IARC MONOGRAPHS

# NIGHT SHIFT WORK

## VOLUME 124

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, 4–11 June 2019

LYON, FRANCE - 2020

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

# 1. EXPOSURE DATA

## 1.1 Identification of the agent

"Night shift work" involves work, including transmeridian travel, that occurs during the regular sleeping hours of the general population. This alters exposure to the natural light–dark schedule and disrupts circadian rhythms.

"Night" or "night time" is generally defined as the period from sunset to sunrise in each 24 hours. Human biological night depends on individual circadian rhythms, but normally includes the timeframe from 23:00 to 07:00 that most adults use for sleeping; this can vary according to, for example, cultural and other differences.

Shift work is defined by the International Labour Organization (ILO) (ILO, 1990a, b) as "a method of organization of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of work of individual workers". According to the European Working Time Directive No. 2003/88/EC (WTD) concerning certain aspects of the organization of working time, "shift work means any method of organising work in shifts whereby workers succeed each other at the same work stations according to a certain pattern, including a rotating pattern, and which may be continuous or discontinuous, entailing the need for workers to work at different times over a given period of days or weeks" and "shift worker means any worker whose work schedule is part of shift work" (European Commission, 2003).

Shift work arrangements may extend work to all 24 hours of the day, including night hours, by alternating different workers and/or teams.

As defined by the ILO, night work means "all work which is performed during a period of not less than seven consecutive hours, including the interval from midnight to 5 a.m."; consequently, "night worker means an employed person whose work requires performance of a substantial number of hours of night work which exceeds a specified limit" (ILO, 1990a, b).

The European Union (EU) WTD definition of "night time" is the same as that set by the ILO, and the "night worker" is someone who (a) "during night time, works at least three hours of his daily working time as a normal course" or (b) "is likely during night time to work a certain proportion of his annual working time, as defined at the choice of the Member State concerned" by national legislation or by collective agreements, or agreement between two sides of industry (European Commission, 2003) (see Section 1.4).

In the present "24/7 society" (24 hours per day, 7 days per week), shift work may involve various forms of flexible, variable, irregular, and non-standard working hours, including evening and night work, split shifts, staggered working hours, compressed work weeks, weekend work, on-call work, and on-demand work. There exists a myriad of shift systems that can differ widely according to the following main features (Knauth, 1993, 1996, 1998; Kogi, 2001; Bambra et al., 2008).

1. *With or without night work*. The working time can be extended to all or part of the night, and the number of nights worked per week, month, or year can vary considerably. "Night work" is generally considered to be work performed during the usual sleeping hours, but the legal "period of night work" varies between countries; for example, it ranges between 19:00–22:00 and 05:00–08:00 in some countries, and between 23:00 to midnight and 05:00–06:00 in others (see Section 1.4).

2. *Continuous or discontinuous*. In the case of continuous shift work, every day of the week is covered by the shift system; in the case of discontinuous shift work, work does not occur every day of the week (e.g. no work takes place during the weekend).

3. *Permanent or rotating*. For permanent shift work, the same shift is always worked by any particular employee (morning, afternoon, or night); for rotating shift work, the shift assigned to a particular employee changes regularly.

4. *Length of the shift cycle*. A "cycle" includes all shifts and rest days up until the series of shifts and rest days restarts from the same point; cycles may range in length from days to weeks or months.

5. *Duration of individual shifts*. In many cases, shift duration is approximately 8 hours; however, it can range from less than 8 hours (more common in part-time work) to 12 hours or longer. [The Working Group noted that long commuting hours can further prolong work time (e.g. Costa et al., 1988).]

6. *Start and end time of individual shifts*. Morning shift may start between 04:00 and 08:00, and night shift may start between 18:00 and midnight. End times vary according to type of shift schedule and duration of shifts.

7. *Number of consecutive shifts*. The number of consecutive night shifts is relevant for both permanent and rotating night work. In studies of rotating night work, "speed of rotation" is sometimes used to describe this concept. A "fast" speed of rotation indicates fewer consecutive night shifts than a "slow" speed of rotation (exact definitions vary).

8. *Direction of shift rotation*. This can be clockwise (also called "forward" or "delaying", i.e. changing from a morning to an afternoon shift, or from an afternoon to a night shift) or counter-clockwise (also called "backward" or "advancing", i.e. changing from an afternoon to a morning shift, or from a morning to a night shift), producing different periods of rest between shifts.

9. *Number and position of rest days along the shift cycle and between shifts*. The number and position of rest days is relevant for both permanent and rotating shift work, with the potential for "quick returns", generally defined as less than 11 hours between shifts.

10. *Regularity or irregularity of the shift schedule*.

A circadian disruption (Haus & Smolensky, 2006; Stevens et al., 2011; Vetter, 2020 of the harmonic organization and synchronization of biological processes can occur to a greater or lesser degree according to the specific characteristics of different shift systems (see Section 1.3.1(b)).

Transmeridian flights typically involve night work and rapid travel across multiple time zones for aircrew. The related interference with circadian rhythms, in terms of both de- and resynchronization, depends on flight direction (i.e. resynchronization is slower and jetlag is more severe when flying eastwards rather than westwards), number of time zones crossed, length of rest period, and the circadian characteristics of the individual (Wegmann et al., 1983; Härmä et al., 1994; Sack et al., 2007).

## 1.2 Applications and drivers of night shift work

In past decades, shift and night work were essentially used for guaranteeing round-the-clock activities related to the provision of essential basic services to the general population (e.g. supply of light, water, and gas; health care; transport; security; and telecommunications), to address technological constraints (e.g. power plants, metallurgy, and the chemical industry), and to increase the labour productivity and economic profitability of enterprises (e.g. the manufacturing industry).

In the modern 24/7 society, shift and night shift work are key features of work organization. They permit globalization of the labour market and enhance economic competition by enabling nonstop activities favoured by the development of new technologies (e.g. information and communication technologies) and productive and commercial strategies (e.g. just-in-time operation and logistics), and the increased exploitation of leisure time (e.g. tourism and entertainment) (Presser, 2003; Anttila & Oinas, 2018).

Shift and night shift work are therefore the cornerstones of the so-called "temporal flexibility" that characterizes current trends in the diversification of working time patterns of modern society. Such working time patterns are rapidly changing in terms of both economic and productive strategies (e.g. the "gig economy"), as well as social organization and individual behaviour (ILO, 2018).

At present, there are large variations in the conceptualization and approaches to "flexible working hours" among countries, industries, and companies, according to different cultures, history, socioeconomic conditions, work sectors, the power of unions, and industrial relations (ILO, 2018). Furthermore, there are different perspectives concerning "temporal flexibility" between employers and employees: employers may view "temporal flexibility" in terms of prompt adaptation of production and/or service systems to market demands and to technological and organizational innovations, whereas employees may tend to view it in terms of decreasing work constraints and increasing control over working time (Costa et al., 2004).

Atypical and irregular working hours may also vary with type of employment. In recent years, increasing numbers of workers have been engaged in temporary jobs (particularly in the tertiary sector, e.g. services), which are often associated with unpredictable and variable working hours (e.g. split shifts, on-call work), including night shift work (Marmot et al., 2006). Consequently, the interaction between employment status and various working time patterns may have a different impact on the health and well-being of workers, depending on different degrees and combinations of job insecurity, self-employment, work intensity, time pressure, and low control over working time experienced by temporary workers (Bartley et al., 2006; Hall, 2017).

Furthermore, there is an increasing global trend for new forms of work organization connected to modern information and communication technologies, which have revolutionized everyday work and life in the 21st century (Boulin et al., 2006). Evolving information and communication technologies have led to the extension of shift and night work to sectors previously not or only marginally involved, such as banking and insurance, radio and television broadcasting, and technical assistance (e.g. call centres) (ILO, 2018). A recent joint ILO–Eurofound report indicated that the working hours of teleworking and/or mobile information and communication technologies workers were typically longer than their office-based counterparts, with blurred lines between work and private life. This was particularly the case for workers who performed supplemental work on top of office work (as opposed to those who substituted work at home for office work) (EuroFound/ILO, 2017).

Because the variability and irregularity of working hours of such work arrangements are also partially linked to autonomous choices of workers, they are difficult to monitor and can elude the usual methods of recording and also assessment in terms of impact on human health.

Section 1.3.1(b) contains additional sector-specific information on night shift work prevalence and trends.

## 1.3 Exposure characterization

### *1.3.1 Prevalence and trends*

The definitions, quality, and extent of statistical data on the number of shift and night shift workers vary worldwide, making direct comparisons between regions difficult. It should also be noted that, particularly in countries with economies in transition, shift work, and night shift work are often associated with poor living and working conditions, high workloads, and long working hours (Ahasan et al., 1999; Fischer, 2001), which may exacerbate the impact of shift and night shift work on health.

#### *(a) General summary*

In Europe, results from the latest EU Labour Force Survey (Eurostat, 2019), covering 28 European countries, indicated that 16.7% of employed men and 9.4% of employed women worked night shifts in 2018. The overall percentage of employed people working nights decreased slightly between the 2009 and 2018 surveys (from 14.9% to 13.3%). The most prevalent types of shift work are alternating or rotating shifts, followed by permanent shifts (EuroFound, 2017). “Atypical work”, including night work, weekend work (working both Saturday and Sunday), and shift work, is more prevalent among men than women, among the self-employed than the non-self-employed, and during the earliest stage of working life; within Europe, it is most prevalent in the Anglo-Saxon, Central–Eastern, and Southern country clusters (EuroFound, 2017).

In Africa, a survey conducted in Senegal in 2005 found that of the nine companies interviewed (covering the business sectors of chemicals, food, oil and gas, energy, agribusiness, metallurgy, textiles, and fishing), 89% used shift systems and 20% of employees reported working at least one night per week (Ndiaye, 2006).

In the USA, the Bureau of Labor Statistics reported that in 2004 over 27 million full-time wage and salary workers had flexible work schedules, with 14.8% usually working a shift other than a daytime schedule: 4.7% worked evening shifts (any time between 14:00 and midnight), 3.2% worked night shifts (anytime between 21:00 and 08:00), 3.1% worked employer-arranged irregular schedules, and 2.5% worked rotating shifts including evenings or nights (US Bureau of Labor Statistics, 2005). More recent estimates from a different data source, the 2015 National Health Interview Survey – Occupational Health Supplements survey (NIOSH, 2015) based on 19 456 adults, indicated that 27% of the working population are involved in shift work (“any alternative shift” including evening, night, and rotating shifts); the unadjusted prevalence is 28% for men and 25% for women. Approximately 11 million adults (7.4% of the working population) were estimated to perform night work (any time between 01:00 and 05:00) frequently (“more than 5 times in the past 30 days”). This was more common among men (9.1% versus (vs) 5.6% for women), blacks (10.5% vs 7.1% for whites and 6.5% for “other”), non-Hispanics (7.6% vs 6.6% for Hispanics), workers with a high school education (10.1% vs 7.7% for less than high school and 6.6% for beyond high school education), and in younger age groups (8.6% of those aged 18–29 years vs 7.8% of those aged 30–44 years, 6.9% of those aged 45–64 years, and 3.7% of those aged 65 years and older) (unadjusted prevalences) (NIOSH, 2015).

In Canada, according to the Survey of Labour and Income Dynamics carried out in 2011, 2.0% of workers were engaged in regular night or graveyard shifts, 9.4% in rotating shifts, and 12.3% in irregular schedules (Statistics Canada, 2013). From 1996 to 2011, decreasing proportions of Canadian workers reported regular day schedules (from 68.4% to 66.1%) and rotating shifts (from 10.1% to 9.4%), and slight increases were noted in the proportions of workers reporting regular night shifts (from 1.7% to 2.0%) and irregular schedules (from 9.7% to 12.3%) (Statistics Canada, 2009a, b, 2013; Hall, 2017).

In South America in 2002, 23% of companies in Chile use shift systems; 61% of these include night work, suggesting that 15% of all employees in this country perform night shift work (Echeverría, 2002). According to the national survey carried out in Brazil in 2016, 7.6% of the working population (or approximately 7 million individuals) performed work at night (PNAD, 2016).

In China, a working time survey of 300 enterprises in three major cities (Beijing, Changsha, and Guangzhou) undertaken between 2003 and 2004 found that 17.5% of employees performed night work at least once per month (Zeng et al., 2005). In Japan, a recent study based on government surveys reported that the prevalence of night shift work among Japanese employees increased over the last two decades from 13.3% in 1997 to 17.8% in 2002, 17.9% in 2007, and 21.8% in 2012 (Kubo, 2014). It was estimated that, in 2012, 12 million workers were engaged in night work (defined as an average of at least 4 times per month during the previous 6 months) (Kubo, 2014).

In Australia, 1.5 million workers (excluding owners and/or managers of incorporated enterprises), or 16% of all workers, usually worked shifts in their main job in 2012; the most common type of shift worked was a rotating shift (45% of those performing shift work). Men were more likely to usually work in shifts (18%, compared with 14% of women) (Australian Bureau of Statistics, 2012).

The globalization of the labour market, and the outsourcing of many productive activities of multinational companies, has led to the increasing use of shift and night shift work in low- and middle-income countries at levels similar to, or even higher than, those of high-income countries; this is particularly the case for the manufacturing and construction sectors. The growing populations of some low- and middle-income countries mean that a large number of workers are involved in shift and night shift work (ILO, 2011b).

### *(b) Industry sector*

Shift systems may differ between industry sectors according to their specific requirements and work organization (EuroFound, 2017).

In health-care sectors worldwide, shift work is mainly based on continuous shift systems, managed with both clockwise and counter-clockwise rotation, variable start and end times, and different blocks of night shifts in succession. Slowly rotating systems were mainly used in the past, but rapidly rotating (every 1–3 days) systems have increased during recent decades; a growing number of workers are also engaged in 12-hour shifts (European Trade Union Confederation, 2011; EuroFound/ILO, 2017).

In manufacturing sectors (e.g. mechanical, graphic, textile, food, and paper), shift work including nights is generally organized in both semi-continuous and continuous three-shift systems, where workers alternate regularly between day and night shifts with relatively stable start and finish times, and fairly homogeneous duty periods (8–9 hours). Semi-continuous shift systems are mainly based on a weekly rotation that involves 5 consecutive night shifts; continuous systems are more variable in terms of shift cycle. In recent decades, faster rotating systems that imply fewer nights in succession (e.g. 3, 2, or 1) have increasingly been adopted. Permanent or slowly rotating (every 15–30 days) shift systems are used in some subsectors (e.g. oil and gas overseas platforms) (EuroFound, 2015).

In the transport sector, particularly in rail and air travel and long-haul driving, individual shift schedules are often irregular with rapid rotation and high variability in shift duration, start and end time of duty periods, and position and number of rest days (which may be spent away from home and family) (European Agency for Safety and Health at Work, 2010). Flight personnel can experience additional disruption in relation to the variable number of time zones crossed (Grajewski et al., 2003).

In the retail sector, the decline of small shops and the proliferation of larger supermarkets, hypermarkets, and shopping centres are associated with a liberalization in opening hours (longer hours and more frequent service at weekends) and the adoption of semi-continuous and continuous rotating shift systems; operating times have been extending into the evening and, in some cases, night time (EuroFound, 2012).

In agriculture, shift and night work are also increasingly used in connection with more intensive and extensive work, mainly linked to livestock breeding, large plantations, and fishing. This can be associated with long working hours (ILO, 2011a).

In Europe, according the 4th EU Working Conditions Survey (EuroFound, 2007), night shift work is used in many work sectors, particularly in: hotels and restaurants (> 45% of the workforce); transport and communication (> 35%); health care (> 30%); public administration and defence (> 25%); manufacturing (> 20%); and electricity, gas, and water (> 20%).

In the USA, the estimated prevalence (adjusted for age, sex, and race using the 2000 United States population) of frequent night work (working between 01:00 and 05:00 more than 5 times per month) by work sector in 2015 was: 18.1% in mining; 15.5% in transportation, warehousing, and utilities; 11.8% in health care and social assistance; 10.8% in manufacturing; 9.8% in agriculture, forestry, and fishing; 6.6% in wholesale and retail trade; 5.3% in services; and 1.3% in construction (NIOSH, 2015).

In Canada, the industry groups with the highest numbers of people working regular night or rotating shifts in 2011 were trade (396 000 workers; 15% of industry), health care and social assistance (318 000 workers; 18% of industry), manufacturing (261 000 workers; 17% of industry), and accommodation and food services (222 000 workers; 20% of industry). The majority of regular night or rotating shift workers in health care and social assistance, trade, and accommodation and food services were women, and men represented the majority in manufacturing and public administration (CAREX Canada, 2019).

Shift and night work are also widely used across sectors in Africa, Asia, and South America (Lee et al., 2007). A survey based in China found that shift work (with and without nights) was most highly concentrated in the manufacturing sector, followed by the wholesale and retail trade, food and beverage, and social services sectors (Zeng et al., 2005). In the Republic of Korea, the proportions of shift work including night work were observed to be highly concentrated in the service sectors, including: 64.9% in transportation, storage, and communications; 48.3% in community, social, and personal services; and 30.2% in the wholesale and retail trade, and hotels and restaurants subsectors (Yoon, 2001). In Jamaica, shift work was the dominant working time arrangement in most industry sectors in 2004, particularly in the service subsectors of transport, storage, communications, wholesale and retail trade, and hotels and restaurants (Taylor, 2004).

### 1.3.2 Methods of measurement

Night shift work is the most common observational proxy for circadian disruption (Vetter, 2020). Transmeridian flights are associated with night shift work and additional circadian disruption as a result of rapid travel over time zones (Härmä et al., 1994).

In relation to measuring exposure to night shift work, a focus on the measurement of exposure to work occurring during the normal sleeping hours of the general population is recommended. Concerning the measurement of exposure to night shift work among aircrew, it is important to consider the cumulative time spent working in the standard sleep interval, as well as the number of time zones crossed.

Subjective methods for detecting and quantifying exposure to night shift work and flying over time zones include questionnaires, interviews, or diary techniques, where workers themselves report on past or current exposures. Objective methods are normally based on historical registry data of individual working hours or company-based flight history records of the aircrew, for example, flight or block hours. It is also possible to estimate past exposure to night shift work using a job-exposure matrix (JEM); this method combines information based on job title with information on average exposure to shift work for each job title, usually based on an earlier evaluation by questionnaire in other populations (e.g. Schwartzbaum et al., 2007).

For aircrew, exposure estimation may be based on subjective or objective data concerning flights to and from specific airports. The exposure data concerning flying over time zones typically include information on the number of time zones crossed in a certain time period, or information on the number of flights crossing time zones, or the number of hours worked during a time period, for example, the standard sleep interval (Grajewski et al., 2003).

The use of objective day-to-day data describing exposure to night shift work (payroll data of working hours; e.g. Härmä et al., 2015; Vistisen et al., 2017) is most accurate, because this is suitable for multidimensional exposure assessment (e.g. Stevens et al., 2011) and is less sensitive to attrition and reporting bias, especially in studies with a long follow-up. However, although objective data on working hours are normally more precise and can provide quantitative information on different dimensions of night shift work over time, good correlation has been observed between self-reported and objective data in relation to some work schedules; examples include permanent night work and rotating shift work with night shifts (Härmä et al., 2018a), and duration of employment as a flight attendant (Schubauer-Berigan et al., 2015). Further, although company-based registry data are more representative for the target population (100% coverage), the availability of such data can vary across regions, sectors, and occupations. The use of questionnaires and/or interviews can yield additional information compared with such registry data, for example, total working hours associated with all jobs and/or unpaid working hours. Scheduled and executed work shifts often differ (e.g. as a result of double shifts or last-minute work shift changes). Analysis of past scheduled rotas is therefore less reliable than the use of registry data that reflect executed shifts (e.g. payroll data). Information on executed shifts offers the additional benefit of capturing and analysing irregular and complicated shift systems.

[The Working Group noted that a limitation of the use of company-based registry data describing working hours is a lack of information about working hours in other jobs in addition to the main job, or before entering the registry. A solution is to combine the objective exposure information on daily registry-based working hours with individual-based survey information, for example, night shift work and lifelong exposure.]

Data collected at the individual level are generally preferred over non-individual (grouped) data such as JEMs, because of their ability to capture inter-individual variability in exposure. Population-based JEMs are especially prone to exposure misclassification, resulting in underestimation of the hypothesized relationship between exposure and outcome. For example, Schwartzbaum et al. (2007) classified day work as occupations in which "less than 30% were normally shift workers". [The Working Group noted that the JEM method is often applied without validation in the country, sector, or time period where it is used. Sensitivity and specificity are seldom reported, and job titles and shift schedules may differ across countries and over time. Industry-based JEMs, where jobs can be directly linked to shift work schedules that include nights, may provide a more accurate picture of shift work exposure compared with population-based JEMs.]

### *1.3.3 Factors that may influence the effects of night shift work on cancer*

Exposure to night shift work may vary according to different schedule and job characteristics (see Sections 1.1, 1.2, and 1.3.1(b)). In addition, other variables, such as individual, lifestyle, and environmental factors (e.g. light exposure), may mediate, confound, or moderate cancer outcomes among night shift workers, including those who fly over time zones (e.g. Lunn et al., 2017) (Table 1.1). These factors may act alone or together, complicating the identification of causal risk factors for cancer in these populations.

#### *(a) Individual characteristics*

Individual characteristics that may influence the impact of exposure to night shift work on cancer include, among others, age, reproductive factors, chronotype or diurnal preference, and sleep patterns.

Exposure to night shift work, and its effects on the risk of chronic disease, may relate to age and its association with lifestyle factors and circadian timing (Duffy et al., 2015; Ramin et al., 2015). In turn, age is related to reproductive factors (e.g. parity, age at first child, and menopause) that have been postulated as potentially important confounders in some health risk analyses (e.g. for cancer of the breast) (Kelsey et al., 1993; Ban & Godellas, 2014). Some recent studies have indicated that such reproductive differences between day and night shift workers do exist, but are not strongly pronounced (Papantoniou et al., 2016; Wegrzyn et al., 2017).

**Table 1.1 Factors that may influence the effects of night shift work on cancer**

| Individual characteristics | Lifestyle-related factors | Light exposure |
|---|---|---|
| Age | Smoking | Altered light patterns |
| Reproductive factors | Physical activity | |
| Chronotype or diurnal preference | Eating behaviour (timing) | |
| Sleep | Alcohol consumption | |

Chronotype is a characteristic of the circadian timing system that varies according to the individual; it is related to individual preference of sleeping and waking hours. Chronotype and individual diurnal preferences have been proposed as important considerations in epidemiological studies of night shift work and cancer (e.g. Section 2.1.1(c)) (Hansen & Lassen, 2012; Erren et al., 2017).

In 1970, Oquist produced a questionnaire to differentiate between morning and evening persons, translated into English by Horne & Ostberg (1976). This questionnaire has five categories of "chronotypes": definitely morning, moderately morning, neither, moderately evening, and definitely evening. [The Working Group noted that this questionnaire measures individual diurnal preference rather than chronotype.] Other questionnaires were subsequently developed, such as those by Folkard et al. (1979) and Torsvall & Akerstedt (1980). More recently, Roenneberg et al. (2003) created the Munich Chronotype Questionnaire that measures individual sleep phase differences (i.e. timing of sleep within the 24-hour day). [The Working Group noted that these questionnaires may be measuring distinct human characteristics; it is therefore relevant to consider which questionnaire was used in a study when interpreting obtained results.]

Night shift work is commonly associated with disturbed sleep (Åkerstedt, 2003; Sallinen & Kecklund, 2010). Disrupted sleep (and its characteristics, such as duration and timing) has been proposed as a potential risk factor for cancer (Haus & Smolensky, 2013; Irwin, 2015).

### *(b) Lifestyle-related factors*

Lifestyle factors, including smoking behaviour, amount of physical activity, eating behaviour, and consumption of alcohol, may be affected by night shift work (Bøggild & Knutsson, 1999; Bushnell et al., 2010).

A cohort study with data from 2004 to 2006 observed increased odds of smoking relapse and reduced odds of smoking cessation in fixed night workers (Nabe-Nielsen et al., 2011). There is sufficient evidence for the carcinogenicity of tobacco smoking in humans, with links to several cancer end-points (IARC, 2004). Patterns of alcohol consumption may also vary according to work schedule timing (Dorrian & Skinner, 2012; Dorrian et al., 2015). Alcohol has been classified as carcinogenic to humans (IARC, 2012).

Several studies have investigated the association between body mass index and/or metabolic problems and night shift work (van Drongelen et al., 2011; Wang et al., 2014; Gan et al., 2015; Proper et al., 2016). Night shift work may impair metabolism, although it is unclear whether physical activity attenuates the effects on weight gain and/or body composition in night shift worker populations (van Drongelen et al., 2011; Marqueze et al., 2014; Neil-Sztramko et al., 2016). Excess body weight (increased body mass index) has been associated with the risk of cancer (Renehan et al., 2008). Some studies have shown differences between shift workers and non-shift workers in relation to eating behaviour (Lowden et al., 2010; Souza et al., 2019). Eating behaviour, including nocturnal nibbling, has also been investigated as a biological factor associated with weight gain and physical activity among night shift workers (Haus et al., 2016). Moreover, dietary intake may be affected by reduced sleep (Dashti et al., 2015). van de Langenberg et al. (2019) observed that, during a night shift, workers have a shorter maximum fasting interval, more eating moments, and a higher fat intake than during work without a night shift. Changes in timing of sleep and eating related to shift work may increase the risk of obesity, which has been linked to an increased risk of cancer (Calle & Kaaks, 2004; IARC, 2018).

### *(c) Light exposure*

Night shift workers experience altered exposures to light during the 24-hour period. Exposure to artificial light at night (particularly in the blue wavelength region of the spectrum) inhibits the physiological nocturnal production of melatonin by the pineal gland (Lewy et al., 1980; Mirick & Davis, 2008), and has been hypothesized as a mechanism for increased risk of cancer (Stevens, 1987). Further details on melatonin are provided in Section 4. In addition, lack of sunlight exposure may increase risk of cancer via its effects on reducing vitamin D levels (Garland et al., 2006; Juzeniene et al., 2011).

Various methods have been used to assess exposure to light and its potential health impacts in night shift workers (Hunter & Figueiro, 2017; Cherrie, 2019). Quantitatively measured light-at-night levels in night shift workers have been shown to differ by season (Daugaard et al., 2019) and workplace characteristics, such as occupation and work site (Hall et al., 2017). Night shift workers in equatorial regions have been observed to experience shorter durations of natural light exposure compared with day workers during work days as well as days off

(Marqueze et al., 2015). In a Dutch study, night shift workers were exposed to daylight for longer durations compared with day workers during non-night shift sessions, but were less exposed to daylight during night shift sessions compared with non-night shift sessions (van de Langenberg et al., 2019). In a Danish investigation of average light exposures, Daugaard et al. (2019) observed higher intensities and durations of light exposures for night workers compared with day workers in the period between midnight and 05:59 and decreased intensities and durations in the 06:00–17:59 period during work days, but not during days off work.

### *1.3.4 Co-exposures in the workplace*

#### *(a) Introduction*

Night shift workers may be occupationally exposed to chemical, physical, or biological agents and ergonomic stressors, and some of these exposures may be known or possible carcinogens (Costa, 2003; Fenga, 2016). The intensity or extent of an occupational co-exposure may differ by shift. Using telephone interviews, Jay et al. (2017) evaluated exposures to workplace hazards across a national sample of the New Zealand population, comparing people who worked a standard daytime work week with those who did not. Participants working non-standard hours were more likely to be exposed to workplace hazards and to multiple hazards than daytime workers. The prevalence of workplace hazards was reported for dusts (odds ratio, OR, 1.55; 95% confidence interval, CI, 1.29–1.87), smoke or fumes (OR, 1.88; 95% CI, 1.53–2.32), gases (OR, 3.35; 95% CI, 2.55–4.40), oils or solvents (OR, 1.50; 95% CI, 1.22–1.83), acids or alkalis (OR, 2.24; 95% CI, 1.72–2.91), fungicides, insecticides, herbicides, or timber preservatives (OR, 1.71; 95% CI, 1.31–2.24), and other chemical products (OR, 1.27; 95% CI, 1.00–1.61), as well as for two or more hazards (OR, 2.45; 95% CI, 2.01–3.0). [The Working Group noted that the observed differences in exposure prevalence did not account for differences in job distributions across night and day shifts.] A study of night shift work in 44 enterprises in Poland, spanning diverse industrial sectors such as manufacturing, printing, transport, sewerage, and electricity supply, indicated that night workers may be exposed to formaldehyde, mineral oils containing polycyclic aromatic hydrocarbons, silica dust, chromium (VI) compounds, vinyl chloride, nickel, benzene, cadmium, wood dust, and diesel exhaust, all of which are IARC Group 1 carcinogens (Pepłońska et al., 2013). [The Working Group noted that this study did not compare exposures in night workers with those in day workers within a single job or sector; differences in exposure prevalence between these groups therefore cannot be discerned.]

Night shift work could influence biological processes that increase the risk associated with exposure to xenobiotics as a result of both the circadian fluctuation in biological susceptibility to them, and the desynchronization of the mechanisms of detoxification (Claudel et al., 2007; Nagai et al., 2011; Lin et al., 2014; Carmona-Antoñanzas et al., 2017). Smolensky et al. (2017) reviewed how circadian time structure influences vulnerability to chemical xenobiotics. Human vaccination trials have demonstrated circadian time-dependent differences in response to bacterial and viral agents (Smolensky et al., 2019). In addition, the timing of drug administration affects the efficacy of treatment (Kaur et al., 2013; Ballesta et al., 2017).

Havet et al. (2017) evaluated varied exposures to carcinogenic, mutagenic, and reprotoxic (CMR) chemicals for French employees and found that over 2.2 million or 10.4% of employees were exposed to one or more CMR agents at their workplace and that 3.4% were exposed to multiple CMR chemicals. Carcinogens accounted for 97% of the CMR exposures. The most prevalent exposures were mineral oil, wood dust, crystalline silica, and, to a lesser extent, diesel exhaust and formaldehyde. Night shift workers were found to be more frequently exposed to at least one CMR agent compared with occupations without night shift work, although comparisons were not restricted to those with the same occupation. Among shift workers and night workers, the prevalence of exposure to at least one CMR agent for more than 20 hours per week was 22% and 18%, respectively. [The Working Group noted that this study did not compare exposures in night workers with those in day workers within a single job or sector; differences in exposure prevalence between these groups therefore cannot be discerned.]

*(b) Aircrew*

Aircrew are exposed to cosmic ionizing radiation in addition to night shift work, crossing time zones, and long work hours (O'Brien & Friedberg, 1994; Hammer et al., 2014). Cosmic radiation from the sun and charged particles from the galaxy interact with the Earth's atmosphere and form secondary and subsequent particles including neutrons, protons, electrons, positrons, photons, and positive and negative muons (UNSCEAR, 2008). The Earth's magnetosphere concentrates radiation at higher latitudes. Radiation dose in aircraft depends on latitude, longitude, and the stage of the 11-year solar cycle. The most important determinant of the dose rate is altitude, with dose doubling every 1500 m (Paretzke & Heinrich, 1993). Neutrons are a major contributor to cosmic radiation dose at flight altitudes (Goldhagen, 2000).

Aircrew are one of the occupational groups with the highest radiation exposures (UNSCEAR, 2008). Depending on flight route patterns, annual doses range from 0.2 to 9.0 mSv in excess of the 2 mSv natural background radiation dose at sea level (UNSCEAR, 2008). Cumulative occupational lifetime doses of ionizing radiation generally remain less than 100 mSv (O'Brien & Friedberg, 1994). Aircrew represent the largest population of people exposed to high-energy neutrons and the only population exposed to high-energy protons (Wilson, 2000). Long-haul high-latitude flights, such as from New York to Hong Kong Special Administrative Region, may have single flight doses ranging from 52 to 102 μSv, depending on the stage of the 11-year solar cycle (Alvarez et al., 2016).

Studies of cancer summarized by the Working Group (see Section 2) that assessed exposure to cosmic radiation are described in Table 1.2, including the method used to estimate cosmic radiation doses. To calculate cumulative dose, a personal flying time metric is folded with a dose metric for the type of flight or aircraft. Flying time may be assessed by logbooks (in the case of pilots), company personnel records, or questionnaires. Studies reported cumulative radiation dose as either absorbed dose or effective dose. Absorbed dose is a measurable quantity of the amount of energy deposited by radiation in a mass, expressed in units of milligrays. Effective dose is a radiation protection quantity computed from the absorbed dose weighted by both radiation effectiveness and organ sensitivity over the whole body, expressed in millisieverts (ICRP, 2007).

*(c) Health-care workers*

Occupational hazards among health-care workers have been reviewed (Vecchio et al., 2003; Gambrell & Moore, 2006; Connor et al., 2010; Lawson et al., 2012; Graeve et al., 2017; Hall et al., 2017; Siama et al., 2019). Hazards include exposure to antineoplastic drugs, sterilizing agents, and ionizing radiation. Antineoplastic drugs are handled in hospitals in shipping and receiving areas, pharmacies, care wards, and laundry areas; exposures can occur during preparation, administration, cleaning, and contact with patient waste products (Hon et al., 2013; Hall et al., 2017). Exposure to antineoplastic drugs can also occur in non-hospital settings such as community pharmacies, veterinary-care facilities, and

**Table 1.2 Estimation of cosmic radiation dose in aircrew epidemiological studies that assessed both night shift work and radiation dose[a]**

| Reference | Country | Aircrew type | Study type and population | Duration estimation method | Cosmic radiation dose estimation | | |
|---|---|---|---|---|---|---|---|
| | | | | | Model | Method | Dose range |
| Pukkala et al. (2003) | Denmark, Finland, Iceland, Norway, Sweden | Cockpit | Cancer incidence study; national cohort (pilots, *n* = 10 211) followed through 1996 or 1997 | Records of annual block hours[b] by aircraft | CARI-5E | Tveten et al. (2000) Aircraft type assigned dose rate per block hour for 5-yr periods from 1960 to 1994 | Cumulative effective dose < 1 to > 20 mSv Four dose categories |
| Yong et al. (2014a) | USA | Cockpit | Cohort mortality study; company (Pan Am[c]) cohort (cockpit crew, *n* = 5964) followed through 2008 | Records of annual flight hours[b] | CARI-6P | Waters et al. (2009); Anderson et al. (2011) Frequency-weighted domicile-based dose for 5-yr periods from 1930 to 1970, 1980, and 1990 | Cumulative effective dose Mean, 28 mSv (median, 31 mSv; range, 0.0047–71.0 mSv) Six dose categories |
| Pinkerton et al. (2012) | USA | Cabin | Cohort mortality study; company (Pan Am, including transfers from National[c]) cohort (FAs, *n* = 11 311) followed through 2007 | Questionnaire or interview with some proxy respondents | CARI-6P | Waters et al. (2009) Frequency-weighted domicile-based dose for 5-yr periods from 1930 to 1970, 1980, and 1990 | Cumulative effective dose Median, 12.7 mSv (range, 0.33–102 mSv) |
| Pinkerton et al. (2016) | USA | Cabin | Breast cancer incidence study; company (Pan Am, including transfers from National[c]) cohort (female FAs participating, self or proxy, in a questionnaire study, *n* = 6093) | Questionnaire or interview with some proxy respondents | CARI-6P | Waters et al. (2009); Anderson et al. (2011) | Cumulative absorbed dose Cases: mean, 10 mGy; median, 5.5 mGy; IQR, 2.6–16 mGy Non-cases: mean, 12 mGy; median, 7.3 mGy; IQR, 2.7–17 mGy |
| Pinkerton et al. (2018) | USA | Cabin | Cancer (melanoma, thyroid, and gynaecological) incidence study; company (Pan Am, including transfers from National[c]) cohort (female FAs participating, self or proxy, in a questionnaire study, *n* = 6095) | Questionnaire or interview with some proxy respondents | CARI-6P | Waters et al. (2009); Anderson et al. (2011) | Cumulative absorbed dose Cohort: mean, 7.3 mGy; IQR, 2.7–17 mGy |

**Table 1.2 (continued)**

| Reference | Country | Aircrew type | Study type and population | Duration estimation method | Cosmic radiation dose estimation | | |
|---|---|---|---|---|---|---|---|
| | | | | | Model | Method | Dose range |
| Pukkala et al. (2012) | Finland, Iceland, Norway, Sweden | Cabin | Cancer incidence study; national cohort (FAs, $n = 8507$) followed for cancer incidence | Records of annual block hours[b] | EPCARD | Tveten et al. (2000); Kojo et al. (2004) Aircraft type assigned dose rate per block hour for 5-yr periods from 1960 to 1994 | Cumulative effective dose < 5 to > 35 mSv |
| Schubauer-Berigan et al. (2015) | USA | Cabin | Breast cancer incidence study; company (Pan Am, including transfers from National[c]) cohort (female FAs participating, self or proxy, in a questionnaire study, $n = 6093$) | Questionnaire or interview with some proxy respondents | CARI-6P | Waters et al. (2009); Anderson et al. (2011) | Cumulative absorbed dose Median, 7.2 mGy (range, 2.7–17 mGy) |

CARI, computer program that estimates cosmic radiation dose received by an individual; EPCARD, European Program Package for the Calculation of Aviation Route Doses; FA, flight attendant; IQR, interquartile range; yr, year.

a Studies that were reviewed by the Working Group but provided no information on cosmic radiation exposure are not included.

b "Block hours" refers to gate departure to gate arrival (aircraft taxi time and air time); "flight hours" refers to wheels off the ground to wheels on the ground (air time).

c Pan American World Airways acquired National Airlines in 1980.

home care settings (Meijster et al., 2006; Hall et al., 2017).

A Dutch study of shift work and breast cancer risk among 59 947 nurses found that 27% reported work with antineoplastic drugs for at least 6 months, 26% with routine X-rays, 10% with anaesthetic gases, and 2% with radiotherapy; however, the co-occurrence of night shift work with other occupational exposures was not reported (Pijpe et al., 2014). Buschini et al. (2013) evaluated DNA damage in Italian nurses who worked with the antineoplastic drugs cyclophosphamide, chlorambucil, melphalan, busulfan, thiotepa, etoposide, and treosulfan, all IARC Group 1 carcinogens, but were unable to identify significant differences between exposed nurses and referents using three versions of the comet assay.

Sterilizing and disinfecting chemicals including formaldehyde and ethylene oxide are used to sterilize and disinfect medical and surgical equipment, and in pathology and anatomy laboratories (Kiran et al., 2010; Costa et al., 2011). Exposures to ionizing radiation in health care include gamma, X-rays, alpha particles, and beta rays (Gorman et al., 2013).

#### *(d) Co-exposures in other occupations*

Co-exposures for industries and occupations within the major sectors where night shift work is common (see Sections 1.2 and 1.3.1(b)) are summarized in Table 1.3. The sectors are manufacturing, transport (other than flying), retail and services, agriculture, and information and communications.

## 1.4 Regulations and guidelines

### *1.4.1 Introduction*

Regulatory approaches for shift work vary widely between countries, industry sectors, and companies. Implementation of international regulations is dependent on national laws and collective agreements, and benefits from participatory strategies for local adjustment (Kogi, 1998). Gärtner et al. (2019) reviewed regulatory approaches towards shift work in four regions: Australasia, East Asia (China, Japan, and the Republic of Korea), Europe, and North America. The most prescriptive regulations are found in European countries, with a focus on limiting features of schedules such as the maximum number of work hours per day, the amount of rest time after shift work, and minimum break times (Gärtner et al., 2019). EU countries have sometimes implemented regulations in a different way at the national, sector, and company levels. Asian countries such as Japan and the Republic of Korea focus more specifically on protecting at-risk workers such as pregnant and nursing women, and requiring health examinations for night shift workers, without night work limits for the general working population. In all four regions, specific industries and occupations have separate regulations for shift work (Gärtner et al., 2019). Examples include: the transport sector, including highway commercial truck, bus, or coach; rail, aviation, and maritime operations; the health-care sector, particularly nurses; and nuclear power plant operations.

The USA is less regulated than Europe with respect to shift work, except for certain sectors such as transport, maritime, and nuclear power plant operation (Gärtner et al., 2019). In Australia, states and territories have adapted national workplace health and safety and labour laws to regulate shift work, with specific industries in the transport and mining sectors governed by an industry regulator. Japan and the Republic of Korea regulate aspects of night work; Japan has sector-specific regulations for drivers and nurses. International guidelines have been issued separately by the ILO and the European Council in the last several decades, addressing the organization of shift and night work. These guidelines are detailed in the following sections.

## Table 1.3 Co-exposures in industries and occupations in which night shift work is common, other than aircrew

| Type of industry or occupation | Agent(s) | Reference(s) |
|---|---|---|
| *Manufacturing* | | |
| Oil refining and petrochemicals | Bitumen, benzene, 1,3-butadiene | Burstyn et al. (2000), Akerstrom et al. (2016) |
| Printing | Trichloroethylene, toluene, ethyl alcohol, ethyl acetate | Fischer et al. (2001), Bakke et al. (2007) |
| Textiles, cloth weaving, knitting, dyeing | Trichloroethylene, formaldehyde, dyes, solvents, metals, cotton and other dusts, pesticides | Wernli et al. (2006), Bakke et al. (2007) |
| Shoe manufacturing | PAHs | Costantini et al. (2009) |
| Rubber and rubber products manufacturing | 1,3-Butadiene, carbon black, vinyl chloride, carbon disulfide, silicates, *N*-nitrosamines, PAHs, solvents | Kromhout et al. (1994), Oury et al. (1997), Dost et al. (2000), De Vocht et al. (2005), Hanley et al. (2012) |
| Plastics and composites manufacturing | Methylene chloride, styrene | Collins et al. (2013), Christensen et al. (2018) |
| Welding, metal working, soldering | Lead fume, lead oxide dust, metalworking fluids, metals, solvents, oil mist | Park et al. (2009a, b), Meeker et al. (2010), Behrens et al. (2012) |
| Metal plating and coating | Metal, acid mists, solvents | Pollán & Gustavsson (1999) |
| Smelting | Benzo[*a*]pyrene, PAHs | Healy et al. (2001), Tuominen et al. (2002), Sanderson et al. (2005) |
| Automobile electronics manufacturing | Fibreglass dust, coatings, lead-based solder, 1,1,1-trichloroethane, trichloroethylene, asbestos | De Bono et al. (2019) |
| *Transportation other than flying* | | |
| Railway employees | Asbestos, diesel exhaust | Preller et al. (2008) |
| Seafarers | Diesel particulate, metal abrasion compounds, asbestos | Oldenburg et al. (2010) |
| Marine transportation | Diesel exhaust, PAHs | Pronk et al. (2009) |
| Large truck and bus drivers | Diesel exhaust, PAHs, gasoline, diesel fuel, asbestos, metals | Pronk et al. (2009), Boffetta (2012) |
| *Retail and services* | | |
| Hairdressers, barbers | Dyes, solvents, talc, formaldehyde | Hollund & Moen (1998) |
| Butcher, meat cutter | PAHs, nitrosamines, animal viruses | Guo et al. (2017) |
| Tollbooth operators | Diesel exhaust, PAHs, gasoline, diesel fuel | Sapkota et al. (2005) |
| *Agriculture* | | |
| Farmers | Pesticides, animal dust, fertilizers, metals, wood dust, solvents, gasoline and/or diesel fuel and/or exhaust | Band et al. (2000) |
| Greenhouse workers | Pesticides | Dolapsakis et al. (2001) |
| *Information and communications* | | |
| Telephone industry | Non-ionizing radiation | Dosemeci & Blair (1994) |
| Radio and telegraph | Non-ionizing radiation | Tynes et al. (1996) |

PAH, polycyclic aromatic hydrocarbon.

### 1.4.2 General working population

ILO night work guidelines include the ILO Night Work Convention, 1990 (No. 171), referred to as C171 (ILO, 1990a), and the ILO Night Work Recommendation, 1990 (No. 178) (ILO, 1990b), referred to as R178. ILO C171 and ILO R178 together establish a comprehensive system for the regulation of night work and the protection of night workers. Guidelines in C171 set the minimum standard for adoption by national authorities and carry more weight than the recommendations in R178. Regarding the length of night work, R178 contains detailed but non-binding guidelines; R178 also calls for night work overtime to be avoided as far as possible.

C171 and R178 (ILO, 1990a, b) define "night work" generally as all work that is performed during a period of not less than 7 consecutive hours, including the interval from midnight to 05:00. "Night worker" refers to employees working a substantial number of hours of night work exceeding a specified limit, although individual national authorities may implement this differently.

Both C171 and R178 apply to all employed persons, except those employed in agriculture, stock raising, fishing, maritime transport, and inland navigation. C171 does not specify limits to night work. R178 recommends that work for night workers should not exceed 8 hours in any 24-hour period, with additional specifications and exceptions.

The EU WTD "Concerning certain aspects of the organisation of working time" (European Commission, 2003) focuses on key aspects of night work in a less detailed manner than the ILO guidelines. The definition of "night" in the directive is similar to that of the ILO guidelines, but the definition of "night worker" in the directive is different from that of ILO C171 and R178.

The EU WTD (European Commission, 2003) sets minimum health and safety requirements for the organization of working time. Although Member States may opt out of certain provisions, they may not opt out of night and shift work limits. The directive is applicable to all sectors of activity with some derogation. "Night time" is defined as any period of not less than 7 hours, as defined by national law, and which must include, in any case, the period between midnight and 05:00. "Night worker" means (a) any worker who normally works at least 3 hours of their daily shift at night time or (b) any worker who works a certain proportion of their annual working time at night time, defined by either Member State legislation or collective agreement.

"Shift work" is defined as "any method of organizing work in shifts whereby workers succeed each other at the same work stations according to a certain pattern, including a rotating pattern, and which may be continuous or discontinuous, entailing the need for workers to work at different times over a given period of days or weeks". "Shift worker" means "any worker whose work schedule is part of shift work". "Shift workers" may also be "night workers" (European Commission, 2017).

The EU WTD defines binding parameters regarding the length of night work, and its Preamble states that night work overtime should be limited. Some European countries have implemented the EU WTD through national legislation, and these implementations vary.

General trends in the use of night work have been summarized by Lee et al. (2007).

### 1.4.3 Women during pregnancy and around childbirth

ILO R178 Section VI recommends that "at any point during pregnancy, once this is known, women night workers who so request should be assigned to day work, as far as is practical" (ILO, 1990b). ILO C171 Article 7 specifies that measures shall be taken to ensure that an alternative to night work is available to women workers before or after childbirth, or if medically necessary (ILO, 1990a).

The EU WTD does not specifically address pregnant or nursing women, but specifies that Member States may do so (European Commission, 2017, p. 14). EU Council Directive 92/85/EEC (EU-OSHA, 1992) forced Member States to ensure that women are not obliged to perform night work during their pregnancy and for a period after childbirth, as determined by the national authority competent for safety and health.

### 1.4.4 Young people

Night work by children or young people is not addressed by either ILO C171 or R178 (ILO, 1990a, b). ILO provisions for children and young people are found in Night Work of Young Persons (Industry) Convention No. 90 (Revised), 1948 (ILO, 1948); Night Work of Young Persons (Non-Industrial Occupations) Convention No. 79, 1946 (ILO, 1946); and Night Work of Children and Young Persons (Agriculture) Recommendation No. 14, 1921 (still in effect) (ILO, 1921). ILO Convention No. 79 applies to all occupations except for industrial, agricultural, or maritime occupations. ILO Convention No. 90 applies to all industries, but particularly to textiles, recycling, mining, construction, transport, shipbuilding, and power.

With some exceptions and additional specifications, the ILO advises that young people aged < 18 years should not be employed at night, with modifications for those aged < 14 years and 14 to < 18 years, and those in agricultural jobs (ILO, 1921, 1946, 1948).

### 1.4.5 Industry sector

#### (a) Long-distance drivers

The ILO has two sets of guidelines for long-distance drivers: Hours of Work and Rest Periods (Road Transport) Convention No. 153 (ILO, 1979a) and Hours of Work and Rest Periods (Road Transport) Recommendation No. 161 (ILO, 1979b). Both limit the maximum total driving time, including overtime, to less than 9 hours per day and 48 hours per week. Night work is not addressed.

In Europe, Regulation (EC) No. 561/2006 regulates driving times and rest periods for all drivers of road haulage and passenger transport vehicles, with specific exceptions and national derogations (European Commission, 2006). The rules limit driving to 9 hours per day (up to 10 hours twice a week), 56 hours per week, and 90 hours per fortnight. Daily rest period is at least 11 hours (9 hours up to 3 times a week) and can be split with specifications. In Australia, the Heavy Vehicle National Regulation governs drive time (Gärtner et al., 2019). Regulations permit either adhering to detailed prescriptive rules or using a fatigue management programme. Drive time is limited to 10 hours in any 11-hour period and 12 hours per 24-hour period. Additional rules govern cumulative work limits, and minimum and cumulative rest limits.

The United States Department of Transportation has established limits for drivers of property-carrying vehicles in interstate commerce (Gärtner et al., 2019). Time on-duty is limited to 14 hours with driving limited to 11 hours. Under "adverse conditions", up to 2 additional hours of driving are permitted. At least 10 hours of off-duty time is required between on-duty periods.

Brazil implemented limits for long-distance drivers in 2015 (Presidência da República Brasil, 2015). The maximum driving interval is limited to 5.5 consecutive hours, with a daily maximum of 14 hours and a minimum of 11 hours rest between two shifts.

#### (b) Seafarers

The ILO recommendations for maritime, fishing, or dock work do not address night work or shift work. ILO Convention No. 180 Concerning Seafarers' Hours of Work and the Manning of Ships (ILO, 1996) applies to seagoing ships and commercial maritime fishing. It advises that the maximum hours of work must not exceed 14 hours in any 24-hour period, with additional specifications. The ILO Maritime Labour Convention No. 96 (ILO, 2006) specifies the same work limits and rest periods as ILO Convention No. 180 (ILO, 1996).

*(c) Aviation*

Shift work and night work are integral to civil aviation and are not directly regulated (Banks et al., 2012). The International Civil Aviation Organization (ICAO) uses a prescriptive approach with defined duty and rest time limits as well as a performance-based approach for fatigue risk management (ICAO, 2016). Missoni et al. (2009) summarized pilot duty time and rest time limits for 10 ICAO member countries. More recently, Banks et al. (2012) reviewed fatigue regulations, duty time limits, and sleep and/or rest requirements for 117 ICAO Member States. Some regulations limit the flight duty period during the circadian low (the period during which the body is programmed to sleep), or recommend avoiding scheduling crews for duty during this time.

An EU Directive (2000/79/EC) (EU-OSHA, 2000) addresses minimum standards for working time in civil aviation. The directive provides for a maximum annual working time of 2000 hours, with total flight time limited to 900 hours, per year.

*(d) Railway*

In both Europe and Australia, rail employee duty time limits are complex and regionalized; Australia also requires the use of a fatigue management system (Gärtner et al., 2019; ONRSR, 2019). The USA regulates duty for freight, passenger, signal, and dispatching train employees (Office of the Federal Register, 2019a, b). Duty time is limited to 12 hours maximum with a rest time of 10 hours per 24-hour period. Minimum rest periods differ by rail type (Gärtner et al., 2019).

*(e) Maritime*

United States non-defence maritime work must comply with Standards of Training, Certification and Watchkeeping for Seafarers (IMO, 2010; Office of the Federal Register, 2019c). Merchant mariners are required to receive a minimum of 10 hours rest within a 24-hour period in one or two periods, with additional limits per week. Watch worker duty limits range from 8–15 hours maximum within 24 hours, with a maximum of 36 hours working during any 72-hour period.

Canadian maritime duty time limits vary by vessel type and location. In general, work time is limited to 14 hours in any 24-hour period and 72 hours in any 7-day period. Workers must receive at least 6 hours of rest every 24 hours and 16 hours of rest during every 48-hour period, with no more than 18 hours between the end of a rest period and the beginning of the next rest period (Minister of Justice, Canada, 2019).

### *1.4.6 Country*

A selection of country-specific regulations on night work are summarized in Table S1.4 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). Regulations vary widely between countries and regions (Lee et al., 2007).

## 1.5 Quality of exposure assessment in key epidemiological studies

Section 1.3.2 introduced the main methods used in the exposure assessment of night shift work and some of their quality issues. Table 1.5 provides recommendations for the categorization of the quality of exposure assessment methodologies, focusing on the type of assessment (objective, subjective, and JEM) and definition of night work.

This section also examines various shift domains, including several presented by the workgroup report of Stevens et al. (2011) that are recommended for the evaluation of exposure to night shift work and transmeridian flights in studies of cancer (Table 1.6). Suggestions for metrics to characterize the quality of various shift domains are also provided. Because the use of night shift work is critical in assessing the relationship between shift work and cancer, shift domains capturing exposure assessment for night work are prioritized. For aircrew, domains capturing exposure assessment for flying over time zones, which include night flying (night work), are considered.

Table 1.6 summarizes categories, definitions, epidemiological relevance, and justification for the different domains of exposure assessment examined. Most categories within domains in this table refer to the order of optimal information for exposure assessment; others provide information about the nature of the exposure that could influence the interpretation of the evidence.

### *1.5.1 Quality of exposure assessment in primary studies*

See Tables S1.7–1.13 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593) for a quality appraisal of the exposure assessment in the studies of human cancer reviewed.

Quality appraisals were based on exposure information and analyses reported in the study under consideration. This does not preclude the possibility that additional information has been collected or reported in other studies based on the same cohorts or populations.

Domains for the review of the quality of the exposure assessment methodologies for night shift work and flying over time zones in epidemiological studies of cancer were evaluated as described above. In brief, "type of assessment" refers to how information on night shift work was collected in each study (i.e. objective, subjective, or JEMs). The "definition of night shift" was compatible with the definitions of the ILO (1990a, b), the EU WTD (European Commission, 2003), and Stevens et al. (2011).

Domains for the review of the quality of the exposure assessment for night shift work and flying over time zones in epidemiological studies of cancer were also assessed for each study as follows.

- *Reference group: past or present schedule includes night shift work* examines whether individuals performing night work could be included in the reference group. Contamination of the reference group can occur when it includes subjects with a limited intensity of night work (e.g. less than one shift per week or month) or those with an alternative schedule (e.g. permanent night workers included in the reference group in analyses of the effects on rotating night workers). It is important to note that contamination of the reference group can also occur as a result of missing information on lifetime tenure (this information is captured in the *duration of exposure to night shift work* domain).
- *Intensity of exposure to night shift work* refers to the number of night shifts performed within a certain period of time (e.g. week or month).
- *Duration of exposure to night shift work* refers to the number of years spent performing night shift work.
- *Temporality of exposure to night shift work* refers to information on start and end dates of night shift work. Such information allows age-specific risk analyses (e.g. stratified analyses by menopausal status).
- *Type of night shift work schedule* refers to the differentiation between, for example, permanent and rotating shift work schedules.

**Table 1.5 Domains for the review of quality of exposure assessment methodologies for night shift work and flying over time zones in epidemiological studies of cancer**

| Domain | Categories | Definition/clarification | Epidemiological relevance | Justification |
|---|---|---|---|---|
| Type of assessment | 1. Objective<br>2. Subjective<br>3. JEM | Objective data include registry data of actual individual-based working hours and analysis of document-based shift rota tables (note that planned and executed shifts may differ)<br>Subjective data include surveys, interview, and diary data, where the information is obtained from the employees themselves<br>JEMs in shift work research combine information on job title with information on estimated average exposure to shift work for each job title, based on earlier questionnaire-based evaluation in other populations | Objective data are generally more accurate than subjective information, as recall bias may affect the latter; however, objective data may be incomplete (e.g. by not capturing second jobs, or because temporary workers, contractors, and small- and medium-sized enterprises may not be captured by registries)<br>General population studies using JEMs are generally less informative than industry-based JEMs (with specific links between occupation and night work) and objective and/or subjective data | The use of objective data is more accurate and less sensitive to selection, attrition, and reporting bias; however, there is a good correlation between self-reported and objective data for some work schedules (e.g. permanent night work and shift work with night shifts) (Härmä et al., 2018a) |
| Definition of night shift | 1. Defined, includes exposure to night work for at least 3 hours between 23:00 and 06:00<br>(For aircrew studies: defined, includes a flight of at least 3 hours between 22:00 and 08:00 based on the local time before the flight)<br>2. Defined, other<br>3. Undefined | Category 1 includes the studies using the earlier recommendation by Stevens et al. (2011) and the definitions based on ILO C171 and R178 and the EU WTD, where the 3-hour exposure window is covered in a period of 7 hours that must include the period from midnight to 05:00 | An operational definition of night work (as provided in Categories 1 and 2) is essential to enable comparisons between studies and to ensure coverage of work during the biological night<br>Studies that do not define night shift (Category 3) should be given less weight, as it is unclear what exact exposure circumstance is covered | At least 3 hours from 23:00 to 06:00 is close to the biological night and compatible with ILO C171 and R178 and the EU WTD definitions, as well as with the Stevens et al. (2011) definition |

C171, (ILO) Night Work Convention, 1990 (No. 171); EU, European Union; ILO, International Labour Organization; JEM, job-exposure matrix; R178, (ILO) Night Work Recommendation, 1990 (No. 178); WTD, European Working Time Directive No. 2003/88/EC.

**Table 1.6 Domains for the review of quality of exposure assessment metrics for night shift work and flying over time zones in epidemiological studies of cancer**

| Domain | Categories | Definition/clarification | Epidemiological relevance | Justification |
|---|---|---|---|---|
| Reference group: past or present schedule includes night shift work | 1. Yes<br>2. No<br>3. Undefined | This domain refers to the definition of the reference group used within an individual study; contamination of the reference group can occur when the applied exposure categorization of the reference group includes subjects with some degree of exposure to night shift work; this may include subjects exposed to a lower intensity of night shift work (e.g. < 1 shift/week or month) or with an alternative schedule (e.g. when permanent night workers are included in the reference group) | Reference populations in night shift work studies may have been exposed to night work, leading to contamination of the reference group; it is important to note that contamination of the reference group can also occur as a result of missing information on lifetime tenure, which is captured in another domain ("Duration of exposure to night shift work")<br>Evidence of a contaminated reference group should be noted, but this is not necessarily a basis for exclusion; the impact of a contaminated control group should be judged on a study-by-study basis | Under the assumption that any form of night shift work increases cancer risk, a contaminated control group results in risk estimates that are biased towards the null |
| Intensity of exposure to night shift work | 1. Precise information available (number of night shifts in a week, month, or year)<br>2. Imprecise, or limited, information available<br>3. No information available | Number of non-day shifts per unit of time (e.g. month or year) | Stevens et al. (2011) defined intensity for non-day shifts but not for night shifts, which are probably most important for circadian disruption; studies with information on intensity are of a higher quality than those without | Different shift working populations within and across studies may differ strongly in relation to intensity of night shift work |

**Table 1.6 (continued)**

| Domain | Categories | Definition/clarification | Epidemiological relevance | Justification |
|---|---|---|---|---|
| Duration of exposure to night shift work | 1. Complete information (includes the number of cumulative exposure years)<br>2. Partial information (information available only for a limited time period of the subject's work history)<br>3. Partial information (information available at one time-point only e.g. "do you currently work night shifts?")<br>4. No information | Completeness of information in cohort studies refers to coverage of the time period up to the point of exposure data collection | Duration of exposure is generally believed to be an important component of risk; however, in some studies there is an extended time period between last exposure data collection and end of health follow-up, which results in incomplete exposure information; studies with partial or no information in this domain should therefore be given less weight | Information on long-term exposure to night shift work can be used to assess cancer risk (Hansen, 2017) |
| Temporality of exposure to night shift work | 1. Complete information<br>2. Partial information<br>3. No information | | Information on timing of exposure could be important to explain heterogeneity in epidemiological studies; however, because of uncertainties about the effect of temporality of exposure and relevant exposure definitions (windows, lags), this criterion alone should not be used to evaluate informativeness of studies | Information on timing of exposure has been noted as a potentially important source of differences between studies (e.g. studies involving older people who had not been exposed to night work recently) |
| Type of night shift work schedule | 1. Permanent night shift<br>2. Rotating night shift<br>3. Imprecise, or limited, information available<br>4. No information available | | Information on type of night work schedule could be important to explain heterogeneity in epidemiological studies; studies with no information on the type of night work should be given less weight because of uncertainty about the definition of the exposure metric | |

**Table 1.6 (continued)**

| Domain | Categories | Definition/clarification | Epidemiological relevance | Justification |
|---|---|---|---|---|
| Number of consecutive night shifts (or speed of rotation) | 1. Precise information available<br>2. Imprecise, or limited, information available<br>3. No information available | The number of consecutive night shifts is relevant for both permanent and rotating night work; in studies of rotating night work, "speed of rotation" is sometimes used to describe this concept | Information on number of consecutive night shifts could be important to explain heterogeneity in epidemiological studies; however, because of uncertainties about the effect of the number of consecutive night shifts worked and relevant exposure definitions, this criterion alone should not be used to evaluate informativeness of studies | The number of consecutive night shifts is associated with circadian adjustment and/or disruption (Härmä et al., 2006, 2018b; Sallinen & Kecklund, 2010) |
| Direction of night shift rotation | 1. Precise information available<br>2. Imprecise, or limited, information available<br>3. No information available | Using 8-hour shifts as an example, forward rotation means that morning or day shifts are followed by afternoon or evening shifts, and finally by night shifts (clockwise); backward rotation follows the opposite pattern (counter-clockwise) | Information on direction of night shift rotation could be important to explain heterogeneity in epidemiological studies; however, because of uncertainties about the effect of night shift rotation direction and relevant exposure definitions, this domain alone should not be used to evaluate informativeness of studies | Direction of rotation, often interacting with the speed of rotation, can influence circadian disruption; quick forward rotating shift systems appear to be less disruptive because of faster re-adaptation after the night shift and fewer quick returns (< 11 hours between work shifts) (Driscoll et al., 2007; Bambra et al., 2008; Sallinen & Kecklund, 2010) |
| Start and end times of all shifts | 1. Precise information available<br>2. Imprecise, or limited, information available<br>3. No information available | | Information on start and end times of all shifts could be used to explain heterogeneity in epidemiological studies; however, because of uncertainties about the effect of start and end times and relevant exposure definitions, this domain alone should not be used to evaluate informativeness of studies | Information on the start and end times of shifts (especially early morning and night) gives additional information on exposure to night work during the biological night; it also allows better estimation of on- and off-job (e.g. commuting) activities during the biological night |

**Table 1.6 (continued)**

| Domain | Categories | Definition/clarification | Epidemiological relevance | Justification |
|---|---|---|---|---|
| Flying over time zones | 1. Information available on the mean number of time zones crossed in a time period, or information on cumulative number of time zones crossed<br>2. Imprecise, or limited, information available (e.g. the number of intercontinental flights in a year)<br>3. No information available | | Accurate information on the number of time zones crossed is essential to judge the extent of circadian disruption, and precise information is preferred; studies with limited information should therefore be given less weight in epidemiological synthesis, and studies with no information (Category 3) are considered non-informative | Flying (quickly) over time zones (transmeridian travel) causes circadian disruption as a result of disparities between external time cues and internal circadian rhythms (Härmä et al., 1994) |

- *Number of consecutive night shifts* refers to the number of successive shifts performed. In studies of rotating night work, "speed of rotation" is sometimes used to describe this concept.
- *Direction of night shift rotation* refers to the ordering of subsequent shifts (e.g. clockwise vs counter-clockwise rotation).
- *Start and end times of all shifts* provides additional information on exposure to night work during the biological night, as well as on- and off-job (e.g. commuting) activities during the biological night.

For each domain, the Working Group indicated whether information existed in detail, if some information was available, or if information was absent; additional detail was provided in some cases (e.g. type of night shift work schedule).

For epidemiological studies among aircrew, the Working Group also examined information on flying over time zones and cumulative time spent working in the standard sleep interval. In this case, a distinction is made between information on mean or cumulative time zones crossed, approximation of transmeridian travel by number of flights within a certain time frame, or other information.

The assessed studies are grouped according to cancer site and study design, with differentiation between aircrew studies and other.

### *(a) Cancer of the breast among night shift workers other than aircrew*

#### *(i) Cohort and nested case–control studies*

Assessments for cohort and nested case–control studies of cancer of the breast among night shift workers other than aircrew are provided in Table S1.7 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). Most studies used objective or subjective methods (Schernhammer et al., 2001, 2006; Lie et al., 2011, 2013; Hansen & Lassen, 2012; Hansen & Stevens, 2012; Knutsson et al., 2013; Koppes et al., 2014; Åkerstedt et al., 2015; Travis et al., 2016_Million Women; Travis et al., 2016_EPIC; Travis et al., 2016_UK Biobank; Vistisen et al., 2017; Wegrzyn et al., 2017; Jones et al., 2019) with individual-level information on exposure. One study combined subjective and JEM methods (Pronk et al., 2010). The remaining studies used JEMs (Tynes et al., 1996; Lie et al., 2006; Li et al., 2015); these were all industry-based studies, for example, in textile workers (Li et al., 2015), in nurses subdivided into jobs with and without night work (Lie et al., 2006), and in radio and telegraph operators or those present in the radio room on ships (Tynes et al., 1996).

"Night shift" was defined as working for 3 hours or more between 23:00 and 06:00 in a small number of studies (Lie et al., 2011; Travis et al., 2016_Million Women; Travis et al., 2016_UK Biobank; Vistisen et al., 2017). Some studies defined "night shift" in other ways (Pronk et al., 2010; Hansen & Lassen, 2012; Hansen & Stevens, 2012; Knutsson et al., 2013; Lie et al., 2013; Koppes et al., 2014; Li et al., 2015; Jones et al., 2019). "Night shift" was undefined in the remaining studies (Tynes et al., 1996; Schernhammer et al., 2001, 2006; Lie et al., 2006; Pronk et al., 2010; Åkerstedt et al., 2015; Travis et al., 2016_EPIC; Wegrzyn et al., 2017). [The Working Group noted that the study by Pronk et al. (2010) contains multiple definitions of "night shift".]

In some studies the reference group was assessed as not including night shift work (Hansen & Lassen, 2012; Hansen & Stevens, 2012; Lie et al., 2013; Li et al., 2015; Travis et al., 2016_Million Women; Travis et al., 2016_UK Biobank). In the remaining studies, it was unclear if the reference group included night shift workers (Tynes et al., 1996; Schernhammer et al., 2001, 2006; Lie et al., 2006; 2011; Pronk et al., 2010; Knutsson et al., 2013; Koppes et al., 2014; Åkerstedt et al., 2015; Travis et al., 2016_EPIC; Vistisen et al., 2017; Wegrzyn et al., 2017; Jones et al., 2019).

Precise information on intensity was available in some studies (Pronk et al., 2010; Lie et al., 2011, 2013; Hansen & Lassen, 2012; Hansen & Stevens, 2012; Li et al., 2015; Jones et al., 2019), but the majority provided imprecise or no information on intensity (Tynes et al., 1996; Schernhammer et al., 2001, 2006; Lie et al., 2006; Pronk et al., 2010; Knutsson et al., 2013; Koppes et al., 2014; Åkerstedt et al., 2015; Travis et al., 2016_Million Women; Travis et al., 2016_EPIC; Travis et al., 2016_UK Biobank; Vistisen et al., 2017; Wegrzyn et al., 2017). [The Working Group noted that the study by Pronk et al. (2010) contains multiple types of information on intensity.]

Complete information on duration of exposure to night shift work, typically lifetime occupational history collected in interviews, was available in the following studies (Schernhammer et al., 2001, 2006; Pronk et al., 2010; Lie et al., 2011; Hansen & Lassen, 2012; Hansen & Stevens, 2012; Åkerstedt et al., 2015; Travis et al., 2016_Million Women; Travis et al., 2016_EPIC; Wegrzyn et al., 2017). Other studies reported partial information in terms of exposure assessment either over a limited time period (Tynes et al., 1996; Lie et al., 2006, 2013; Knutsson et al., 2013; Li et al., 2015; Vistisen et al., 2017; Jones et al., 2019) or at a single time-point only (Koppes et al., 2014; Travis et al., 2016_UK Biobank). [The Working Group noted that the study by Wegrzyn et al. (2017) contains multiple types of information on duration.]

Only a few studies included complete information on temporality of exposure (Pronk et al., 2010; Travis et al., 2016_Million Women; Vistisen et al., 2017; Jones et al., 2019).

Precise information on number of consecutive night shifts was provided in the studies by Lie et al. (2011, 2013).

Precise information on type of night shift work schedule was reported in Lie et al. (2011, 2013), Hansen & Stevens (2012), and Li et al. (2015).

Information on direction of night shift rotation and precise information on start and end time of shifts were not reported in any of the evaluated studies.

*(ii) Case–control studies*

Table S1.8 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593) provides summaries of case–control studies of cancer of the breast among night shift workers other than aircrew. A detailed description of exposure assessment considerations for the case–control study deemed most informative (i.e. Cordina-Duverger et al., 2018) is provided below, followed by such considerations across all case–control studies.

Cordina-Duverger et al. (2018) conducted a pooled analysis of five population-based case–control studies with complete work history; all were conducted using interview- or questionnaire-based exposure assessment. Information on work schedules was obtained for each job held longer than 6 months (12 months in Spain). The definition of night work exposure varied across studies; in the combined analyses night work was defined as any job that included 3 hours or more of work between midnight and 05:00. Based on this definition, exposure indicators included ever/never, duration in years, length of night shifts (hours), and years since last night shift. Additional analyses that considered shift frequency (including four of the five studies) examined intensity of night work (nights per week), lifetime cumulative number of night shifts, and number of night hours worked per week. Combined variables (intensity × duration of night work, intensity × length of night shift, and intensity × years since last night shift) were also considered.

All studies used objective or subjective methods (Davis et al., 2001; O'Leary et al., 2006; Pesch et al., 2010; Grundy et al., 2013; Menegaux et al., 2013; Rabstein et al., 2013, 2014; Wang et al., 2015a; Cordina-Duverger et al., 2016, 2018; Papantoniou et al., 2016; Fritschi et al., 2013, 2018; Yang et al., 2019) with individual-level information on exposure.

In the majority of studies, exposure to night shift was defined as at least 3 hours working time between 23:00 and 06:00 (Davis et al., 2001; Pesch et al., 2010; Menegaux et al., 2013; Rabstein et al., 2013, 2014; Wang et al., 2015a; Cordina-Duverger et al., 2016, 2018; Papantoniou et al., 2016; Fritschi et al., 2018). Three studies used other definitions (O'Leary et al., 2006; Fritschi et al., 2013; Grundy et al., 2013), and night shift work was undefined in the studies by Grundy et al. (2013) and Yang et al. (2019). [The Working Group noted that the study by Grundy et al. (2013) contains multiple definitions of night shift.]

In most studies the reference group was assessed as not including night shift work (Davis et al., 2001; Grundy et al., 2013; Menegaux et al., 2013; Wang et al., 2015a; Cordina-Duverger et al., 2016, 2018; Papantoniou et al., 2016; Fritschi et al., 2018; Yang et al., 2019); it was unclear if the reference group included night shift work in the remaining studies (O'Leary et al., 2006; Pesch et al., 2010; Fritschi et al., 2013; Rabstein et al., 2013, 2014).

Precise information on intensity was available in some studies (Davis et al., 2001; O'Leary et al., 2006; Grundy et al., 2013; Menegaux et al., 2013; Cordina-Duverger et al., 2016, 2018; Papantoniou et al., 2016); the remainder reported imprecise or no information on intensity (Pesch et al., 2010; Rabstein et al., 2013, 2014; Wang et al., 2015a; Fritschi et al., 2013, 2018; Yang et al., 2019).

Complete information on duration of exposure to night work was reported in some studies (Davis et al., 2001; Grundy et al., 2013; Menegaux et al., 2013; Cordina-Duverger et al., 2016, 2018; Papantoniou et al., 2016), typically in the form of lifetime occupational history collected in interviews. Others had partial information in terms of exposure assessment over a limited time period (O'Leary et al., 2006; Pesch et al., 2010; Rabstein et al., 2013, 2014; Fritschi et al., 2013, 2018). No information on duration of exposure to night work was noted in the studies by Wang et al. (2015a) and Yang et al. (2019).

Some studies included analysis using information on temporality of exposure (Davis et al., 2001; O'Leary et al., 2006; Pesch et al., 2010; Grundy et al., 2013; Menegaux et al., 2013; Cordina-Duverger et al., 2016, 2018), for example, time since last night shift (Cordina-Duverger et al., 2018), whether night work had been undertaken before first pregnancy (Cordina-Duverger et al., 2018), and night work in the 10 years before diagnosis (Davis et al., 2001).

Precise information on type of night shift work schedule was reported in Davis et al. (2001), O'Leary et al. (2006), and Papantoniou et al. (2016).

Precise information on start and end time of shifts was available in the studies by Davis et al. (2001), Menegaux et al. (2013), Cordina-Duverger et al. (2018), Fritschi et al., 2013, 2018).

No information on number of consecutive night shifts and direction of night shift rotation was provided in any of the studies evaluated.

#### (b) *Cancer of the prostate among night shift workers other than aircrew*

Summaries of studies of cancer of the prostate among night shift workers other than aircrew (any design) are reported in Table S1.9 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). All studies used objective or subjective methods (Kubo et al., 2006, 2011; Conlon et al., 2007; Parent et al., 2012; Gapstur et al., 2014; Yong et al., 2014a, b; Hammer et al., 2015; Papantoniou et al., 2015; Dickerman et al., 2016; Åkerstedt et al., 2017; Behrens et al., 2017; Tse et al., 2017; Wendeu-Foyet et al., 2018; Barul et al., 2019; Kogevinas et al., 2019) with individual-level information on exposure.

Exposure to night shift was defined as at least 3 hours of work between 23:00 and 06:00 in some studies (Parent et al., 2012; Yong et al., 2014a, b; Hammer et al., 2015; Barul et al., 2019); most studies used other definitions (Kubo et al., 2011; Gapstur et al., 2014; Papantoniou et al., 2015; Behrens et al., 2017; Tse et al., 2017; Wendeu-Foyet et al., 2018; Kogevinas et al., 2019) and night shift was undefined in the remainder (Kubo et al., 2006; Conlon et al., 2007; Dickerman et al., 2016; Åkerstedt et al., 2017).

In most studies the reference group was assessed as not including those exposed to night shift work (Kubo et al., 2011; Parent et al., 2012; Yong et al., 2014a, b; Papantoniou et al., 2015; Behrens et al., 2017; Tse et al., 2017; Wendeu-Foyet et al., 2018; Barul et al., 2019). It was unclear if the reference group included those exposed to night shift work in the following studies: (Kubo et al., 2006; Conlon et al., 2007; Gapstur et al., 2014; Dickerman et al., 2016; Åkerstedt et al., 2017). The reference group included those exposed to night shift work in the studies by Hammer et al. (2015) and Kogevinas et al. (2019).

A few of the studies had precise information on intensity of night shift work (Wendeu-Foyet et al., 2018; Barul et al., 2019; Kogevinas et al., 2019); all other studies had imprecise or no information.

Most studies had complete information on duration of exposure to night shift work, typically in the form of lifetime occupational history collected in interviews (Parent et al., 2012; Hammer et al., 2015; Papantoniou et al., 2015; Åkerstedt et al., 2017; Behrens et al., 2017; Wendeu-Foyet et al., 2018; Barul et al., 2019; Kogevinas et al., 2019). Other studies had partial information in terms of assessment over a limited time period (Conlon et al., 2007; Kubo et al., 2011; Yong et al., 2014a, b) or at a single time-point (Gapstur et al., 2014). No information on duration of exposure was available from the remainder of the studies (Kubo et al., 2006; Dickerman et al., 2016; Tse et al., 2017).

Some studies included analyses using complete information on temporality (Conlon et al., 2007; Parent et al., 2012; Yong et al., 2014a, b; Kogevinas et al., 2019).

Precise information on the number of consecutive night shifts worked was available in the studies by Wendeu-Foyet et al. (2018) and Barul et al. (2019). Direction of night shift rotation was reported in the studies by Kubo et al. (2011), Hammer et al. (2015), Wendeu-Foyet et al. (2018), and Barul et al. (2019).

Precise information on type of night shift work schedule was reported by Kubo et al. (2006, 2011), Gapstur et al. (2014), Yong et al. (2014a, b), Hammer et al. (2015), Papantoniou et al. (2015), Wendeu-Foyet et al. (2018), Barul et al. (2019), and Kogevinas et al. (2019).

Precise information on start and end time of shifts was available in the studies by Hammer et al. (2015) and Wendeu-Foyet et al. (2018).

#### (c) *Cancer of the colon and rectum among night shift workers other than aircrew*

Assessments of studies of cancer of the colon and rectum among night shift workers other than aircrew (any design) are reported in Table S1.10 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). All studies used objective or subjective methods (Schernhammer et al., 2003; Parent et al., 2012; Yong et al., 2014a, b; Gu et al., 2015; Devore et al., 2017; Jørgensen et al., 2017; Papantoniou et al., 2017, 2018) with individual-level information on exposure.

Exposure to night shift was defined as at least 3 hours of work between 23:00 and 06:00 in studies by Yong et al. (2014a, b) and Papantoniou et al. (2017). Parent et al. (2012) and Jørgensen et al. (2017) used other definitions for night shift, and it was undefined in the remaining studies (Schernhammer et al., 2003; Gu et al., 2015; Devore et al., 2017; Papantoniou et al., 2018).

The reference group was assessed as not including those exposed to night shift work in some studies (Parent et al., 2012; Yong et al., 2014a, b; Papantoniou et al., 2017), but it was unclear if the reference group included those exposed to night shift work in others (Schernhammer et al., 2003; Gu et al., 2015; Devore et al., 2017; Jørgensen et al., 2017; Papantoniou et al., 2018).

One study reported precise information on intensity (Papantoniou et al., 2017); all other studies had imprecise or no information on intensity.

Complete information on duration of exposure to night shift work, typically in the form of lifetime occupational history collected in interviews, was reported in some studies (Schernhammer et al., 2003; Parent et al., 2012; Devore et al., 2017; Papantoniou et al., 2017, 2018). The remaining studies had partial information on duration of exposure to night shift work, assessed either for a limited time period (Yong et al., 2014a, b; Gu et al., 2015) or at a single time-point (Jørgensen et al., 2017).

Some studies included analysis using complete information on temporality of exposure (Yong et al., 2014a, b; Parent et al., 2012).

Precise information on type of night shift work schedule was reported by Yong et al. (2014a, b) and Papantoniou et al. (2017).

None of the studies provided information on the number of consecutive night shifts worked, the direction of night shift rotation, or start and end times of shifts.

#### *(d) Cancer at other organ sites among night shift workers other than aircrew*

Assessments of studies of cancer of other sites among night shift workers other than aircrew (any design) are reported in Table S1.11 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). All studies used objective or subjective methods with individual information on exposure.

Exposure to night shift was defined as 3 hours or longer of work between 23:00 and 06:00 in some studies (Bhatti et al., 2013; Carter et al., 2014; Yong et al., 2014a, b; Kwon et al., 2015; Costas et al., 2016; Gyarmati et al., 2016). Different definitions were used in other studies (Parent et al., 2012; Lin et al., 2013, 2015; Carreón et al., 2014; Carter et al., 2014; Leung et al., 2019), and night shift work was undefined in the remainder of the studies (Viswanathan et al., 2007; Poole et al., 2011; Schernhammer et al., 2013; Gu et al., 2015; Heckman et al., 2017). [The Working Group noted that the study by Carter et al. (2014) contains multiple definitions of night shift.]

In several studies the reference group was assessed as not including those exposed to night shift work (Parent et al., 2012; Bhatti et al., 2013; Yong et al., 2014a, b; Kwon et al., 2015; Costas et al., 2016; Gyarmati et al., 2016; Leung et al., 2019). In other studies it was unclear if the reference group included those exposed to night shift work (Viswanathan et al., 2007; Poole et al., 2011; Lin et al., 2013, 2015; Schernhammer et al., 2013; Carreón et al., 2014; Carter et al., 2014; Gu et al., 2015; Heckman et al., 2017).

Some studies reported precise information on intensity of night shift work (Kwon et al., 2015; Costas et al., 2016; Gyarmati et al., 2016; Leung et al., 2019); all other studies had imprecise or no information on intensity.

Most studies had complete information on duration of exposure to night shift work, typically in the form of lifetime occupational history collected in interviews (Viswanathan et al., 2007; Poole et al., 2011; Parent et al., 2012; Kwon et al., 2015; Costas et al., 2016; Gyarmati et al., 2016; Heckman et al., 2017; Leung et al., 2019). Other studies reported partial information on duration of exposure, assessed either over a limited period (Bhatti et al., 2013; Schernhammer et al., 2013; Carreón et al., 2014; Yong et al., 2014a, b; Gu et al., 2015) or at a single time-point (Carter et al., 2014), or did not report any information (Lin et al., 2013, 2015).

Some studies included analysis using complete information on temporality (Parent et al., 2012; Bhatti et al., 2013; Carreón et al., 2014; Yong et al., 2014a, b; Kwon et al., 2015; Costas et al., 2016; Gyarmati et al., 2016; Leung et al., 2019).

Precise information on the number of consecutive night shifts worked and direction of night shift rotation was provided by Carreón et al. (2014) only.

Precise information on type of night shift work schedule was available in studies by Carreón et al. (2014), Carter et al. (2014), Yong et al. (2014a, b), Kwon et al. (2015), Costas et al. (2016), Gyarmati et al. (2016), and Leung et al. (2019).

Precise information on start and end time of shifts was not available in any of the studies reviewed.

#### (e) *Cancer among aircraft cockpit crew*

Assessments of studies of cancer among aircraft cockpit crew (Rafnsson et al., 2000; Pukkala et al., 2003; Yong et al., 2014c) are reported in Table S1.12 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). All studies used JEMs based on information on block hours and flight hours [The Working Group noted that “block hours” refers to gate departure to gate arrival (aircraft taxi time and air time), and “flight hours” refers to wheels off the ground to wheels on the ground (air time).] All studies reported limited or no information on flying over time zones, and night shift work was undefined. Whether the reference group included those exposed to night shift work was also unreported in all studies, and none provided precise information on intensity of night shift work. One study (Rafnsson et al., 2000) had complete information on duration of work as a pilot. One study (Pukkala et al., 2003) had complete information on temporality of exposure.

#### (f) *Cancer among aircraft cabin crew*

Summaries of studies of cancer among aircraft cabin crew are reported in Table S1.13 (Annex 1, Supplementary material for Section 1, web only; available from: http://publications.iarc.fr/593). All studies used JEMs based on information on aircraft type or airport, for example.

Some studies defined exposure to night shift as at least 3 hours of work between 22:00 and 08:00 local time at origin (Pinkerton et al., 2012, 2016, 2018; Schubauer-Berigan et al., 2015), and night shift work was undefined in other studies (Reynolds et al., 2002; Linnersjö et al., 2003; Pukkala et al., 2012).

The reference group was assessed as not including those exposed to night shift work in studies by Schubauer-Berigan et al. (2015) and Pinkerton et al. (2016, 2018); in other studies, the reference group included those exposed to night shift work (Pinkerton et al., 2012) or this was not reported (Reynolds et al., 2002; Linnersjö et al., 2003; Pukkala et al., 2012).

Precise information on intensity of night shift work was available in studies by Pinkerton et al. (2012), Pukkala et al. (2012), and Schubauer-Berigan et al. (2015).

Schubauer-Berigan et al. (2015) and Pinkerton et al. (2016, 2018) provided complete information on duration of work as a flight attendant from individual interviews; the other studies had partial information (limited period) on duration of work as a flight attendant.

Most studies had precise information on time zones crossed (Pinkerton et al., 2012, 2016, 2018; Pukkala et al., 2012; Schubauer-Berigan et al., 2015); the remainder had limited information on flying over time zones (Reynolds et al., 2002; Linnersjö et al., 2003).

Temporality of exposure to night shift work was not available in any of the studies assessed.

### 1.5.2 *Quality of exposure assessment in meta-analyses*

#### (a) *Cancer of the breast*

In the study by Liu et al. (2018), the analyses of multiple cancers were stratified by sex. Work schedules were divided into rotating shift (working a regular shift schedule), fixed shift (permanent night work), and mixed (with no clear work schedule) when this information was available for each study; in some cases, "evening" work was also considered. There were no definitions of night shift. The exposure indicators for analyses were the odds ratios of the longest (from ≥ 0.6 years to ≥ 30 years) versus shortest exposure time when this was reported in the articles considered. When exposure time was not reported, the authors used "ever versus never" exposure to the work schedule evaluated (which occurred for 10 of the 26 studies included on cancer of the breast). [The Working Group noted that 37 risk estimates for cancer of the breast are summarized in table 2 of Liu et al. (2018), although only 26 studies are described in table 1; the summary description of the exposure assessment may therefore be incomplete.] Other specific shift work properties were not characterized. Most study exposure assessments were subjective (9 based on questionnaires, 15 based on interviews, and 2 from databases).

Liu et al. (2016) examined breast cancer outcomes among female cabin crew, where this occupational title (yes/no) was used as the exposure variable. No detail on exposure assessment was provided. Specific shift work variables (e.g. time zones crossed or individual duration of exposure) and co-exposure to cosmic radiation were not considered.

Travis et al. (2016) examined 10 prospective studies (defined as those where exposure data were recorded before the onset of cancer of the breast), including 3 prospective UK studies and 7 other studies located through a literature search. Shift work schedules involving nights were variably defined across studies. The exposure indicator of ever/never worked night shifts included individual studies with varying types of indicators; for example, detail provided for the three UK studies indicated that "ever versus never exposure to night shift work" was reported in two of the studies, while "yes/no current exposure to night shift work" was reported in the other. Additional analyses assessed relative risks associated with duration of exposure to long-term shift work of 20 years or longer (eight studies included) and 30 years or longer (four studies included). Other shift work properties were not characterized.

The meta-analysis conducted by He et al. (2015) included 28 studies that evaluated the association between risk of cancer of the breast and any type of circadian disruption. Studies with differing exposures, including shift work (assessed in 15 studies), exposure to light at night (6 studies), sleep deficiency (7 studies), and employment as a flight attendant (3 studies), were grouped within one overall meta-analysis. Shift work schedules, including those involving nights, were not clearly defined. Subgroup analyses were conducted by source of circadian disruption (yes/no) as described above. Additional subgroup analyses examined studies of shift work and flight attendants combined and all studies except for those of flight attendants. Dose–response meta-analyses examined increments of 10 years of shift work (reference group: never exposed).

### *(b) Other cancers*

Studies of cancer of the prostate where the exposure of interest was shift work were examined by Du et al. (2017) and Gan et al. (2018).

Gan et al. (2018) included 15 studies; of these, 3 reported more than one shift work category. Shift work schedules were classified as rotating shifts (six studies), night shifts (eight studies), mixed schedules (four studies, three of which were aircrew populations), and evening shifts (one study). Shift work schedules, including those involving nights, were not clearly defined in most original studies included in the analyses. Exposure indicators used in full analyses were ever versus never exposure; a subset of three studies (including four reports) with information on duration of exposure was also examined in a separate analysis. Subgroup analyses by shift schedule were performed.

Nine cohort studies were included in the meta-analysis conducted by Du et al. (2017). Exposure was to shift work (six studies), night work (three studies), or occupations "related with shift work", such as aircrew (three studies) (some studies included both shift and night work). The shift work schedules under consideration, including those involving nights, were not clearly defined. The exposure indicator used was ever versus never exposure; other shift work characteristics (e.g. duration) were not assessed. Subgroup analyses examined night work and shift work separately.

Wang et al. (2015b) conducted a meta-analysis of six studies focused on night shift work and cancer of the colon and rectum. Exposure assessment was conducted via interview (four studies), questionnaire (one study), and database (one study). The shift work schedules under consideration, including shift work involving nights, were not clearly defined. The exposure indicator used in the main analyses was longest versus shortest period of night shift work reported; this consisted of ever/never exposure for four of the six studies. In a "dose-response meta-analysis" examining duration of night shift work, it was not clear which studies were included. Other specific shift work properties were not characterized. In additional analyses, stratification was conducted by exposure assessment type (e.g. self-administered questionnaire or interview).

The methods used in the meta-analysis by Liu et al. (2018) for cancers other than breast are described in the previous section on meta-analyses of cancer of the breast. When exposure time was not reported, the authors used "ever versus never" exposure to the work schedule evaluated (which occurred for 24 of the 58 studies included in this meta-analysis). Most study exposure assessments were subjective (28 based on questionnaire, 24 based on interview, and 6 from databases), with no information available on individual- versus group-level assessment. Dose information from ordinal categorical data (three or more levels of the exposure category) was used in a dose–response meta-analysis.

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