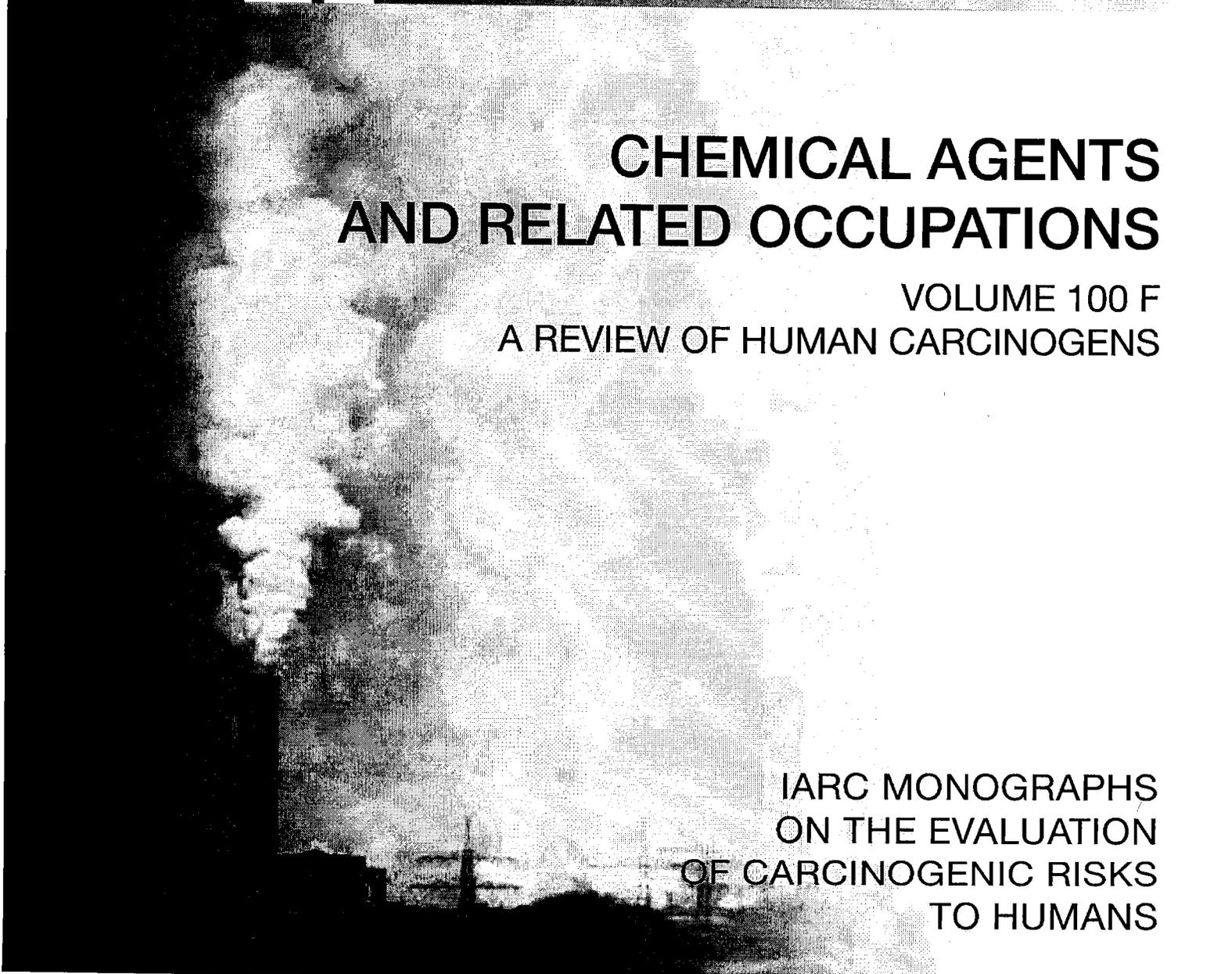
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sweeps: the 1-hydroxypyrene concentrations were in the same wide range as those reported for the chimney sweeps in Germany and Poland (Letzel et al., 1999).

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.

[handwritten margin note: Group 1 Carcinogen]

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

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

In the framework of the previous Canadian multisite population-based case–control study of occupational exposures and risks for various cancers (Siemiatycki et al., 1988), Goldberg et al. (2001) assessed the associations of colon cancer with diesel engine emissions, and many other occupational exposures, in 497 male case patients compared with 1514 other cancer patients (excluding lung and peritoneal cancer,

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

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

used a job–exposure matrix to assess exposure to diesel engine exhaust – were also given greater weight in the evaluation. An excess risk of urinary bladder cancer was found among subjects with the highest exposure to diesel engine exhaust in the studies from British Columbia, Belgium and Stockholm. In the Montreal study, no excess risk for substantial exposure (the most comprehensive measure of exposure) was found, but elevated risks were observed among individuals in the expert-assessed categories for the highest confidence, frequency or duration of exposure to diesel engine exhaust. In all five studies, the odds ratios were generally greatest among individuals with the highest exposure, according to various metrics, but risk estimates in the different exposure categories were imprecise and most were not statistically significant. Of the two studies that reported trend tests for the level of exposure, only the study from British Columbia found a statistically significant trend in risk with increasing exposure. These studies adjusted for tobacco smoking in the analyses; however, the observed risks were small and subject to potential residual confounding from tobacco smoking or other occupational exposures.

The Working Group gave less weight to the evidence from six case–control studies that provided less accurate assessments of exposure to diesel engine exhaust and studies of occupations (heavy-duty vehicle, bus and taxi cab drivers, railroad workers and automobile mechanics) associated with potential exposure to diesel engine exhaust. Statistically non-significantly elevated risks were observed among subjects with the highest exposure to diesel engine exhaust in studies based only on job titles, but attribution of the association specifically to exposure to diesel engine exhaust was difficult.

Ten mortality risk estimates for urinary bladder cancer were based on nine occupational cohort studies. Standardized mortality ratios were 1.0 or less for six estimates and between 1.0 and 1.3 for four estimates. None of these studies

included exposure–response analyses for urinary bladder cancer. The mortality studies had a limited ability to detect a positive association because they investigated mortality rather than incidence, which resulted in smaller numbers of cases, and lacked accurate exposure assessments.

Eight studies provided risk estimates for the incidence of urinary bladder cancer among workers potentially exposed to diesel engine exhaust. Four were record-linkage or population-based cohort studies and reported estimates based on a job–exposure matrix, self-reported exposure to diesel or unspecified engine exhaust or job title; only one risk estimate was significantly greater than 1.0. The studies were limited by low-quality exposure assessment, which was based on occupation at one point in time. In addition, three occupational cohort studies and a case–control study nested in one of the cohorts were available. Significantly increased standardized incidence rates for urinary bladder cancer were found in two cohorts of bus drivers. No association was found between occupation and the incidence of urinary bladder cancer in another cohort study. Most analyses in these studies did not adjust for tobacco smoking.

Overall, the epidemiological studies provide some evidence of a positive association between potential exposure to diesel engine exhaust and the risk for urinary bladder cancer.

(c)   Cancer at other sites

Twenty-five case–control studies of adult cancers at sites other than the lung or urinary bladder were reviewed with regard to potential associations with exposure to diesel or gasoline engine exhausts. For most cancer sites in adults, only a small set of studies was available, the majority of which were limited with regard to exposure assessment, the number of exposed cases and other methodological problems. Occupational cohort studies showed no consistent patterns for other sites based on external comparisons and could not address potential confounders. Some

case–control studies of cancers of the larynx and colon suggested a positive association with exposure to engine exhaust (unspecified mixtures of diesel and gasoline) or proxies of exposure; however, these were not consistently supported by results from cohort studies. For pancreatic cancer, prostate cancer, multiple myeloma, leukaemia and lymphoma, the overall evidence did not support an effect of exposure to diesel and/or gasoline engine exhausts.

(d) Childhood cancer

Thirteen case–control studies assessed associations between exposure to unspecified mixtures of diesel and gasoline engine exhausts (or proxies of exposure) and childhood cancer, most of which focused on childhood leukaemia and brain tumours. The studies generally relied on the occupational titles of fathers and mothers to assess exposure, and most investigated parental occupation as a proxy for exposure to engine exhaust. Although several studies showed positive associations for acute leukaemias, the exposure assessment was generally not specific for diesel engine exhaust, which hampered their interpretation. Overall, no consistent evidence of associations between parental exposures to diesel and gasoline engine exhausts and the risk of childhood cancer was found.

5.2.2 Gasoline engine exhaust

(a) Cancer of the lung

Few studies attempted to disentangle the effects of diesel engine exhaust from those of gasoline engine exhaust. In some occupational environments, diesel engine exhaust is the only or primary source of exposure (e.g. those of railroad workers and non-metal miners), while many motor exhaust-related occupations involve exposure to a mixture of diesel and gasoline engine exhausts. The separate effects of gasoline and diesel engine exhausts have been investigated in US transport industry workers and in

population-based studies in Sweden and Canada. The relative risks associated with exposure were consistently higher for diesel engine exhaust than for gasoline engine exhaust, and the modest excess risks associated with exposure to gasoline engine exhaust were possibly confounded by concomitant exposure to diesel engine exhaust. Little evidence was found for the carcinogenic effect of gasoline engine exhaust in these studies, but such an effect cannot be excluded.

(b) Cancer at other sites

The available data were too sparse and inconsistent to assess the carcinogenicity of gasoline engine exhaust at other sites.

5.3 Animal carcinogenicity data

5.3.1 Diesel engine exhaust

The whole diesel engine exhaust in these studies were generated from fuels and diesel engines produced before the year 2000, and included three basic components: elemental carbon particles in respirable clusters; organic matter adsorbed onto the surface of the carbon particles, which is readily extractable with organic solvents; and a mixture of gas and vapour phases that include volatile organic compounds. Many studies have been carried out using four animal species to evaluate the potential carcinogenicity of exposure to whole exhaust from diesel engines and its components. The studies were considered within four subgroupings: (i) whole diesel engine exhaust; (ii) gas-phase diesel engine exhaust (with particles removed); (iii) diesel engine exhaust particles or extracts of diesel engine exhaust particles; and (iv) whole or gas-phase diesel engine exhaust in combination with known carcinogens.

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