FIREFIGHTER OCCUPATIONAL CANCER

ESOPHAGEAL CANCER

IARC MONOGRAPHS

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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

1987

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ALUMINIUM PRODUCTION (Group 1)

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

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

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

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

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

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

Coal Tar pitch is a Grap 1 carcinogen. It is found in the overhaul phase of Structure Fires. * Reference P-2 OF Chemical List (IARC 105)

See attached page from National Cancer Institute regarding Coal Tar Pitch Roofing. These are common on most commercial roofs.

NIH NATIONAL CANCER INSTITUTE

Coal Tar and Coal-Tar Pitch

What is coal tar?

Coal tar is derived from coal. It is a byproduct of the production of coke, a solid fuel that contains mostly carbon, and coal gas. Coal tar is used primarily for the production of refined chemicals and coal-tar products, such as creosote and coal-tar pitch. Certain preparations of coal tar have long been used to treat various skin conditions, such as eczema, psoriasis, and dandruff.

Coal-tar pitch is found in some types of asphalt and other coal-tar products.

What is coal-tar pitch?

Coal-tar pitch is a thick black liquid that remains after the distillation of coal tar. It is used as a base for coatings and paint, in roofing and paving, and as a binder in asphalt products. Both coal tar and coal-tar pitch contain many chemical compounds, including carcinogens such as benzene.

How are people exposed to coal tar and coal-tar pitch?

The primary routes of human exposure to coal tars and coal-tar products are inhalation, ingestion, and absorption through the skin. Exposure to coal tars and coal-tar pitches may occur at foundries and during coke production, coal gasification, and aluminum production. Other workers who may be exposed to coal-tar pitches include those who produce or use pavement tar, roofing tar, coal-tar paints, coal-tar enamels, other coal-tar coatings, or refractory bricks.

The general population may be exposed to coal tars in environmental contaminants and through the use of coal tar preparations to treat skin disorders such as eczema, psoriasis, and dandruff.

Which cancers are associated with exposure to coal tar and coal-tar pitch?

Occupational exposure to coal tar or coal-tar pitch is associated with an increased risk of skin cancer. Other types of cancer, including lung, bladder, kidney, and digestive tract cancer, have also been linked to occupational exposure to coal tar and coal-tar pitch.

How can exposures be reduced?

Exposures to coal tar and coal-tart pitch are regulated under the U.S. Occupational Safety and Health Administration's (OSHA) Air Contaminants Standard for general industry, shipyard employment, and the construction industry. OSHA provides detailed safety and health information about coal-tar pitch to the public.

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SOOTS (Group 1)

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

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

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

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

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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

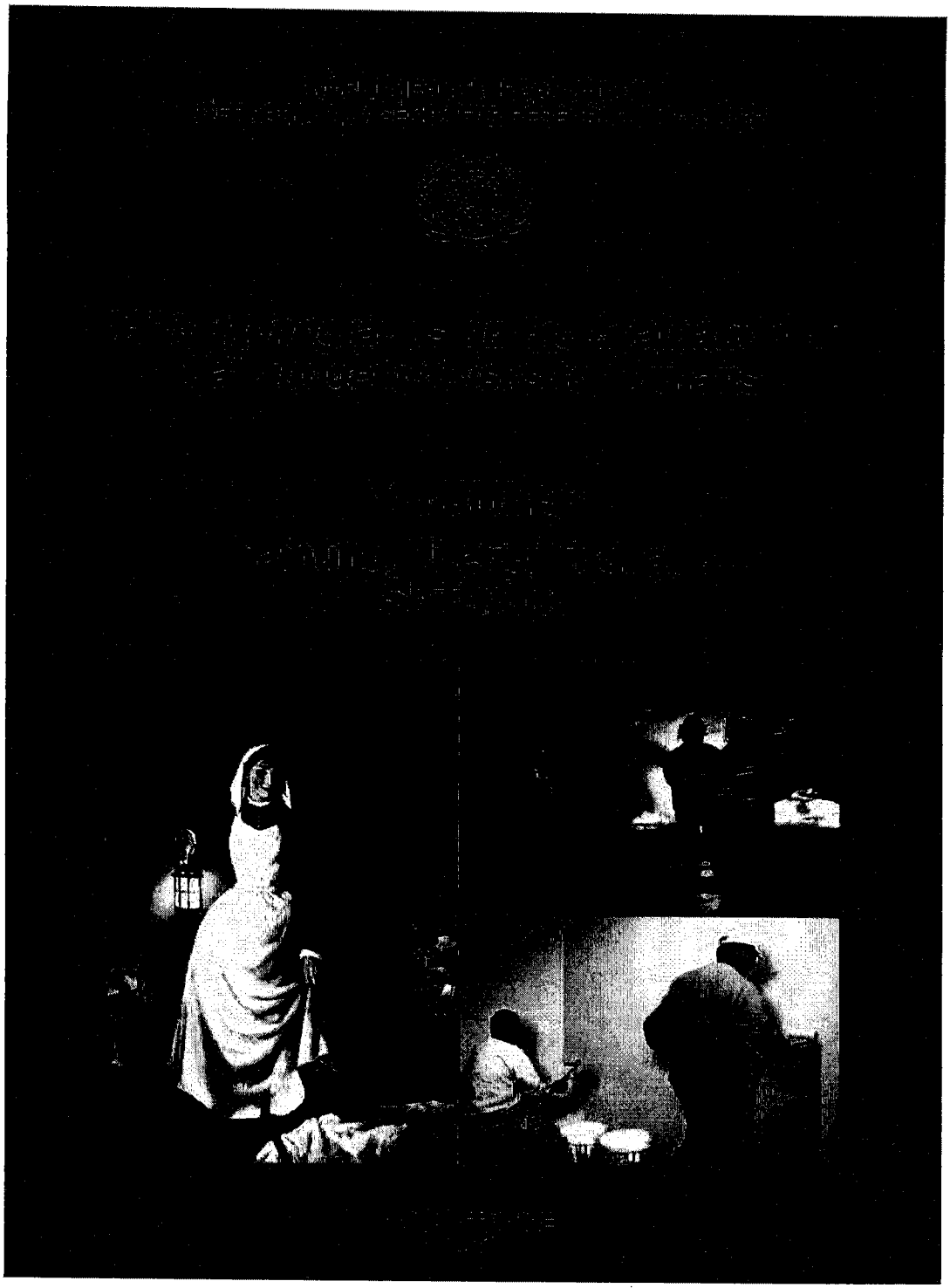
the study group was compared with that expected on the basis of mortality rates among men in England and Wales for the English and Welsh refineries and among men in Scotland for the Scottish refineries, adjusted for age and calendar period; 73 men (0.2%) could not be traced. The SMR for all causes of death was significantly less than 1. The only significant excesses of site-specific cancer mortality noted were for cancer of the nasal cavities and sinuses and for melanoma (Rushton & Alderson, 1980). Among the 9589 men who had worked as operators, excess mortality was seen for oesophageal cancer when results for all the refineries were combined, for intestinal cancer at refinery B and for rectal cancer at refinery F. Labourers experienced elevated mortality from stomach cancer at all refineries combined, at refinery F and at refinery J; riggers and fire and safety workers at refinery J also had elevated risks for stomach cancer. Scientists experienced higher than expected mortality from intestinal cancer at all refineries combined and at refinery J. Stomach cancer mortality decreased with duration of employment overall and at refinery J, but increased with duration of employment at refinery F. Intestinal cancer mortality increased with duration of employment overall and at refineries B and F (Rushton & Alderson, 1981a).

Men who had been employed in methyl ethyl ketone dewaxing plants in two of the refineries included in the study described above were the subject of a separate report (Alderson & Rattan, 1980). Among the 446 men who had worked in these plants, site-specific excess mortality was noted for cancers of the buccal cavity and pharynx and of the digestive tract.

In a nested case-control study, Rushton and Alderson (1981b) compared exposure to benzene among men who had died from leukaemia and among controls selected from the study population of the eight UK oil refineries described above. Two control groups were used: one matched by refinery and year of birth, and a second matched by refinery, year of birth and length of service. There was no excess of leukaemia overall when observed mortality in the refinery population was compared with national rates; however, there were excesses for specific categories: unspecified lymphatic leukaemia, unspecified myeloid leukaemia and acute monocytic leukaemia. The SMRs for all lymphatic leukaemia combined and for all myeloid leukaemia combined were not significantly elevated. A nested case-control analysis suggested a relationship between elevated risk for leukaemia and exposure to benzene, which the authors suggested was confounded by length of service. The odds ratio for leukaemia among men with medium or high exposure to benzene relative to those with low exposure was 2.0, and risk increased with duration of service in the refinery. None of these results was significant.

(iv) *Sweden*

An investigation of occupational risk factors for histologically confirmed biliary tract cancer in Sweden was conducted by linking 1960 census information on occupation with cancer incidence data from the National Swedish Cancer Registry for 1961–79 (Malker *et al.*, 1986). SIRs among workers in specific industries and occupations were calculated by dividing the observed number of cases in each occupational group by the number expected on the basis of national rates among all employed persons, adjusting for birth cohort and sex. Men employed in petroleum refining had significantly elevated SIRs for gall-bladder and other biliary tract cancer.



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

completed in 1954 and 1957, and 107 563 deaths were recorded during 1954–1970. Excesses of rectal, bladder, and brain cancers were observed based on very small numbers.

Gallagher *et al.* (1989) conducted a study of mortality by occupation and industry using death certificate data during 1950–1984 from the Canadian province of British Columbia. There were 1202 deaths among firefighters identified based on occupational titles on death certificates. PMRs were calculated with adjustment for 5-year age and calendar period. There were 197 cancer deaths, and a small excess of overall cancer as well as a significant excess of pancreatic cancer was observed.

In the USA, Sama *et al.* (1990) examined cancer incidence among firefighters using the Massachusetts Cancer Registry records for 1982–1986. Employment as a firefighter was based on the usual occupation reported to the Registry. The analysis was restricted to 315 Caucasian male firefighters. Case–control analyses were conducted for nine different cancer types and two 'unexposed' reference populations were used: policemen and statewide males. Standardized morbidity odds ratios (SMORs) were calculated and significant excesses of malignant melanoma and bladder cancer were observed compared to the general population. Excesses of bladder cancer and non-Hodgkin lymphoma were observed when compared to policemen.

An analysis of deaths in England and Wales (1979–1980 and 1982–1990) were examined by occupation (OPCS, 1995). A total of 2968 deaths among male firefighters and 16 deaths among their female counterparts were observed based on the last occupation listed on death certificates. Only statistically significant results were reported, and excesses of oesophageal, stomach, and gall bladder cancer mortality were observed among men.

A follow-up study was conducted in the Finnish working-age population identified in the 1970 census (Pukkala, 1995). A total of 1436 male firefighters were identified during the follow-up period during 1971–1985 through linkage with the Finnish tumour registry. No statistically significant excesses were observed. The largest excess reported was for non-localized prostate cancer.

In Canada, Finkelstein (1995) examined occupations associated with lung cancer using a case–control study based on death certificates in two Ontario cities, and observed an excess among firefighters based on small numbers.

Milham (1997) conducted a study of mortality by occupation and industry using death certificate data (1950–1989) from the state of Washington, USA. A total of 2266 deaths among firefighters were identified based on the occupational titles on death certificates. PMRs were calculated and adjusted by 5-year age group and calendar period. There were 197 cancer deaths and a small excess of overall cancer was observed as well as significant excesses of melanoma and lympho- and reticulosarcoma. [The Working Group noted that there was an overlap between this and the multistate studies conducted by NIOSH, but that this had the longest follow-up period and was the earliest study of its kind in North America.]

Two studies examined the impact of continuous high-intensity light versus low-intensity light on tumour development in mice. One study demonstrated clear increases in the incidence of lung adenocarcinomas, leukaemias and lymphomas combined. The second study showed an increase in the incidence of and mortality from mammary tumours in one substrain that had normal vision, and no increase in a substrain of the same strain that had retinal degeneration due to genetic predisposition. A third study showed no effects.

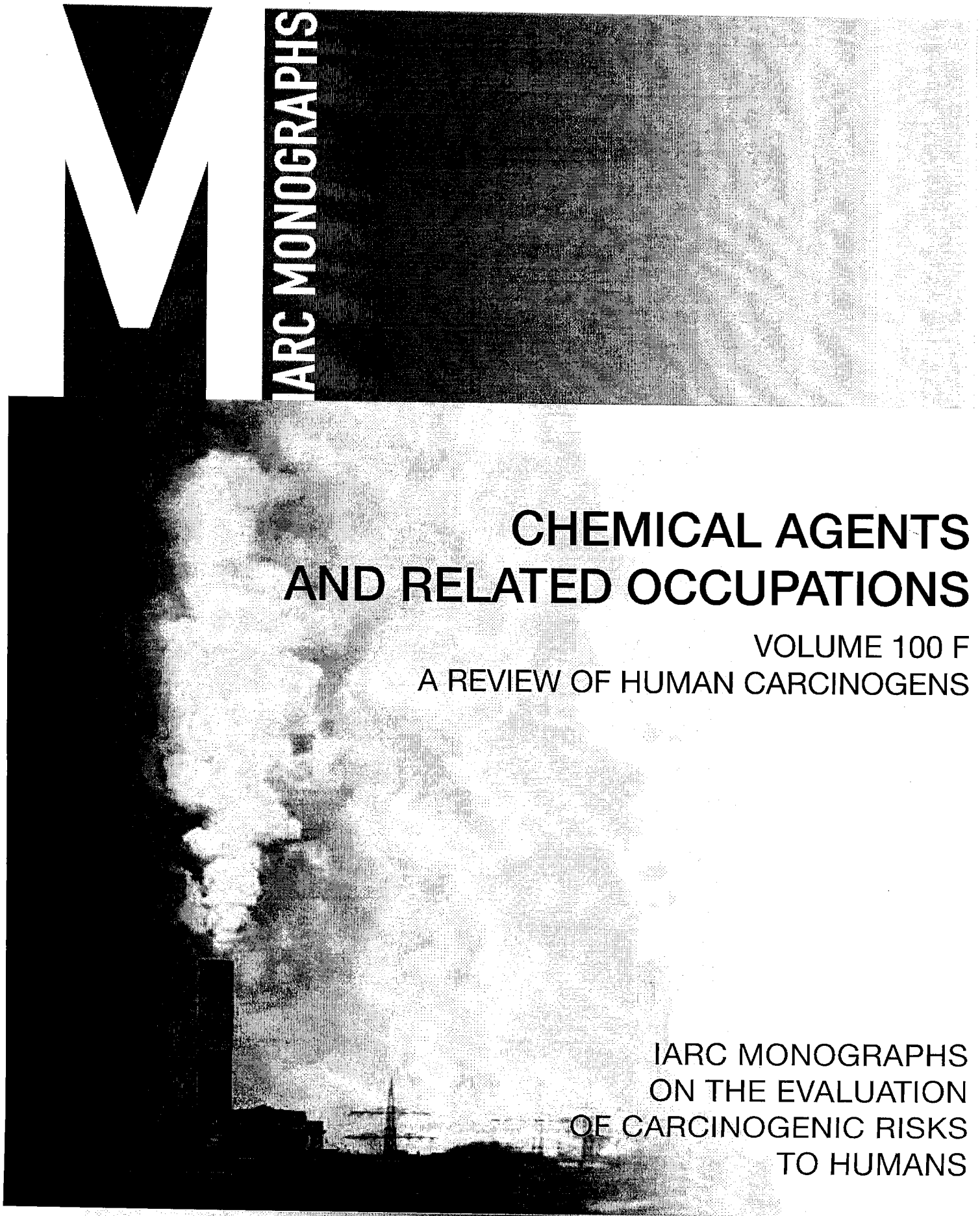
All of the remaining experimental studies used initiation–promotion protocols or tumour growth models following the transplantation of syngeneic tumour fragments, cells, or human cancer xenografts. The species used in these studies included both sexes of rats, mice and hamsters, all of which yielded positive results in at least one study. The types of rodent model systems studied included mammary adenocarcinoma/fibroadenoma, cancers of the peripheral nervous system and kidney, hepatocarcinoma, pancreatic adenocarcinoma, colon adenocarcinoma, prostate adenocarcinoma, squamous-cell carcinoma and fibrosarcoma, osteosarcoma and carcinosarcoma, melanoma, neuroblastoma, and undifferentiated neoplasms.

possible relation of Prostate to Esophagel

The model systems used to study the role of the central circadian function and its disruption on cancer development and/or growth encompassed the exposure of animals to chronic alterations in the light–dark environment (i.e. constant bright light, constant darkness, altered light–dark schedules, intermittent light during darkness, single light pulse during darkness). Other model systems used more focused experimental manipulations that included phase-shifting central circadian activity only (i.e. exposure to experimental chronic jet lag), suppression or ablation of the nocturnal circadian melatonin signal (i.e. pinealectomy or exposure to dim light during darkness), ablation of the central circadian activity and of melatonin production (i.e. induction of lesions in suprachiasmatic nuclei), clock gene mutations (i.e. mPer2 knockouts) and the impact of carcinogen administration at different circadian times on tumorigenesis. A specialized model system evaluated the acute proliferative activity of tissue-isolated melatonin-receptor-positive murine or human tumours perfused *in situ* with different physiological levels of melatonin from natural diurnal blood changes and artificial manipulation.

The major patterns of light–dark environments that have an impact on cancer development and/or growth (i.e. stimulation) are constant light exposure (two positive of three studies, five positive of six initiation–promotion studies, five positive of five tumour-growth studies), dim light during darkness (five positive of five studies), experimental chronic jet lag (two positive of two studies), and circadian timing of carcinogens (four positive of four studies). Two conditions that produced no clear effects or even slowed tumour growth were light pulses during the dark period (two of two studies), and constant darkness (two of two studies). Mechanistically oriented animal studies specifically aimed at investigating the role of the pineal gland (i.e. pinealectomy-induced stimulation of cancer development and/or growth) and the nocturnal melatonin profile (i.e. inhibition of cancer proliferative activity) also had a major impact on cancer (18 positive of 26 studies). Furthermore, a limited number of studies on suprachiasmatic nuclei or clock genes yielded important results with respect to increased tumorigenesis (two positive of three studies).

IARC MONOGRAPHS



CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

Group 1 carcinogen
Pages 1 & 2 of Chemical List (IARC 105)

3.8 Buccal pouch application

Repeated application of benzo[*a*]pyrene to the buccal pouch mucosa of male hamsters resulted in a high incidence of forestomach papillomas (Solt *et al.*, 1987).

3.9 Subcutaneous tracheal grafts transplantation

In one study conducted in rats transplanted with subcutaneous rat tracheal grafts exposed to beeswax pellets containing various amounts of benzo[*a*]pyrene, a high incidence of squamous-cell carcinomas was reported (Nettesheim *et al.*, 1977).

3.10 Intramammilary administration

In three studies in rats, benign and malignant mammary gland tumours developed after intrammilary injection of benzo[*a*]pyrene (Cavalieri *et al.*, 1988a, b, 1991).

3.11 Intracolonic instillation

In three experiments in mice, intracolonic instillation of benzo[*a*]pyrene induced lymphomas and a variety of benign and malignant tumours in various organs including the forestomach (Toth, 1980; Anderson *et al.*, 1983).

3.12 Intravaginal application

Intravaginal application of benzo[*a*]pyrene in mice produced invasive cervical carcinoma; no such tumours were seen in controls (Näslund *et al.*, 1987).

3.13 Intrafetal injection

In one study in male and female Swiss mice, intrafetal injection of benzo[*a*]pyrene produced lung adenomas (Rossi *et al.*, 1983).

4. Other Relevant Data

Benzo[*a*]pyrene is a carcinogen that induces tumours in many animal species. Some of the examples relevant for this review are: lung tumours in mice, rats, and hamsters; skin tumours in mice; liver tumours in mice; forestomach tumours in mice and hamsters; and mammary gland tumours in rats (Osborne & Crosby, 1987; IARC, 2010). In humans, occupational exposures to benzo[*a*]pyrene-containing mixtures have been associated with a series of cancers: coke production: lung; coal gasification: lung, bladder; paving and roofing: lung; coal tar distillation: skin; soots: lung, oesophagus, haematolymphatic system, skin; aluminum smelting: lung, bladder; tobacco smoking: lung, lip, oral cavity, pharynx, oesophagus, larynx, bladder (IARC, 1984, 1985, 1986, 2010).

Studies on the mechanisms of action of benzo[*a*]pyrene have been reviewed (Xue & Warshawsky, 2005; IARC, 2010).

4.1 Metabolism

Benzo[*a*]pyrene is metabolized by both phase-I and phase-II enzymes to form a series of arene oxides, dihydrodiols, phenols, and quinones and their polar conjugates with glutathione, sulfate, and glucuronide (Osborne & Crosby, 1987). Benzo[*a*]pyrene-7,8-diol is a key metabolite that is formed by the action of epoxide hydrolase on benzo[*a*]pyrene-7,8-epoxide. This dihydrodiol can be further metabolized by cytochrome P450s (CYPs) to a series of benzo[*a*]pyrene-7,8-diol-9,10-epoxides, which form one class of ultimate carcinogenic metabolites of benzo[*a*]pyrene.

Soot is a Group 1 carcinogen (IARC Chemical List IARC 105)

SOOT, AS FOUND IN OCCUPATIONAL EXPOSURE OF CHIMNEY SWEEPS

Soot was considered by previous IARC Working Groups in 1972, 1984, and 1987 (IARC, 1973, 1985, 1987). Chimney sweeping and other exposures to soot were evaluated in 2005 (IARC, 2010). Since that time new data have become available, which have been incorporated in this *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

For hundreds of years, chimneys have been swept with long steel brushes inserted manually into the chimney from the top and from the bottom. Chimney sweeps are exposed to soot, with concurrent exposure to sulfur dioxide and arsenic (Bagchi & Zimmerman, 1980).

Soot is black particulate matter that is formed as a by-product of combustion or pyrolysis of organic (carbon-containing) materials, such as coal, wood, fuel oil, waste oil, paper, plastics and household refuse. The chemical composition and properties of soots are highly variable and depend on the type of starting material and the conditions of combustion. Soots vary considerably with respect to their relative content of carbon, their particle type, size and shape, and the types of organic and inorganic compounds adsorbed onto the particles. In general, soots have a total carbon content of up to 60%, a high content of inorganic material, and a soluble organic fraction. The latter is extractable with organic solvents and consists largely of PAHs and their derivatives. Inorganic constituents may include oxides, salts, metals, sulfur and nitrogen compounds, water, and other adsorbed liquids and gases (IARC, 1985; Watson & Valberg, 2001).

Table 1.1 summarizes several recent studies that investigated exposure of chimney sweeps to PAHs. Knecht *et al.* (1989) assessed exposures in the breathing zone of chimney sweeps during so-called 'dirty' or 'black work' on 11 working days. Samples were taken per 'job category', based on the type of fuel fired: oil fuel, oil/solid or solid fuels. Twenty PAHs were quantified in a total of 115 samples. Higher concentrations were seen in soots that originated from burning of solid fuels. A bio-monitoring study carried out in Germany (n = 93) and Poland (n = 7) in 1995 reported 1-hydroxypyrene concentrations in the urine ranging from below the detection limit (0.1 µg/L) up to 12.8 µg/L (Letzel *et al.*, 1999). Urinary concentrations in the samples from Poland were on average five times higher, most probably due to the fact that coal and wood are used more often as fuels in Poland. The concentrations in urine samples from workers in Germany were relatively low. The use of personal protective devices among this group of 100 chimney sweeps was not mentioned. In an Italian study, Pavanello *et al.* (2000) analysed the urine of 27 chimney

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 dibenzofurans were found in blood lipids of 227 chimney sweeps from Bavaria (Wrbitzky *et al.*, 2001).

2. Cancer in Humans

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

Evanoff *et al.* (1993) conducted large cohort study of Swedish chimney sweeps and found an excess of cancer of the lung, bladder, oesophagus and haematolymphatic organs; a study from Finland corroborated these findings (Pukkala, 1995). These studies did not include individual adjustments for tobacco smoking, but in the Swedish study an adjustment was made for smoking at the group level, whereas in the Finnish study adjustment was for social class. Both analyses indicated that confounding from tobacco smoking did not explain the findings regarding lung cancer. In two Danish cohort studies an excess of total cancer was found, but the studies were too small to evaluate individual cancer sites (Hansen *et al.*, 1982; Hansen, 1983; see Table 2.1, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-16-Table2.1.pdf).

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

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

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

limited. The incidence of oesophageal cancer is highly correlated with smoking and alcohol consumption, and in the absence of control for these two factors, the evidence of an association with occupational exposure as a chimney sweep is inadequate. From historical case reports there is sufficient evidence of an increased risk for (scrotal) skin cancer among chimney sweeps.

3. Cancer in Experimental Animals

Coal soot was tested in two experiments in mice by whole-body exposure, but these studies were inadequate for evaluation. Coal-soot extracts applied to the skin of mice produced skin tumours in two studies (IARC, 1985).

In limited studies, subcutaneous implants of wood soot in female rats produced a few local sarcomas. Similar implants in the scrotal sac of rats did not produce tumours. One study of wood-soot extract applied to the skin of mice was uninformative (IARC, 1985).

One study of an extract of fuel-oil soot applied to the skin of mice was uninformative. Extracts of soot from the combustion of oil shale produced skin tumours in mice after dermal application and lung tumours in rats after intratracheal instillation (IARC, 1985).

Extracts of soot from the combustion of heating oil produced from shale oil produced skin tumours in mice in two skin-application experiments (IARC, 1985).

4. Other Relevant Data

4.1 Mechanistic evidence relevant to the carcinogenic hazards from occupational exposure as a chimney sweep

4.1.1 Experimental systems

Experimental studies on soots have been evaluated in *IARC Monograph* Volume 35 and in Supplement 7 (IARC, 1985, 1987). In one study, extracts of soot samples from domestic sources were mutagenic in *Salmonella typhimurium*, both in the presence and absence of an exogenous metabolic system. Extracts of an experimentally-derived soot were mutagenic in forward-mutation assays in *S. typhimurium* and in cultured human lymphoblasts in the presence of metabolic activation (IARC, 1985). Extracts of particulate emissions from wood-combustion induced sister chromatid exchange in Chinese hamster ovary cells, transformation of Syrian hamster embryo cells, and mutation in *S. typhimurium*. An experimentally prepared, intact particulate soot and an extract of this material were both mutagenic in a human lymphoblastoid cell line (IARC, 1987).

Chemical analyses of chimney-soot extracts have identified several polycyclic aromatic hydrocarbons that are genotoxic and carcinogenic in experimental studies. These include benz[*a*]anthracene, benzo[*c*]phenanthrene, benzo[*a*]pyrene, dibenz[*a,h*]anthracene, chrysene, and indeno[1,2,3-*cd*]pyrene (IARC, 1983, 1985, 2010). These polycyclic aromatic hydrocarbons may contribute to the genotoxic and tumorigenic activities of soots.

4.1.2 Humans

The frequency of micronuclei in peripheral B- or T-lymphocytes was studied in 71 Swedish chimney sweeps. Genetic polymorphisms in enzymes involved in metabolic activation were

investigated to explain some of the variation in micronucleus formation. The sweeps did not have higher frequencies of micronuclei in either cell type when the results were adjusted for age and smoking, and there was no association between years of work and micronucleus formation (Carstensen *et al.*, 1993).

The same group of workers was studied for the presence of aromatic DNA adducts and micronuclei, and also genotyped for *CYP1A1* and *GST1*. While no specific DNA adducts were identified, the sweeps had higher total DNA-adduct levels in white blood cells, but the increase was not statistically significant. There were no systematic differences in DNA-adduct patterns between the sweeps and the controls. DNA adducts in sweeps were moderately but statistically significantly correlated with micronuclei in both T- and B-lymphocytes. The correlation between adduct-levels and micronuclei was most marked in T-lymphocytes of individuals lacking the *GST1* gene (Ichiba *et al.*, 1994).

Groups of 45 Swedish chimney sweeps and 49 controls were investigated for micronucleus formation in blood lymphocytes stimulated by phytohaemagglutinin or pokeweed mitogen, and by analysis of lymphocyte subgroups and neutrophilic leukocytes. There were higher frequencies of micronuclei among sweeps than in controls, with both methods of stimulation. The effect on micronucleus formation in lymphocytes was more significant in cells stimulated with pokeweed mitogen, suggesting that the T4 lymphocytes were preferentially damaged by the occupational exposure (Holmén *et al.*, 1994).

Analysis of *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adducts in a group of 19 chimney sweeps showed that four of them (21%) had adduct levels exceeding the 95 percentile control-subject value (Pavanello *et al.*, 1999a). These higher levels were associated with the lack of GSTM1 activity: three of the chimney sweeps had the *GSTM1* *0/*0 genotype (Pavanello *et al.*, 1999b).

4.2 Synthesis

Extracts of soots contain carcinogenic polycyclic aromatic hydrocarbons and are genotoxic. Based on a small number of genotoxicity studies in exposed humans, there is moderate evidence of a genotoxic mode of action for the carcinogenic hazards associated with occupational exposures as a chimney sweep. The detection of *anti*-benzo[*a*]pyrene-7,8-diol-9,10-epoxide-DNA adducts in the peripheral blood lymphocytes of chimney sweeps suggests involvement of benzo[*a*]pyrene in the genotoxic effect of this exposure in humans.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of soot as found in occupational exposure of chimney sweeps. Soot, as found in occupational exposure of chimney sweeps, causes cancer of the skin (observed in the scrotum), and of the lung.

Also, a positive association has been observed between exposure to soot as found in occupational exposure of chimney sweeps and cancer of the bladder.

There is *inadequate* evidence in experimental animals for the carcinogenicity of soot.

There is *sufficient evidence* in experimental animals for the carcinogenicity of soot extracts.

Extracts of soots contain carcinogenic polycyclic aromatic hydrocarbons and are genotoxic. Based on a small number of genotoxicity studies in humans there is moderate evidence for a genotoxic mechanism for occupational exposures as a chimney sweep.

Soot as found in occupational exposure of chimney sweeps is *carcinogenic to humans (Group 1).*

embalmers 1.6 (95%CI: 1.2–2.0); and for pathologists and anatomists 1.4 (95%CI: 1.0–1.9), with an overall mRR of 1.1 (95%CI: 1.0–1.2) (Collins & Lineker, 2004). In another meta-analysis, analysis was restricted to 13 cohort or proportionate mortality studies and similar results were found, with a pooled RR based on the weighted average of the SMRs for leukaemia among industrial workers of 0.9 (95%CI: 0.75–1.07), based on 122 deaths, and of 1.39 (95%CI: 1.15–1.68) among professionals, based on 106 deaths (Bosetti *et al.*, 2008). A further meta-analysis differed from these two previous ones by excluding all proportionate mortality studies and including the most recent update of the NCI cohort (Bachand *et al.*, 2010). For leukaemia overall, a risk estimate of 1.05 (95%CI: 0.93–1.20) was calculated for 'ever exposure', based on 15 studies with the use of a fixed-effects model. For myeloid leukaemia, the calculated mRR was 1.09 (95%CI: 0.84–1.40, based on three studies) and for lymphatic leukaemia the mRR was 1.11 (95%CI: 0.81–1.52, based on two studies).

Zhang *et al.* (2009) published a meta-analysis that included 15 cohort or case–control studies. The authors selected only studies where it was clear that the workers had been exposed to formaldehyde. In contrast to the other meta-analyses, this one used one exposure metric from each study and considered the highest exposure category for calculating the mRR. For leukaemia, the mRR was 1.54 (95%CI: 1.18–2.00). In addition, a separate analysis of myeloid leukaemia – for the six studies that reported it – found an mRR of 1.90 (95%CI: 1.31–2.76).

2.3 Cancer of the nasal sinuses

2.3.1 Cohort studies

An analysis of proportionate cancer incidence among industrial workers in Denmark showed an increased risk for squamous-cell carcinomas (Hansen & Olsen, 1995, 1996). No excess of mortality from sinonasal cancer was observed in the three recently updated studies of industrial and garment workers in the USA, and of chemical workers in the United Kingdom (see Table 2.1 online; Coggon *et al.*, 2003; Hauptmann *et al.*, 2004; Pinkerton *et al.*, 2004).

2.3.2 Case–control studies

The association between exposure to formaldehyde and the risk for sinonasal cancer has been evaluated in six case–control studies that primarily focused on formaldehyde (see Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-24-Table2.4.pdf; Olsen *et al.*, 1984; Hayes *et al.*, 1986; Olsen & Asnaes, 1986; Vaughan *et al.*, 1986a; Roush *et al.*, 1987; Luce *et al.*, 1993; Pesch *et al.*, 2008). Four of these six studies reported an increased risk (Olsen *et al.*, 1984; Hayes *et al.*, 1986; Vaughan *et al.*, 1986a; Luce *et al.*, 1993).

2.3.3 Pooled analysis

Four of the cohort studies contributed to a pooled analysis that collated occupational data from 12 case–control investigations (Luce *et al.*, 2002). After adjustment for known occupational confounders, this analysis showed an increased risk for adenocarcinoma associated with high exposure (> 1 ppm) to formaldehyde in both men (OR, 3.0; 95%CI: 1.5–5.7) and women (OR, 6.3; 95%CI: 2.0–19.7). An exposure–response trend was observed in relation to an index of cumulative exposure. There was some evidence of an association with squamous-cell carcinoma.

[Most epidemiological studies of sinonasal cancer have not distinguished between tumours that arise in the nose and those that develop in the nasal sinuses. Thus, any effect on the risk for nasal cancer specifically would tend to be diluted if there were no corresponding effect on the risk for cancer in the sinuses and could mask its detection, particularly in cohort studies that

have relatively low statistical power. However, the apparent discrepancy between the results of the case–control as compared with the cohort studies might also reflect residual confounding by wood dust in the former. Almost all of the formaldehyde-exposed cases in the case–control studies were also exposed to wood dust, which resulted in a high relative risk, particularly for adenocarcinomas.

2.4 Other cancers

Several studies have identified statistically significant positive associations between exposure to formaldehyde and cancer at other sites, including the oral cavity, oro-and hypopharynx, larynx, lung, brain, pancreas, Hodgkin lymphoma, and multiple myeloma. However, the results are inconsistent (see Tables 2.4 and 2.5 online; Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-24-Table2.6.pdf, and Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-24-Table2.7.pdf).

2.5 Synthesis

The Working Group noted one industrial cohort study with both a strong overall association between exposure to formaldehyde and nasopharyngeal cancer, and the most elevated risks in the highest exposure category. Positive associations were also observed in many of the case–control studies, in particular those of larger size and higher-quality exposure assessment. While there was no association observed in the two other large industrial cohort studies, the expected number of cases in those studies was quite small. It is concluded that occupational exposure to formaldehyde causes nasopharyngeal cancer in humans. The Working Group noted that it was unlikely that confounding or bias could explain the observed association.

Elevated risks of leukaemia have been consistently observed in proportionate mortality studies of professionals exposed to formaldehyde (i.e. embalmers, workers in the funeral industry, pathologists and anatomists). Results from a nested case–control study of workers in the funeral industry show elevated risks for many measures of exposure, which are strongest for myeloid leukaemia. In two of the three large industrial cohort studies positive associations were observed for leukaemia, which were somewhat stronger for myeloid leukaemia. It is difficult to reconcile the lack of association observed in the third industrial cohort study with the overall positive associations in the others. However, there seems to be no strong evidence that confounding or bias explains the positive associations seen in multiple settings. On balance, the Working Group concluded that the epidemiologic evidence shows that occupational exposure to formaldehyde causes leukaemia.

Many case–control studies show positive associations for exposure to formaldehyde and sinonasal cancer, some with evidence of an exposure–response pattern. However, many of these cases were also exposed to wood dust, which was strongly associated with sinonasal cancer in these studies. The industrial cohort studies show no such association, which may be due to lack of statistical power, or could indicate that uncontrolled confounding to wood dust partially explains the observed associations in the case–control studies. The Working Group could not rule out the possibility of residual confounding in the case–control studies and noted the discordant results between the cohort and case–control studies.

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World Health Organization

who were employed 1900–94. In Copenhagen, the first diesel-powered buses were introduced in 1936, but, during the Second World War, all buses were fuelled with gasoline. Diesel-powered buses gradually replaced gasoline-powered models after that time, and, in the 1960s, they also replaced the trams. Cancer rates were compared with those of the general population of Denmark by linkage to the Danish Cancer Registry and National Death Index to identify cancers that occurred after 1943. Among male workers employed for 3 months or longer, the standardized incidence ratio was 1.6 (95% CI, 1.5–1.8; 473 cases) for lung cancer, 1.0 (95% CI, 0.8–1.3; 82 cases) for stomach cancer, 1.2 (95% CI, 1.0–1.5; 105 cases) for rectal cancer, 1.4 (95% CI, 1.0–1.9; 39 cases) for laryngeal cancer, 1.6 (95% CI, 1.3–1.6; 83 cases) for kidney cancer, 1.4 (95% CI, 1.2–1.6; 177 cases) for urinary bladder cancer, 1.9 (95% CI, 1.2–2.8; 22 cases) for pharyngeal cancer and 1.1 (95% CI, 0.8–1.5; 46 cases) for leukaemia. In women, the standardized incidence ratio for lung cancer was 2.6 (95% CI, 1.5–4.3; 15 cases). In both men and women, a greater risk of lung cancer was observed with longer time since first employment. No trend in lung cancer risk was found based on periods of predominantly gasoline or diesel vehicle use, and the risks were similarly elevated for workers who started before, at the onset, or during the use of diesel buses. [The Working Group noted that no information on specific exposures or tobacco smoking was available and the periods of diesel and gasoline emissions overlapped. Compared with other men in Copenhagen, the smoking rates among the bus drivers were slightly higher during some time periods, suggesting the possibility of some confounding by smoking.]

A nested case–control study (Soll-Johanning *et al.*, 2003) was conducted with 153 cases of lung cancer and 84 cases of urinary bladder cancer included in the cohort of Copenhagen bus drivers and tramway employees. The cases and controls or next of kin were interviewed regarding tobacco smoking history. Deaths from cancer or non-neoplastic respiratory disease were excluded from the control group and cases and controls were matched on date of birth. Both 10-year lag and no lag models, based on duration of employment, were assessed, adjusting for smoking history in seven categories based on pack–years. No consistent increase in lung cancer risk was observed based on categories of duration of employment in either lag model. The risk, although not statistically significant, increased with greater number of years of employment, but then decreased after > 20 years. With a 10-year exposure lag, there was a suggestion of an increased risk for urinary bladder cancer in persons with 10– < 20 years of work (relative risk, 1.61; 95% CI, 0.57–4.55).

In the cohort study described in Section 2.2.1, Guo *et al.* (2004a) reported on lung cancer risk in male bus drivers who had exposure to both gasoline and diesel exhausts; the standardized incidence ratio was not significantly elevated (SIR, 0.89; 95% CI, 0.78–1.00; 253 cases). [The Working Group noted that this study was limited due to the lack of detailed work histories relating to exposures to exhaust and information on tobacco smoking.]

In a separate report, Guo *et al.* (2004b) presented data for other cancers in bus drivers. The risk was elevated for urinary bladder cancer (SIR, 1.29; 95% CI, 1.02–1.62; 75 cases), oesophageal cancer (SIR, 1.10; 95% CI, 0.60–1.85; 14 cases), kidney cancer (SIR, 1.29; 95% CI, 1.00–1.64; 67 cases) and leukaemia (SIR, 1.04; 95% CI, 0.68–1.51; 27 cases). [The Working Group noted that this study was limited due to the lack of detailed work histories relating to exposures to exhaust and information on tobacco smoking.]

Petersen *et al.* (2010) studied the cancer incidence in a cohort, established in 1978, of 2037 male Danish urban bus drivers over a 25-year period of follow-up (1979–2003). In 1978, public bus drivers in the three largest cities of Denmark received a mailed questionnaire on occupational

historical trends in background exposures. Although uncertainty is inherent when estimating historical exposures, systemic bias was improbable. It was not possible to adjust directly for tobacco smoking, but previous adjustment in the same cohort revealed little difference in the risk for lung cancer with or without adjustment. A possible interaction between average exposure and duration of employment on mortality from lung cancer may explain some of the apparent paradoxes of the results, such as the observation that cumulative exposure, adjusted for duration of employment, had a greater effect while average exposure, adjusted for duration of employment, did not. The study provided evidence for an association between sources of EC (predominantly diesel) and the risk for lung cancer.]

2.2.4 Miners

In the cohort described in Section 2.2.1, Boffetta *et al.* (1988) studied 2034 men who reported working as a miner on the basis of any past employment in this occupation. The age- and tobacco smoking-adjusted relative risk for lung cancer was 2.67 (95% CI, 1.63–4.37; 15 deaths) compared with other men who did not report working as a miner and who reported no exposure to diesel exhaust. [The Working Group noted that this study was limited by the small number of miners and the lack of information regarding specific exposures to exhaust. Only 14% of miners reported exposure to diesel exhaust; these miners may also have been exposed to other lung carcinogens, such as silica or radon.]

In the cohort described in Section 2.2.1, Guo *et al.* (2004a) reported that male miners in three different occupational categories had an elevated risk of lung cancer. These included mine and quarry work involving metal ore (SIR, 3.26; 95% CI, 2.28–4.51; 36 cases), mine and quarry work involving non-metal ore (SIR, 1.85; 95% CI, 1.59–2.14; 181 cases) and other unspecified mine and quarry work (SIR, 1.73; 95% CI, 1.35–2.19; 70 cases). All three groups were classified by an expert review as having been exposed to diesel exhaust but not gasoline exhaust. In a separate report, Guo *et al.* (2004b) presented data for other cancers in male miners. In non-metal ore miners and quarry workers, the risks were elevated for leukaemia (SIR, 2.31; 95% CI, 1.39–3.61; 19 cases), oesophageal cancer (SIR, 1.74; 95% CI, 0.70–3.58; seven cases), kidney cancer (SIR, 0.88; 95% CI, 0.47–1.50; 13 cases) and urinary bladder cancer (SIR, 1.16; 95% CI, 0.73–1.76; 22 cases). Too few cases occurred in other mining groups to carry out a meaningful assessment. [The Working Group noted that these studies were limited due to the lack of detailed work histories and information on tobacco smoking. In particular, for lung cancer, these miners may have had confounding exposures to other substances, such as silica and radon.]

Neumeyer-Gromen *et al.* (2009) updated the mortality from lung cancer in a cohort of 5862 German underground potash miners, first described by Säverin *et al.* (1999), from 1970 up to 2001. Diesel equipment was introduced into potash mines in 1969 and, in 1991, the mines were closed. Tobacco smoking histories were available from medical and personnel records for 80% of the cohort. Estimates of diesel exposure were obtained in 1992, and expressed as total carbon in respirable dust. Because technology had not changed, these levels were assumed to be representative of previous exposure and were used for its categorization. The overall standardized mortality ratio was not elevated for lung cancer (SMR, 0.73; 95% CI, 0.57–0.93; 61 deaths) or urinary bladder cancer (SMR, 0.80; 95% CI, 0.40–1.60; 8 deaths). Using Cox regression modelling, the smoking-adjusted relative risk in the highest category of exposure dichotomized at 4.90 mg/m^3–years was 1.28 (95% CI, 0.61–2.71; 61 cases). In a subgroup of 3335 workers who had worked underground for at least 10 years, the age- and smoking-adjusted relative risk was 1.50 (95% CI, 0.66–3.43; 37 cases). Adjusting for smoking

resulted in higher risk estimates. In a model that further adjusted for time since hire and calendar year, the relative risk in the entire cohort was 2.53 (95% CI, 1.13–5.69) and that in the subcohort of workers who had worked for more than 10 years after 1969 was 3.30 (95% CI, 1.30–8.37). Using time since first hire as the time variable in a Cox regression analysis to account for duration of employment, and adjusting for age and smoking, a non-significant trend (P = 0.19) in risk for mortality from lung cancer was observed with greater exposure in the entire cohort (RR, 1.81; 95% CI, 0.92–3.58; and 1.59; 95% CI, 0.75–3.40; for the second and third tertiles, respectively). A non-significant increased trend (P = 0.17) in risk of was also found within the subcohort, for which more accurate information on exposure was available. [The Working Group noted that, although the power of the study was limited by the sample size, one of its strengths was that the effects of smoking were considered together with quantitative estimates of exposure based on measurements. The study also used an internal comparison group. Another strength in the design was the control of confounding for other mining-related occupational risk factors for lung cancer, because exposure to radon, silica dust, asbestos and heavy metals were not significant in potash mining. This study was supportive of an effect of exposure to diesel exhaust on the risk of lung cancer.]

Attfield *et al.* (2012) studied the mortality of a cohort of 12 315 blue-collar workers who were employed in one of eight non-metal mines in the USA for at least 1 year after diesel equipment had been introduced. The mines were selected to minimize exposures to silica, radon and asbestos. Detailed work histories were abstracted from company records and mortality was assessed up to 1997. The dates of the introduction of diesel equipment ranged from 1947 to 1967. Historical estimates of exposure to respirable EC were constructed on the basis of personal measurements taken in the mines in 1998–2001, which were extrapolated retroactively based on a model using diesel exhaust-related determinants, including diesel engine horse power and ventilation rates, and historical measurements of carbon monoxide. The modelled trends in concentrations of CO for previous years were then used to adjust the 1998–2001 levels of exposure to respirable EC to estimate historical annual concentrations of respirable EC for each job. Estimates of exposure to silica, asbestos, respirable dust, radon and other PAHs were also made. Estimates of exposure to diesel exhaust in surface workers were based on measurements made in 1998–2001 and no reconstruction of historical exposure was carried out. The mean exposure of surface workers only was 1.7 μg/m^3 and that of the ever-underground miners was 128.2 μg/m^3. Standardized mortality ratios using external referents were determined from state-specific mortality rates, and their calculation was limited to persons employed since 1960 (12 270 subjects), because state-specific rates were not available for earlier years. The standardized mortality ratio for lung cancer was 1.26 (95% CI, 1.09–1.44) for the complete cohort, 1.21 (95% CI, 1.01–1.45) for workers involved in any underground work and 1.33 (95% CI, 1.06–1.66) for workers involved exclusively in surface work. In the complete cohort, standardized mortality ratios were 1.09 (95% CI, 0.58–1.86) for urinary bladder cancer, 1.18 (95% CI, 0.76–1.74) for leukaemia, 0.98 (95% CI, 0.54–1.64) for kidney cancer, 1.12 (95% CI, 0.76–1.60) for pancreatic cancer and 0.85 (95% CI, 0.60–1.16) for prostate cancer. Mortality from oesophageal cancer was significantly elevated in all workers (SMR, 1.83; 95% CI, 1.16–2.75). In an internal analysis of the entire cohort, adjustment for the location of work (ever surface or underground) and a 15-year lag for cumulative exposure resulted in relative risks by quartile of 1.0, 0.55 (95% CI, 0.35–0.85), 1.03 (95% CI, 0.60–1.77) and 1.39 (95% CI, 0.78–2.48). In an analysis of surface workers only, the corresponding relative risks by quartiles of cumulative exposure