BREAST CANCER

(FEMALE AND MALE)

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IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 98

Painting, Firefighting, and Shiftwork

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GENERAL REMARKS

This ninety-eighth volume of *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of painting, firefighting, and shiftwork. This is the first evaluation of shiftwork and firefighting by IARC. Painting had been evaluated previously in Volume 47, and newer epidemiological and experimental studies are reviewed in this volume. A common feature that led to the assessment of these human activities in one volume is that each is associated with diverse and complex exposures.

Firefighters can work in the profession full time or on a volunteer basis, holding other jobs at the same time. They can battle household fires, chemical fires, oil fires, forest fires, and fires of many other types, resulting in exposures to a vast variety of smoke, dusts, and chemical agents. Exposures are generally intermittent but intense. Many occupational records apply the term "firefighter" rather broadly, including logistics and support personnel as well as the people who enter a fire. The average time spent actually in fires is rather short overall, raising some concern that results for subgroups of highly exposed individuals might be difficult to observe in cohorts that are more broadly defined.

Painters, too, can work in the profession full time, but the term also includes artists and day workers who take different odd jobs on other days. Several studies include job categories such as decorators and wallpaper hangers along with painters, and there are also studies involving residential exposure to freshly painted rooms. Painters can work indoors or outdoors, with varying degrees of ventilation and protective equipment, and some work in construction zones with exposure to various dusts and chemical substances. The paints and coatings themselves have changed in composition over time and can be based on natural oils, synthetic oils, or latex. They include pigments derived from metals and chemical additives for many purposes, including those with pesticidal properties. In addition, painters are exposed to dusts and chlorinated solvents during preparation and cleanup operations.

Shiftwork is perhaps the most wide-ranging classification of all, with various definitions of shiftwork used in the epidemiological studies. As a causal factor, shiftwork is difficult to disentangle from related measures such as circadian disruption, sleep deprivation, and exposure to light at night. Analysis of epidemiological studies is further complicated by the fact that reference populations, too, are invariably exposed to these factors to some degree. The social and physical

environment associated with working at night provides additional factors that complicate the analysis of these studies. The strongest evidence so far is for breast cancer, which is associated with childbearing history, which in turn might affect willingness to take on shiftwork. There are surprisingly few studies of the effects of shiftwork for men working in industrial settings, however.

It is hoped that the critical reviews that appear in this volume will stimulate further research that addresses these aspects and leads to a resolution of the cancer hazards associated with firefighting and shiftwork.

A summary of the findings of this volume appears in *The Lancet Oncology* (Straif et al., 2007).

Reference

Straif K, Baan R, Grosse Y et al. (2007). Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol*, 8:1065–1066 doi:10.1016/S1470-2045(07)70373-X. PMID:19271347 http://www.thelancet.com/journals/lanonc/article/PIIS147020450770373X/fulltext

some studies, overall, a consistent excess risk of lung cancer was observed over time. Of the 29 studies, three had an odds ratio < 1 with large confidence intervals that included the null value, and the others had odds ratios > 1, 14 of which showed a statistically significant or borderline significant increase. When all independent studies that appropriately adjusted for potential confounders were used in a meta-analysis, a statistically significant excess risk of 35% was obtained. When the analysis and results from the above and from population-based studies were restricted to smoking-adjusted estimates, the statistically significant excess risks were 34% and 41%, respectively.

A borderline significant excess of mortality from mesothelioma was observed in cohort studies and positive results were obtained in two case–control studies of this tumour, which is consistent with the presence of asbestos at some sites where painters work.

The 11 cohort and linkage studies of painters showed consistent, although moderate (21%), excesses of mortality from urinary bladder cancer. Two of these studies provided information on tobacco smoking which is strongly associated with this neoplasm. These excesses are consistent with case–control studies of painters that controlled for smoking in which an excess risk for urinary bladder cancer was seen. Most of the studies that were evaluated had odds ratios > 1. When all independent studies that appropriately adjusted for confounding were used in a meta-analysis, a statistically significant excess risk of 28% was obtained. When the analysis and results from the above and from population-based studies were restricted to smoking-adjusted estimates, the statistically significant excess risks were 26% and 27%, respectively.

Other statistically significant excesses of mortality were observed in the cohort studies for cancers of the pharynx, oesophagus, and liver. Cancers at these sites are associated with tobacco smoking (pharynx and oesophagus) and alcoholic beverage consumption (pharynx, oesophagus, and liver), both of which have been shown to be increased among painters compared with the national populations typically used as referent groups; hence, these might act as positive confounders. However, there are inadequate supportive data from case–control studies of these cancers that control for these potential confounders to conclude that confounding can be excluded as a cause of these excesses. The data were insufficient for evaluation, but the Working Group noted some consistency between case–control and cohort studies for cancers of the pharynx and oesophagus.

More case–control studies evaluated the risk for lymphatic and haematopoietic cancers among painters than that for cancers at other sites. Although some excesses were observed, the data are inadequate to draw a conclusion because of inconsistency among results from these studies, and the lack of any excess mortality from these cancers in the cohort studies. A few case–control studies of cancers of the nose, nasopharynx, larynx, oesophagus, stomach, pancreas, small bowel, kidney, brain, prostate, ovary and breast, mesothelioma, melanoma, and soft–tissue sarcoma were conducted among painters.

Several case–control studies evaluated the risk for childhood cancer and parental occupation as a painter or parental exposure to paints. Seven studies focused on

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.

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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.

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

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

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

2.2 Case–control studies

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

Table 2.5 (contd)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratios (OR) (95% CI)	Adjustment for potential confounders	Comments
Elci *et al.* (2003) Istanbul and Marmara region, Turkey 1979–84	Lung (ICD: 162.0 and 162.2 combined, and compared to 162.3, 162,4, 162.5 and 162.9)	1354 male cases of lung cancer; 442 cases without histological confirmation	1519 male cancer and non-cancer controls diagnosed with Hodgkin disease, soft tissue sarcoma, testis, bone, male breast and non-cancer benign pathologies	Standardized questionnair eJobs classified by Standard occupational and Industrial codes	*Lung Cancer by* Firefighter Squamous cell All bronchus and parenchyma	 10 4 9	 6.8 (1.3–37.4) 6.2 (0.8–46.2) 7.0 (1.3–39.1)	Age and smoking	22 women were excluded from analyses

Among the cases, two were employed as firefighters. Of those occupations which self-reported exposure to diesel exhaust, including truck drivers, firefighters, road workers, and mine workers (5.5 cases and 4.4 controls), the adjusted OR was 1.47 (95% CI: 0.5–4.1). For those occupations which self-reported exposure to diesel 'fumes', firefighter was not listed amongst them The authors noted that the self-reported exposure to diesel exhaust or diesel fumes may reflect uncontrolled confounding with cigarette smoking and alcohol consumption as almost all patients who reported diesel exposure were also heavy cigarette smokers, and consumed large amounts of alcohol.

Elci *et al.* (2003) examined the link between occupations and risk of lung cancer by histological types in Turkey. Cases were identified from an oncology treatment centre at one of the largest cancer hospitals, including treatment for workers, in Istanbul. After admission to hospital, all patients completed a standardized questionnaire administered by trained interviewers. There were 1354 male lung cancer cases with complete interview information identified during 1979–1984. An oncologist reviewed hospital records for diagnostic verification and classification of cancer types. When there were four or more cases per cancer type, histopathology and morphological type was examined. Patient controls "with the same sociodemographic background as the cases" were selected having the following diagnoses: cancers of the skin (non-melanoma), testis, bone, male breast, Hodgkin disease, soft-tissue sarcoma, and non-cancer patients. Of the 27 occupations, firefighting ($n = 10$ cases) had an excess risk of lung cancer, with an age- and smoking-adjusted OR of 6.8 (95% CI: 1.3–37.4). In firefighters, for squamous-cell carcinoma ($n = 4$), the age- and smoking-adjusted OR was 6.2 (95% CI: 0.8–46.2), and for peripheral tumours including bronchus and parenchyma ($n = 9$), the age- and smoking-adjusted OR was 7.0 (95% CI: 1.3–39.1).

Bates (2007) investigated cancers of the lung and bronchus in firefighters as described above under kidney cancer and in Table 2.6. There were 495 firefighters with these cancers. The adjusted OR was 0.98 (95% CI: 0.88–1.09).

2.2.4 *Cancers at other sites*

(a) Multiple myeloma, non-Hodgkin lymphoma, and leukaemia

Demers *et al.* (1993) identified cases of multiple myeloma through SEER tumour registries in four geographic locations including two counties in Washington State, two in Utah including Salt Lake City, five counties of metropolitan Atlanta, Georgia, and three metropolitan Detroit, Michigan, counties. All those potentially eligible included all incident cases diagnosed during 1977–1981. Controls were selected to be similar in age, gender, and region. In Washington State, 1683 population-based controls were selected by using two sampling units of four households. In other areas, a random-digit dialling method was used for selecting controls. Interviews were obtained from 692 (89%) of the cases or their survivors, and from 1683 (83%) of the controls.

2. Studies of Cancer in Humans

2.1 Introduction

Airline personnel flying over time zones are exposed to frequent disruptions of circadian rhythm, which has similarities with exposure to shiftwork. There are studies reporting cancer risk in about ten cohorts of airline cabin crew and a similar number of studies in cockpit personnel. The cabin crew cohorts support the strong evidence of significantly increased risk of breast cancer incidence found in most independent studies. Higher diagnostic activity (screening during annual health controls) may explain part of the excess when comparing with national population rates, and it should not confound internal comparisons within differently exposed subcohorts of cabin crew. Unfortunately, the studies published so far do not demonstrate precise dose–response evaluations according to the frequency of disruptions of circadian rhythm, for which the best proxy has been duration of work as flight attendant. In most studies, the excess is observed at around 10 years after first employment, and increases weakly with increasing duration. Differences in reproductive factors explain only a small fraction of the excess, while risk attributable to radiation may explain a quarter of the excess. It is unclear whether the substantial neutron component of cosmic radiation (25–50% of the effective dose but less than 5% of the absorbed dose) increases the proportion of risk attributable to radiation – this exposure can only be studied in flight crew personnel – but it is likely that there is a major part of the excess risk in breast that must be attributable to factors others than the factors listed above. Disruptions of circadian rhythm and related hormonal effects have been repeatedly mentioned as possible causal factors, and there are no data to exclude this possibility.

Prostate cancer incidence rates from the airline pilot cohorts are above the national reference levels. This excess has decreased over decades and is likely to be related to the prostate-specific antigen tests, common among pilots much earlier they became so in the general population. In the most recent follow-up reports, the SIRs among pilots have been only slightly increased. Only one study that combined cohorts of all pilots from five Nordic countries, with detailed individual level flight histories, was able to study the independent role of the long-haul flights over time zones in an internal analysis. A significant trend in risk for prostate cancer with increasing number of long-haul flights was observed, though there were only eight cases in the highest exposure category. Hence, the evidence related to the role of circadian rhythm disruptions in causing prostate cancer is weak.

2.2 Shiftwork

2.2.1 *Breast cancer*

Eight studies reported relative risk estimates for histologically confirmed breast cancer for female night shiftworkers, with vastly differing definitions of shiftwork in each study. The characteristics of these studies are presented in Tables 2.1–2.3. Two were prospective cohort studies (Schernhammer *et al.*, 2001; Schernhammer & Hankinson, 2005), one was a nationwide census-based cohort study (Schwartzbaum *et al.*, 2007), three were nested case–control studies (Tynes *et al.*, 1996; Hansen, 2001a; Lie *et al.*, 2006), and two were retrospective case–control studies (Davis *et al.*, 2001; O'Leary *et al.*, 2006). All eligible studies included caucasian women; only one study (O'Leary *et al.*, 2006) included a small proportion of Latino and African-American women (less than 10%). The majority of women studied were postmenopausal.

(a) *Prospective cohort studies* (Table 2.1)

The two prospective cohort studies of night shiftwork and breast cancer risk used data from the Nurses' Health Study cohorts (NHS and NHS II) (Schernhammer *et al.*, 2001; Schernhammer *et al.*, 2006). The NHS began in 1976, when 121 701 registered nurses 30–55 years of age and living in 11 large US states were enrolled and completed a questionnaire comprising items about their health status, medical history, and known or suspected risk factors for cancer. Since baseline, questionnaires have been mailed biannually with the exception of lifetime history of night work in years, which was only assessed once (in 1988). Follow-up data are available for more than 90% of the ongoing cohort. In 1988, the study participants were asked how many years in total they had worked rotating night shifts with at least three nights per month, in addition to days or evenings in that month. The second cohort, NHS II, was designed in a very similar fashion. It started in 1989, when 116 671 registered female nurses (no overlap with NHS) 25–42 years of age, and from 14 US states were enrolled. Since 1989, they have completed biennial questionnaires that include items about their health status risk factors for chronic disease. Response rates to questionnaires are at 90%. In NHS II, the 1989 baseline questionnaire included detailed questions on total months during which study participants had worked on rotating night shifts for at least three nights per month in addition to days or evenings in that month. This information was updated in 1991, 1993, 1997, and 2001. Questions were asked regarding both rotating night shifts and permanent night shifts for 6 months or more in this cohort.

In the NHS, Schernhammer *et al.* (2001) followed a total of 78 562 women who answered the 1988 question on night work and were cancer-free at baseline over 10 years (1988–1998): of these women, 2441 incident breast cancer cases were documented during that time. The relative risks (RRs) for breast cancer associated with rotating night work compared to women who reported never having worked rotating night shifts, after

Table 2.1. Cohort studies of night shiftwork and breast cancer

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Schernhammer *et al.* (2001) USA Nurses' Health Study (NHS)	Prospective cohort study of 121 701 registered nurses from 11 large states, established in 1976; follow-up from 1988–1998	Self-reported life time years on rotating night shifts, one-timed assessment in 1988; rotating night shifts were defined as "at least 3 nights per month, in addition to evenings and afternoons in that month"	Breast cancer	*Years of rotating night work* Never 1–15 15–29 ≥30 *P* for trend	 925 1324 134 58	 1.0 (ref) 1.08 (0.99–1.18) 1.08 (0.90–1.30) 1.36 (1.0–1.78) 0.02	Age, age at menarche, parity, age at first birth, weight change, BMI, family history of breast cancer, benign breast disease, oral contraceptive use, age at menopause, alcohol consumption, use of postmenopausal hormones, menopausal status, height	

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Schernhammer *et al.* (2006) USA Nurses' Health Study II (NHS II)	Prospective cohort study of 116 087 registered nurses from 14 states, established in 1989; follow-up from 1989–2001	Self-reported life time years on rotating night shifts, one-timed assessment in 1989; biannual update; rotating night shifts were defined as "at least 3 nights per month, in addition to evenings and afternoons in that month"	Breast cancer	*Years of rotating night work* Never 1–9 10–19 20+ *P* for trend	 441 816 80 15	 1.0 0.98 (0.87–1.10) 0.91 (0.72–1.16) 1.79 (1.06–3.01) 0.65	Age, age at menarche, parity, age at first birth, BMI, family history of breast cancer, benign breast disease, alcohol consumption, oral contraceptive use, smoking status, menopausal status, age at menopause, physical activity, postmenopausal hormone use	

controlling for known breast-cancer risk factors, were as follows: for 1–14 years, 1.08 (95% CI: 0.99–1.18); for 15–29 years, 1.08 (95% CI: 0.90–1.30); and for 30 or more years, 1.36 (95% CI: 1.04–1.78). The risk increased with increasing numbers of years in shiftwork (P for trend = 0.02). [The main strengths of this study are the prospective assessment of night work information and a wide range of potential confounding factors in a well defined occupation cohort of nurses, as well as the high follow-up rate (> 90%). Limitations of this study are its one-time assessment of night work and the inclusion of permanent night workers as well as those who worked < 3 nights per month among the unexposed reference group, which may have skewed the results towards the null].

Similarly, in 115 022 predominantly premenopausal women in the NHS II, Schernhammer *et al.* (2006) found an elevated breast cancer risk of 1.79 (95% CI: 1.06–3.01; $P = 0.65$) among women who worked 20 or more years of rotating night shiftwork compared with women who reported never having worked rotating night shifts, with 1352 incident breast cancer cases accruing over 12 years of follow-up (1989–2001). [The main strengths of this study are the prospective and updated assessment of rotating night work history and a wide range of potential confounding factors in a well defined occupational cohort of nurses, as well as the high follow-up rate (90%). Limitations are the inclusion of those who worked < 3 nights per month among the unexposed reference group, and the relatively small number of women ($n = 15$ women) in the category with longer durations of night work].

Schwartzbaum *et al.* (2007) found no increase in risk in female breast cancer from their definition of night work, based on 28 observed breast cancers versus 28.91 expected, diagnosed during 1971–1989. The design is a retrospective registry-based ecological cohort study comprising all 1 148 661 Swedish women that were active in the workforce according to both 1960 and 1970 census reports. Workers were followed up for breast cancer morbidity by linkage to the Swedish Cancer Registry. Information on occupation was derived from the censuses, which included each worker's industry and socioeconomic status. The annual surveys of living conditions (conducted during 1977–1981) among 46 438 randomly selected Swedish subjects who participated in a personal interview were used for assessing night work. Questions were asked regarding the usual occupation, work hours, and when they had started and ended working each day during the week preceding the interview. Shiftworkers were then defined as those who reported that their workplace had a rotating schedule with three or more possible shifts per day or had work hours during the night (any hour between 01:00 and 04:00) at least one day during the week preceding the interview. They classified as shiftworkers people working in job titles and industry combinations (from the censuses) with at least 40% shiftwork (as defined above). The reference group in their analyses comprised people in occupation–industry combinations in which less than 30% stated that they were shiftworkers. In analyses using 1970 census information for the definition of exposure, no increase in risk was reported among women with an occupation that was classified as shiftwork. Sub-analyses in this paper (which comprised all men and women working in Sweden) also considered 70% of shiftworkers as definition for occupation classification but due to

small sample size, this was not done for the women. [The weaknesses of this study include the implausibly small proportion of women working night shifts (only 0.3% worked in occupations with at least 40% shiftworkers working at least 20 hours per week), inadequate control for confounding, and that the three most common occupations that fell into their shiftwork classification were rather unusual (crane and hoist operators, delivery women in paper and paper-products manufacturing, printing and publishing industries, and midwives)].

(b) Nested case-control studies (Table 2.2)

Tynes *et al.* (1996) conducted a case–control study nested within a population-based cohort study of 2619 female Norwegian radio and telegraph operators working at sea and certified to work between 1920–1980, and followed up during 1961–1991. In total, 50 breast cancer cases were identified by linkage to the National Norwegian Cancer Registry, and each case was matched to four to seven disease-free controls from the cohort. For cases and controls, job histories on ships were collected and shiftwork as well as travel through time zones were classified for each ship mentioned in the job histories to define shiftwork. Shiftwork constituted frequent presence in the radio room both at night and during the day. After controlling for duration of employment, the SIR for breast cancer in this cohort was 1.5 (95% CI: 1.1–2.0). In the nested case–control study, there appeared to be an increased risk of breast cancer in women ≥ 50 years of age with increasing cumulative exposure to shiftwork, compared to no shiftwork (low exposure 0–3.1 years, adjusted for duration of employment, RR, 3.2, 95% CI: 0.6–17.3; high exposure 3.1–20.7 years, adjusted for duration of employment, RR, 4.3, 95% CI: 0.7–26.0; P for trend = 0.13). [The strength of this study is the use of internal controls, whereas the main limitation is its lack of control for confounding by breast cancer risk factors].

Hansen (2001a) conducted a population-based case–control study nested within the cohort of all female employees in Denmark established from the nationwide pension fund data, including information on all employments held since 1964. In total, 7035 women with incident breast cancer were identified by individual linkage to the files of the nationwide Danish Cancer Registry. Control subjects free of breast cancer were randomly drawn from the pension fund files and matched on year of birth and sex. The individual employment histories for cases and controls were reconstructed using files of the nationwide pension fund. Night work definition was based on information obtained from a nationwide interview-based survey on living and working environment conditions in 1976 among 2603 women. Trades in which at least 60% of female responders worked at night were considered to have a predominant night time schedule, whereas responders working in most trades with less than 40% reported night time schedules were regarded as day workers. The RR of breast cancer was 1.5 (95% CI: 1.3–1.7; 434 cases) among women who worked at least half a year at least 5 years before diagnosis in such trades, after controlling for age, social class, age at birth of first child, age at birth of last child, and number of children. For the subgroup of women with more than 6 years predominantly working at night, the RR was 1.7 (95% CI: 1.3–1.7; 117 cases). In further

Table 2.2. Nested case–control studies of night shiftwork and breast cancer

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Tynes *et.al.* (1996) Norway Telecom cohort	Cohort of 2619 female radio and telegraph operators at sea, certified between 1920–1980; follow-up from 1961–1991. The nested case–control component comprised 50 cancer registry-identified cases and 4–7 matched (year of birth) controls	Collected detailed job histories from Norwegian seamen registry; "Work at night with exposure to artificial light." From cases and controls, detailed information on job histories on ship as well as shiftwork and travel through time zones was collected, classified by "ship"	*Shiftwork in women age < 50*			Age, duration of employment, parity, and age at first birth	
			None	12	1.0 (ref)		
			<3.1 yrs.	5	0.3 (0.1–1.2)		
			>3.1 yrs	12	0.9 (0.3–2.9)		
			P for trend		0.97		
			Aged 50+				
			None	3	1.0 (ref)		
			<3.1 yrs.	6	3.2 (0.6–17.3)		
			>3.1 yrs	12	4.3 (0.7–26.0)		
			P for trend		0.13		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Hansen (2001a,b) Denmark Linkage of Nationwide registries	Nested case–controls study; 7565 cancer-registry-derived women with breast cancer, 1:1 matched controls (year of birth and sex), follow-up 1964–1999	Individual employment histories were obtained from files of national pension fund	All night work combined in trades with >60% night work	434	1.5 (1.3–1.7)	Age, social class, age at birth of first child, age at birth of last child, number of children	Considered as night workers if employed ≥0.5 year in ≥1 trade in which ≥60% of the female responders had night time schedules Trades: beverage manufacture, land transport, catering, air transport
			Employed >6 years	117	1.7 (1.3–1.7)		
			Nurses	–	1.3 (1.1–1.4)		

sub-analyses, the RR for nurses was also evaluated, a group in which 41% were considered having predominant night work (Hansen, 2001b), and a significantly increased risk of breast cancer was found (RR, 1.3; 95% CI: 1.1–1.4). [The strength of this study is its high number of incident cases and the apparent lack of selection and information bias due to use of routine data; its limitations include the crude exposure assessment with potential for non-differential misclassification as well as incomplete adjustment for confounding, in particular alcohol drinking.]

Lie *et al.* (2006) conducted a nested case–control study within a cohort of 44 835 Norwegian nurses based on information from the registry of the Norwegian Board on Health,established in 1949. In total, 537 breast cancer cases diagnosed during 1960–1982 were identified by linkage with the files of the nationwide cancer registry. Four age-matched controls were selected at random from the cohort, using incidence density sampling. Reconstruction of total work history was based on the nurses' registry (self-report of work history; until 1960 yearly updates, thereafter sporadically) and census information (1960, 1970, and 1980), accumulating from first year of employment until termination of the last employment. Based on experience, it was assumed that nurses employed at infirmaries worked nights (with the exception of managerial jobs, teaching, physiotherapy, and outpatients departments), whereas it was assumed that work sites other than infirmaries involved day work only. The authors found an association between duration of night work and breast cancer risk (P for trend = 0.01). The RR associated with > 30 years of night work was 2.21 (95% CI: 1.10–4.45), after adjustment for total employment time as a nurse and parity. [The main strength of this study is its high number of cases and the internal comparison, whereas limitations of this study are a lack of complete control for confounding as well as the potential for exposure misclassification, which is likely to be non-differential.]

(c) Case–control studies (Table 2.3)

Davis *et al.* (2001) conducted a case–control study of 813 women with breast cancer aged 20–75 years and 793 controls free from breast cancer. Cases were identified by the Cancer Surveillance System of Seattle, Washington, USA and controls were identified by random-digit dialling, frequency-matched on age (75% participation rate for controls). In-person interviews were performed from 1992–1995 to collect information about sleeping habits and light-at-night exposure during the 10 years before diagnosis as well as lifetime occupational history. The authors defined night work as at least one "graveyard" shift per week in the 10 years before diagnosis. "Graveyard" shiftwork was described as "beginning work after 19:00 and leaving work before 09:00". The RR of breast cancer was 1.6 (95% CI: 1.0–2.5) among women who had ever worked "graveyard" shifts. The RR of breast cancer was 1.06 for each hour increase per week of "graveyard" shift work (P = 0.03), after controlling for parity, family history of breast cancer, oral contraceptive use, as well as recent discontinued use of hormone replacement therapy. [The strengths of this study include its attempt to accurately define shiftwork assessment. One of the main

limitations is the retrospective assessment of shiftwork with a modest potential for recall bias].

O'Leary *et al.*, (2006) conducted a case–control study in Long Island, New York, USA – the Electromagnetic Fields and Breast Cancer on Long Island Study (EBCLIS). They did not observe an association between night work and breast cancer risk (any evening or overnight shiftwork versus none, OR, 1.04; 95% CI: 0.79–1.38; only overnight shiftwork, OR, 0.55; 95% CI: 0.32–0.94). This study was built into another population-based case–control study among residents of Nassau and Suffolk counties. Cases were recorded during 1996–1997. Controls were frequency-matched by age and came from two different sources: 1) controls less than 65 years old were identified by random-digit dialling; 2) controls of age 65 and above were selected from the Health Care Financing Administration rosters. To evaluate the effects of electromagnetic frequency, women from within this case–control study were selected according to their degree of residential stability (EBCLIS component). EBCLIS comprised 576 breast cancer cases and 585 matched (1:1) population-based controls. In-person interviews were held to gather information on occupational history since the age 16 years as well as residential light-at-night exposures (sleep hours; frequency of turning on lights during night; length of time light was on). Shiftwork was defined as 'ever' working in at least one job during the past 15 years that included evening shifts (could start in the afternoon and end as late as 02:00), overnight shifts (could start as early as 19:00 and continue until the following morning), and various combinations thereof. The reference group comprised women who reported never having had a job involving shiftwork. Results were adjusted for age (matched by 5-year age groups), parity, education, family history of breast cancer, and history of benign breast disease. [An extreme and unlikely high proportion of controls (36.9%) and cases (35.7%) reported any 'evening or overnight shiftwork'; other limitations were the retrospective assessment of exposures and that the control selection was conducted from two different sources, introducing additional potential for bias].

(d) Meta-analysis

Megdal *et al.* (2005) conducted a meta-analysis that summarized six of the eight studies on night work (excluding the two most recent studies that gave negative results) and breast cancer, and found an increased risk for breast cancer (RR, 1.51; 95% CI: 1.36–1.68).

(e) Studies of biomarkers for night work (urinary melatonin) and breast cancer risk (Table 2.4)

Melatonin, the main biomarker for circadian dysregulation, can be measured in the urine by 6-sulphatoxymelatonin (aMT6s), the major metabolite of melatonin.

Skene *et al.* (1990) compared mean urinary aMT6s levels (measured by RIA) collected from 24-hour urine samples from British women attending a breast cancer screening clinic before biopsy and 160 normal female residents of Guernsey, the United Kingdom.

For most cabin crew, annual exposure to radiation ranges from 1–6 mSv, compared with approximately 2.4 mSv annually from background radiation. Cosmic radiation includes a substantial neutron component (25–50% of effective dose but less than 5% of absorbed dose). Because flight personnel are the only source of human data on the health effects of exposure to neutron radiation, it is hard to estimate how a large excess risk would be expected due to cosmic radiation. This further makes it difficult to judge how much of the observed excess could be for other risk factors such as shiftwork.

The number of flights over several time zones is used as a proxy of frequency of circadian rhythm disruptions. This number correlates with the dose of cosmic radiation, and therefore estimates of cancer risk in cumulative dose categories can also be interpreted to roughly reflect frequency of circadian rhythm disruptions. On the other hand, separation of the independent roles of these two factors is possible only in large studies with precise information on flight histories. Only one study, combining information on all pilots from the five Nordic cancer registries has been able to make this distinction to a certain extent. In general, the detailed flight histories of airline pilots are known quite well; while for cabin crew, normally only the beginning and end of employment is known. In the airline companies where the principle has been that all cabin crew members fly all routes, an approximation of the radiation dose and numbers of long flights over time zones for each person can be made based on his/her own annual numbers of flight hours, and the flight profile of the company.

All studies published on aircraft crew have been included in this evaluation, irrespective of whether they mention shiftwork or not. Only observations related to breast cancer and prostate cancer have been included in this review, because they are the only ones which have been considered to be associated with shiftwork. The observations related to breast cancer come from cabin crew personnel and those related to prostate cancer mainly from cockpit personnel, because almost all airline pilots are male, and the majority of the cabin crew, female.

In addition to the breast and prostate cancer findings presented below in detail, there is a consistent pattern of increased incidence of skin melanoma and basal cell carcinoma of the skin that are likely to be related to the more frequent sunbathing and sunburns among flight personnel in previous decades. Male cabin crew have also been shown to have a significantly increased risk of Kaposi sarcoma in most studies that included this cancer category. The risk of leukaemia, one of the main target sites in studies on effects of radiation, has been shown to be non-elevated in most studies.

2.3.1 *Breast cancer* (Table 2.7)

(a) Cohort studies

Pukkala *et al.* (1995) collected a cohort of 1577 all-female flight attendants who had ever worked for Finnish airline companies (first employment starting in the 1930s). This cohort was followed-up for cancer incidence during 1967–1992. The SIR for breast cancer was 1.87 (95% CI: 1.15–2.23, 20 cases), and the SIR was highest 15–19 years after

Table 2.7. Cohort studies of flight personnel and breast cancer

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustement for potential confounders	Comments
Pukkala *et al.* (1995), Finland	1577 female cabin attendants who worked for Finnish airline companies; from files of Finnair Flight Company; follow-up for cancer incidence from date of recruitment as cabin crew worker (or January 1967 if later) to emigration, death, or December 1992	Calendar period, length of employment	Breast			**SIR**	Age	Control for parity on group level (cohort vs. reference population): parity cannot explain the difference
				Any	20	1.87 (1.15–2.23)		
				Employment ≥2 years	NG	2.0 (1.2–3.2)		
Lynge (1996), Denmark	915 female airline cabin attendants in Denmark, follow-up for cancer incidence from 1970–1996	Cross-sectional census occupation 1970	Breast			**SIR**	Age	
				Any	14	1.61 (0.90–2.70)		
Wartenberg & Stapleton (1998), USA	287 retired flight attendants from one US airline; follow-up for cancer incidence		Breast			**SIR**	Age	
				Any	7	2.0 (1.0–4.3)		

4.2 Proposed mechanisms for carcinogenicity of shiftwork and circadian disruption

Epidemiological studies on genetic polymorphisms in clock-related genes and phenotypes such as morning/evening preference and depressive symptoms, have shown a significant association between a single-nucleotide polymorphism in the *PER3* gene and diurnal preference. In a wider sense, the circadian clock may function as a tumour suppressor at the systemic, cellular, and molecular levels. Clock-controlled genes and related factors involved in cell-cycle control include c-*Myc*, *Mdm2*, *Tp53* and *Gadd45a*, as well as caspases, cyclins, and various transcription factors. In transgenic mice, a deletion in *Per2* results in a shorter circadian period, a higher susceptibility to radiation-induced tumours, and reduced apoptosis in thymocytes. Disruption of the circadian rhythm in mice is associated with an accelerated growth of malignant tumours.

4.2.1 *Melatonin and cancer*

(a) Oncostatic effects of melatonin

Thirty years ago, it was hypothesized that diminished pineal function may promote the development of human breast cancer (Cohen *et al.*, 1978). The primary argument was that increased pineal calcification, presumably leading to lowered melatonin production, was most strongly associated with increased breast cancer risk. Although this was the first reference to environmental lighting, which necessarily includes both sunlight and artificial light, as a potential source of one of several endocrine abnormalities that may underlie the development of breast cancer, light at night was not specifically postulated as an etiological factor. It was proposed incorrectly that altered visual stimulation, by blindness or darkness, would impair pineal melatonin production, thereby leading to unopposed estrogen secretion and increased breast cancer risk. It is now known that overall melatonin production is not compromised in blind individuals (Lockley *et al.*, 1997) and that breast cancer risk is actually diminished in blind women (Hahn, 1991; Verkasalo *et al.*, 1999). It was postulated by Stevens (1987) that light exposure at night may represent a unique risk factor for breast cancer in westernized societies via its ability to suppress nocturnal melatonin production by the pineal gland. This postulate, referred to as the 'melatonin hypothesis', was based on in-vivo studies demonstrating that melatonin inhibits, while pinealectomy or constant bright light stimulates, the development and growth of experimental breast cancer in rodents, and by in-vitro studies showing that the proliferation of estrogen receptor positive (ER+) human breast cancer cells was directly suppressed by nocturnal physiological levels of melatonin (Stevens, 2006).

Many studies using pharmacological concentrations of melatonin have demonstrated a direct antiproliferative and/or apoptotic effect on cancer cells (usually human cancer cell lines) *in vitro*. A substantial number of investigations have also shown that nocturnal physiological concentrations of melatonin exert direct oncostatic effects on cancer cell

5.2 Human carcinogenicity data

Female breast cancer

Eight studies from various geographic regions have been designed to assess the relationship between breast cancer and shiftwork that involves night work. Six of these eight studies, including two prospective cohort studies in nurses, have consistently pointed towards a modestly increased risk of breast cancer among long-term employees who performed night shiftwork, defined in different ways. Most studies reported this increased risk after controlling for potential confounders. Two of the eight studies, one of which appeared to be hampered by important limitations in design, were not supportive of an association between shiftwork and breast cancer. There were a relatively limited number of studies (most focused on a single profession, i.e. nurses), some potential for confounding by unknown risk factors, and inconsistent and inaccurate exposure assessments of shiftwork, which may have biased the results towards the null.

Another occupational group of shiftworkers is flight cabin crew personnel, who also experience circadian disruption due to the crossing of time zones. The incidence of breast cancer has been studied in eight cohorts of female flight attendants, all but one consistently reported an increased risk for breast cancer which was greater after a longer duration of employment. Limitations of these studies included the potential for detection bias among female cabin crew due to a higher prevalence of breast cancer screening in this occupational group, proxy measures of exposure used in dose–response relationships, and potential confounding by reproductive factors and cosmic radiation.

The Working Group concluded that the evidence for an association with breast cancer and shiftwork that involves night work was consistent in the studies that were specifically designed to address this question. The studies of cabin crews provided additional support.

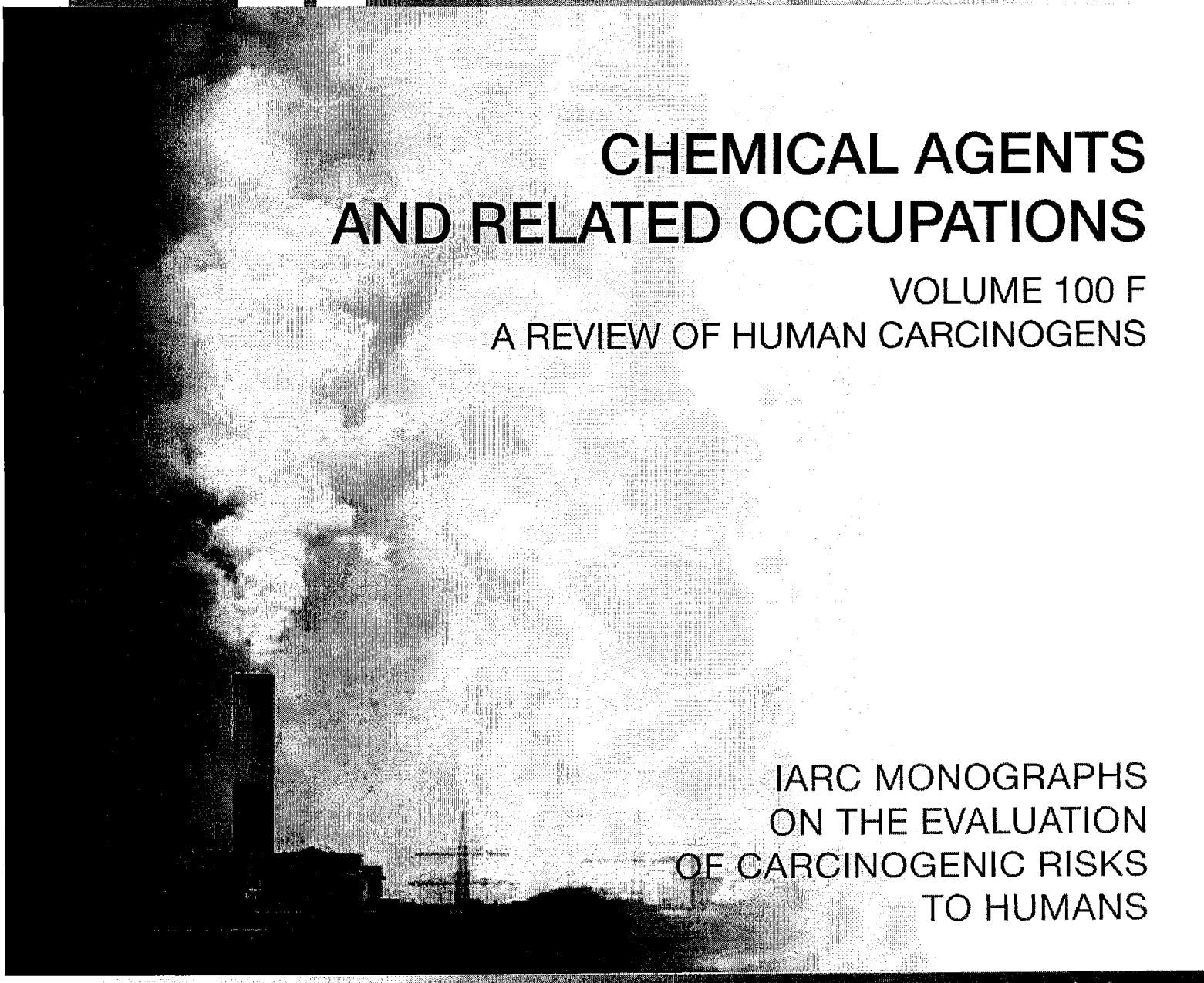
Other cancers

Few studies have investigated the association between shiftwork and cancers at other organ sites. Increased risks of cancers of the prostate, colon, and endometrium have been reported. The earliest studies of airline pilots also showed a markedly elevated incidence of prostate cancer compared with national reference levels, but limitations of these studies included the potential for detection bias due to a higher prevelance of screening for prostate cancer in this occupational group.

5.3 Animal carcinogenicity data

Animal models have been used extensively to test the impact of the circadian system (central circadian pacemaker in the suprachiasmatic nuclei and the pineal gland/melatonin-generating system) and its disruption (i.e. phase shifts, light during the dark period, melatonin suppression) on tumour development and growth at all stages of oncogenesis.

IARC MONOGRAPHS



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2.4 Soft-tissue sarcoma

An association between soft-tissue sarcoma and spraying of phenoxy herbicides was first suggested by results from case–control studies in Umea, Sweden (Hardell & Sandström, 1979). Exposure to TCDD in these and other community-based case–control studies is, however, not accurately estimated. An excess risk for soft-tissue sarcoma, based on a small number of deaths, has been reported in the largest industrial cohorts, specifically those of NIOSH and IARC (see Table 2.4, online). In both, the mortality ratios (SMRs) tended to be higher among the most exposed subcohorts. Incidence data for soft-tissue sarcoma were generally not available. A dose–response relationship, with estimated exposure to TCDD, was found in a case–control study nested in the IARC cohort; however, strong positive trends were also found with exposure estimates for 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). In Seveso, there were no cases of soft-tissue sarcoma in the most heavily contaminated Zones A and B. [Soft-tissue sarcomas are subject to serious misclassification on death certificates. Although it is unlikely that this occurs differentially in the exposed and the referent populations, re-classification of a few cases would have important consequences on results based on small numbers.]

2.5 Non-Hodgkin lymphoma

An increased risk for non-Hodgkin lymphoma was found in most of the populations studied in the four industrial cohort studies and in the Seveso population, although the relative risks were mostly non-significant and below 2 (see Table 2.5, online). A case–control study nested in the IARC cohort provided weak evidence of a dose–response relationship with estimated exposure to TCDD. [Although it is plausible that other chemicals cause non-Hodgkin lymphoma, strong potential confounding factors are not known. The lack of complete consistency among the cohorts and the weak effect detected in most of the positive studies, however, caution against a causal interpretation of the findings.]

2.6 Other cancers

[Increased risks for several other malignant neoplasms have been sporadically reported among workers exposed to TCDD, and at Seveso. Most notable are risks for breast and rectal cancers and myeloid leukaemia in Seveso, bladder cancer in the NIOSH and Dutch cohorts, multiple myeloma in the NIOSH cohort, cancers of the oral cavity and pharynx in the German cohorts, genital cancers in the Dutch cohort, and kidney cancer in the IARC cohort. [The available results are not fully consistent, and several studies have not reported the results for each individual cancer site.]

2.7 Synthesis

Overall, the strongest evidence for the carcinogenicity of TCDD is for all cancers combined, rather than for any specific site. The relative risk for all cancers combined in the most highly exposed and longer-latency subcohorts is around 1.4. In dose–response analyses, higher relative risks are observed for the groups with the highest measured and modelled exposure to TCDD. This relative risk for all neoplasms does not appear likely to be explained by confounding, particularly since dose–response was typically based on internal comparisons among workers of the same cohort. The evidence for specific cancers is strongest for lung cancer, soft-tissue sarcoma and non-Hodgkin lymphoma, but confounding cannot be ruled out for lung cancer, while the findings on soft-tissue sarcoma are based on small numbers. Several studies identified statistically significant increases in many cancers, but findings for other

[The Working Group noted that evaluation of the possible risks for lymphatic and haematopoietic cancer was hampered by inconsistencies in the histopathological classification of diagnoses over time. The interpretation of results for these malignancies was constrained by the diagnostic groupings that had been used by researchers when the studies were conducted.]

2.2 Cancer of the breast

Studies from four cohorts of workers exposed to ethylene oxide provided useful information on the association between this exposure and breast cancer (Gardner *et al.*, 1989; Hagmar *et al.*, 1991, 1995; Norman *et al.*, 1995; Steenland *et al.*, 2003, 2004; Coggon *et al.*, 2004; see Table 2.2, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-23-Table2.2.pdf). The NIOSH study (Steenland *et al.*, 2004) and a cohort study of hospital-based sterilization workers in the United Kingdom (Gardner *et al.*, 1989; Coggon *et al.*, 2004) examined mortality from breast cancer and found no overall excess risk. Three studies examined the incidence of breast cancer: the NIOSH study (Steenland *et al.*, 2003) and a cohort study from Sweden (Hagmar *et al.*, 1991, 1995) found no overall excess risk, while another cohort study from New York State, USA, found an excess risk of about 60%, which was borderline significant (Norman *et al.*, 1995). Internal analyses with inclusion of questionnaire data were carried out in the NIOSH study (Steenland *et al.*, 2003) showing increased relative risks for breast cancer at the highest level of cumulative exposure to ethylene oxide (> 11620 ppm–days, 15-year lag, OR = 1.87, 95%CI: 1.12–3.10), with a significant exposure–response relationship [*P* for trend = 0.002), after controlling for parity and history of breast cancer in a first-degree relative.

2.3 Other cancers

Several cohort studies provided data on exposure to ethylene oxide and mortality from other cancers (stomach, brain, pancreas; see Table 2.2, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-23-Table2.2.pdf). There was no consistent evidence of an association of these cancers with exposure to ethylene oxide.

2.4 Synthesis

The Working Group found some epidemiological evidence for associations between exposure to ethylene oxide and lymphatic and haematopoietic cancers, and specifically lymphoid tumours (i.e. non-Hodgkin lymphoma, multiple myeloma and chronic lymphocytic leukaemia).

3. Cancer in Experimental Animals

Carcinogenicity studies with mice and rats exposed to ethylene oxide by inhalation, oral gavage, and subcutaneous injection were previously reviewed (IARC, 1994, 2008). Results of adequately conducted carcinogenicity studies are summarized in Table 3.1. There have been no additional carcinogenicity studies in animals reported since the previous evaluation in *IARC Monograph* Volume 97 (IARC, 2008).

3.1 Inhalation exposure

In two inhalation studies in mice, there was an increased incidence of alveolar bronchiolar carcinomas and combined adenomas and carcinomas in male and female B6C3F$_1$ mice (NTP, 1987) and of lung adenomas in strain A/J female mice (Adkins *et al.*, 1986). Treatment-related increases in lymphomas, Harderian gland

Table 4.1 Comparison of the evidence for key events – cytogenetic, genetic, and related changes – induced by ethylene oxide in humans, human cells, and experimental animals

End-point	In-vivo exposure		In-vitro exposure
	Animals	Humans	Human cells
Haemoglobin-adduct formation	Strong	Strong	Strong
DNA-adduct formation	Strong	Weak[a]	Strong
Mutations in reporter genes in somatic cells	Strong	Weak[a]	Strong
Mutations in cancer-related genes in tumours	Strong	NR	not applicable
Increased levels of cancer-related proteins in tumours	Strong	NR	not applicable
Cytogenetic alterations in somatic cells			
Sister chromatid exchange	Strong	Strong	Strong
Structural chromosomal aberrations	Strong[b]	Strong	Moderate
Micronucleus formation	Strong[b]	Strong	NR

[a] Possibly due to a lack of adequate studies

[b] Positive responses were seen only at exposure concentrations above those used in the rodent cancer-bioassays

NR, not reported

From IARC (2008)

1998; Liou *et al.*, 1999; Smerhovsky *et al.*, 2001; Hagmar *et al.*, 2004; Boffetta *et al.*, 2007; Bonassi *et al.*, 2007).

A comparison of the evidence for ethylene oxide-induced genetic and related changes in experimental animals and humans is summarized in Table 4.1.

In conclusion, the numerous studies on ethylene oxide that focused on toxicokinetics, DNA-adduct formation, biomarkers, genotoxicity, and molecular biology provide strong evidence that the carcinogenicity of ethylene oxide, a direct-acting alkylating agent, involves a genotoxic mechanism of action. The direct reaction of ethylene oxide with DNA is thought to initiate the cascade of genetic and related events that lead to cancer. Ethylene oxide induces a dose-related increase in the frequency of ethylene oxide-derived haemoglobin adducts in exposed humans and rodents, induces a dose-related increase in the frequency of ethylene oxide-derived DNA adducts in exposed rodents, consistently acts as a mutagen and clastogen at all phylogenetic levels, induces heritable translocations in the germ cells of exposed rodents, and induces a dose-related increase in the frequency of sister chromatid exchange, chromosomal aberrations and micronucleus formation in the lymphocytes of exposed workers.

5. Evaluation

There is *limited evidence* in humans for a causal association of ethylene oxide with lymphatic and haematopoietic cancers (specifically lymphoid tumours, i.e. non-Hodgkin lymphoma, multiple myeloma and chronic lymphocytic leukaemia), and breast cancer.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethylene oxide.

There is strong evidence that the carcinogenicity of ethylene oxide, a direct-acting alkylating agent, operates by a genotoxic mechanism. A dose-related increase in the frequency of ethylene oxide-derived haemoglobin adducts has been observed in exposed humans and rodents, and a dose-related increase in the frequency of ethylene oxide-derived DNA adducts has been demonstrated in exposed rodents. Ethylene oxide consistently acts as a mutagen and clastogen at all phylogenetic levels, it induces heritable