SHIFTWORK

1. Definition and Occurrence of Exposure

1.1 Definition of shiftwork

The International Labour Office (International Labour Organization, 1990a) defines working in shifts 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."

The European Council Directive 93/104 (1993) declares that "concerning certain aspects of the organisation of working time, shiftwork shall mean any method of organising work in shifts whereby workers succeed each other at the same work stations according to a certain pattern. Shiftworker shall mean any worker whose work schedule is part of shiftwork."

Besides these definitions, in the scientific literature, the term "shiftwork" has been widely used and generally includes any arrangement of daily working hours other than the standard daylight hours (7/8 am – 5/6 pm).

In most cases, shiftwork is synonymous of irregular, odd, flexible, variable, unusual, non-standard working hours.

1.2 Types of shiftwork

Several types of shiftwork exist and can be described as follows:

(*a*) permanent – people work regularly on one shift only, i.e. morning or afternoon or night; or rotating – people alternate more or less periodically on different shifts;

(*b*) continuous – all days of the week are covered; or discontinuous – interruption on weekends or on sundays;

(*c*) 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/year can vary

considerably. Moreover, the definition of "period of night work" varies from country to country, i.e. in some countries it ranges from 8, 9 or 10 pm to 5, 6 or 7 am, and in many others from 11 or 12 pm to 5 or 6 am (See Table 1.1).

Table 1.1. Definitions of night work and night worker in some European countries

COUNTRY	NIGHT TIME/NIGHT WORK	NIGHT WORKER
AUSTRIA	Night work: period between 22:00 and 05:00	The workers who work at least 3 hours between 22:00 and 05:00 on at least 48 nights per year (EU-Nachtarbeits-Anpassungsgesetz 2002)
BELGIUM	Night work: a period, generally of 8 hours, between 20:00 and 06:00	Loi du 17/02/1997 et Loi du 04/12/1998: Act of 17 February 1997
FINLAND	Night work: Work carried out between 23:00 and 06:00	Night shift refers to a work shift with at least 3 hours of duty between 23:00 and 06:00 (Working Hours Act 605/1996)
FRANCE	Night time: a period between 22:00 and 05:00 Night work: whichever work period between midnight and 05:00	Any employee working usually at least 2 times per week for at least 3 hours over the period defined as night work (Loi 461/1998)
GERMANY	Night time: the time between 23:00 and 06:00 (in case of bakers between 22:00 and 05:00). Night work: all work which occupies more than 2 hours of night time	"Night workers" means workers who usually work nights on rotating shifts schedules, or work at night for not less than 48 days in a calendar year (Arbeitszeitgesetz 1994)
GREECE	Night time: a period of 8 hours which includes the period between 22:00 and 06:00	A worker who during night time works at least 3 hours of his/her daily working time or a worker who has to perform night work for at least 726 hours of his/her annual working time (Presidential Decree n. 88/1999)
IRELAND	Night time: period between midnight and 07:00	a) an employee who normally works at least 3 hours of his/ her daily working time during night time; b) an employee whose working hours during night time, in each year, equals or exceeds 50 per cent of the total number of hours worked during the year (Statutory Instruments n. 485/1998)

Table 1.1 (contd)

COUNTRY	NIGHT TIME/NIGHT WORK	NIGHT WORKER
ITALY	Night work: the activity carried out in a period of at least 7 consecutive hours comprising the interval between midnight and 05:00	a) any worker who during the night period carries out, as a normal course, at least 3 hours of his/her daily working time; b) any worker who during the night period, carries out part of his/her daily working time as defined by collective agreements; in default of collective agreements, any worker who works at night at least 80 working days per year (D.Lgs. 66/2003)
NETHERLANDS	Night work: work which covers all or part of the period from midnight to 06:00	
PORTUGAL	Night time: a period between 20:00 and 07:00	a) any worker who works at least 3 hours during the night period; b) any worker who during the night period, carries out part of its daily working time as defined by collective agreements (Decreto Lei 73/1998)
SPAIN	Night time: a period which includes the interval between 22:00 and 06:00	A worker who at night carries out at least 3 hours of his/her daily working time (Real Decreto Lei 1/1995)
SWEDEN	Hours between midnight and 05:00	A worker that works at least 3 hours of his/her daily work during night time, or a worker that most likely will work at least 38% of his/her annual work during the night (Working Hours Act 1982)
UK	Night time: a period lasting not less than 7 hours, and which includes the period between midnight and 05:00	A worker who, as a normal course, works at least 3 hours of his/her daily working time during night time, or who is likely, during night time, to work at least such proportion of his annual working time as may be specified for the purposes of these Regulations in a collective agreement or a workforce agreement (Statutory Instrument No.1833/1998).

Table compiled by the Working Group

The shift systems can also differ widely in relation to other organizational factors:

(*a*) length of shift cycle – a "cycle" includes all shifts and rest days lasting as long as the series of shifts restart from the same point; there can be short (6–9 days), intermediate (20–30 days), or long (up to 6 months or more) cycles.

(*b*) duration of shifts – in general, the length of a shift is 8 hours, but can range from 6 to 12 hours.

(*c*) number of workers/crews who alternate during the working day.

(*d*) start and finish time of the duty periods.

(*e*) speed of shift rotation – this depends on the number of consecutive days worked before changing shift. It can be fast (i.e. every 1, 2 or 3 days), intermediate (i.e. every week), or slow (i.e. every 15, 20 or 30 days). This factor has considerable influence on the number of consecutive night shifts and rest days.

(*f*) direction of shift rotation – it can be clockwise (i.e. morning/afternoon/night) or counter-clockwise (i.e. afternoon/morning/night) with consequent different duration of the intervals between shifts. Clockwise rotation is also referred to as "phase delay" or "forward rotation," and counter-clockwise rotation, "phase advance" or "backward rotation". They have a different impact on the adjustment of the circadian rhythm.

(*g*) number and position of rest days between shifts.

(*h*) regularity/irregularity of the shift schedules.

All of these factors can be combined in different ways depending on the demands specific to the occupation.

In the industrial sectors (i.e. mechanical and chemical), shiftwork is usually arranged in continuous three-shift systems. A similar number of crews/workers work both on day and night shifts, with regular shift schedules either on fast or slow rotating cycles, with fixed start and finishing times.

In the transport sector, schedules are often quite irregular, both in terms of number of consecutive shifts, shift rotation, start and finishing times, duration of the duty periods, location, and amount of rest days.

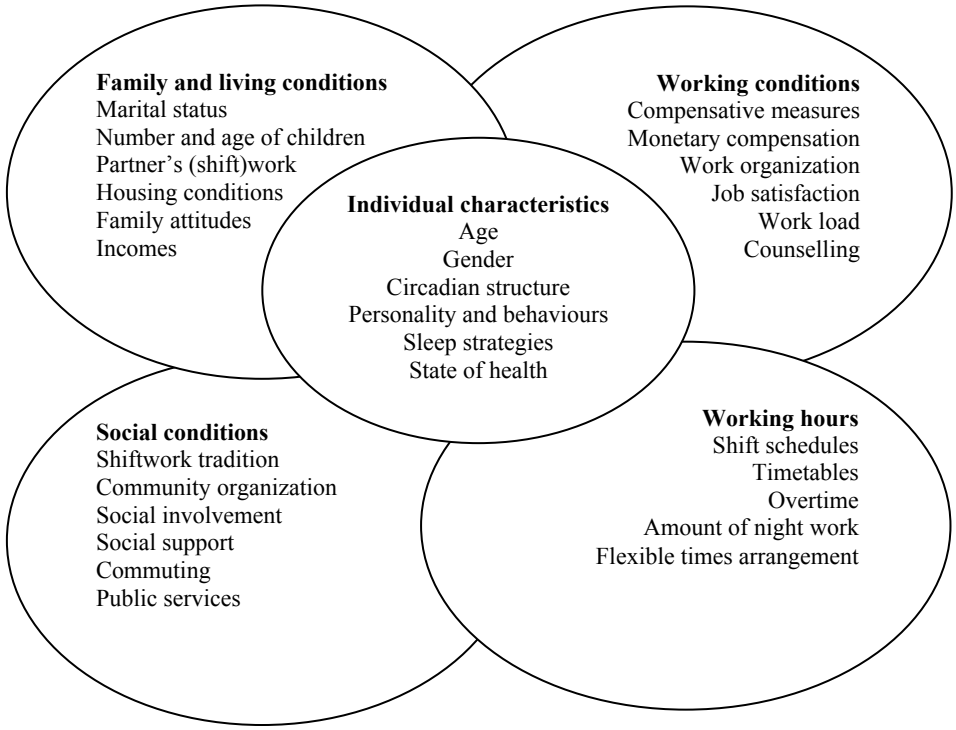
In the health-care sector, quite different shift schedules are operated with different rotation (clockwise or counter-clockwise), variable start and finishing time, and different amount of night shifts.

In the service sector, workers are commonly employed on split shifts, for example, very early morning and late afternoon shifts in road- and office-cleaning, merchandise delivery, or permanent night work (security guards).

In the leisure sector, work is mainly performed during the late afternoon and night hours, with a long duration of shifts.

Different shiftwork systems have potentially different impacts on the health of the workforce, disturbing the circadian rhythm, an essential biological function, in different ways, and also inducing sleep deprivation (see Section 4). In addition to shiftwork schedules, other factors can affect tolerance to shiftwork and night work such as individual characteristics, family situation, social conditions, and working conditions (Fig. 1.1; Costa *et al.*, 1989; Costa, 1996, 2003; Knauth, 1996; Knauth & Hornberger, 2003).

Figure 1.1. Factors that can affect tolerance to shiftwork and night work



(Costa, 2003)

1.3 Occurrence of shiftwork

Increasingly, shiftwork and night work are becoming more common in our so-called "24-hour" (or "24/7") society. Shiftwork and night work enable round-the-clock activities required for meeting technological needs (e.g. power plants, oil refinery, and steel industry), social services/utilities functions (e.g. hospitals, transports, police and security forces, firefighting, hotels, and telecommunications), productive and economic demands (e.g. textile, paper, food, mechanical, and chemical industry), and the needs of the leisure industry.

More than two and a half billion people are officially recognized as workers according to the most recent statistics of the International Labour Organization (International Labour Organization, 2006), two-thirds of which in the Asiatic continent. Reliable data on the numbers of workers employed in shiftwork is not easy to collect due to the lack of robust statistics in many countries, and/or differences in methods of data collection not always being comparable.

However, in Europe, the European Foundation for the Improvement of Living and Working Conditions has been carrying out periodical surveys on working conditions, including working hours, every 5 years since 1990. According to the third survey, carried out in 2000 in 15 European countries and involving 21703 workers, people who do normal or standard daytime work (that is those who do not work more than 40 hours per week, more than 10 hours per day, on shifts, at night, on sundays and/or saturdays, and part-time) represented only 24% of the whole population, 27% of employed workers, 8% of self-employed workers, with men and women sharing the same proportion (24%) (Costa *et al.*, 2004).

According to the results of the fourth survey carried out in 2005 (European Foundation, 2007), the weekly working hours among the 31 European countries examined ranged from an average of 34 hours in the Netherlands to 55 hours in Turkey, and from a minimum of 8 hours (as part-time work) to a maximum of 90 hours (as overtime work). Shiftwork, including night work, involved more than 17% of the total European Union (EU) working population (Table 1.2), with large variations among countries, and between old and new member States (from 6.4% to 30%). There were also quite large differences among EU countries when looking at evening (from 36% to 58%) and night work (from 18% to 24%) (Fig. 1.2). Evening and night work are mostly used in the hotel and restaurant industry, health care, and transport and communication sectors, usually employing an older workforce (Fig. 1.3). More generally, shiftwork in its different definitions is used by one-third of people working in the health-care sector and the hotel and restaurant industry, and in one fourth of cases in the manufacturing, transport, and communication sectors (Table 1.3). According to age and gender (Table 1.4), the average percentage of shiftwork including night work is quite similar in both men and women, with quite a high percentage of workers aged over 55 employed in night work (10.5%).

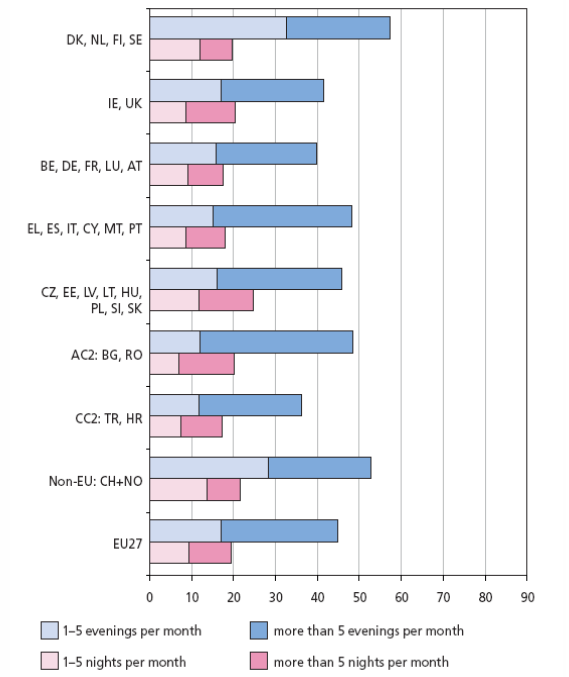
In the USA, according to the Bureau of Labor Statistics (US Bureau of Labor Statistics, 2005), in 2004, almost 15% of full-time salaried workers usually worked on alternate shifts. Men were more likely than women to work such shifts (16.7% and 12.4%, respectively). This was also true for the black population when compared to the caucasian, hispanic or latino, or asian populations, with shiftwork progressively decreasing with increasing age (Table 1.5). The prevalence of shiftwork was greatest among workers in the service industry (32.6%; Table 1.6), particularly the protective service industry (50.4%, includes police, firefighters and guards), food preparation and serving (49.4%), and those employed in production, transportation, and material-moving occupations (29%). The proportion of workers on alternate shifts was highest in the leisure and hospitality (45.8%), mining (31.5%), and transportation and utilities (27.8%) industries.

Table 1.2. Prevalence (%) of shiftwork that includes night work, by country in Europe in 2005 (4th EU Survey on working conditions)

Austria	13.2
Belgium	13.2
Bulgaria	21.0
Croatia*	33.5
Cyprus	11.8
Czech Republic	22.2
Denmark	9.3
Estonia	20.4
Finland	24.3
France	14.9
Germany	15.7
Greece	13.0
Hungary	20.7
Ireland	12.0
Italy	18.1
Latvia	21.9
Lithuania	19.4
Luxembourg	13.9
Malta	22.3
Netherlands	11.8
Norway	23.4
Poland	10.3
Romania	21.0
Slovakia	27.5
Slovenia	30.0
Spain	22.2
Sweden	16.0
Switzerland	12.9
Turkey*	6.4
United Kingdom	15.4
EU27	17.3
EU25	17.1
EU15	16.0
NMS	23.0

EU27: 25 EU Member States, plus the two countries that joined the European Union in 2007 – Bulgaria and Romania
EU25: 15 EU Member States. plus the 10 new Member States that joined in 2004
EU15: 15 EU Member States prior to enlargement in 2004
NMS: 10 New Member States that joined in 2004
* Two candidate countries for membership of the EU: Croatia and Turkey

Figure 1.2. Prevalence of evening and night work by group of country in Europe in 2005 (4th EU Survey on working conditions)



Country codes

EU15	15 EU Member States prior to enlargement in 2004		
NMS	10 new Member States that joined in 2004		
EU25	15 EU Member States, plus the 10 NMS		
EU27	25 EU Member States, plus the AC2		
AC2	Two countries that joined the European Union in 2007: Bulgaria and Romania		
CC2	Two candidate countries for membership of the EU: Croatia and Turkey		
AT	Austria	LU	Luxembourg
BE	Belgium	MT	Malta
BG	Bulgaria	NL	Netherlands
CY	Cyprus	PL	Poland
CZ	Czech Republic	PT	Portugal
DK	Denmark	RO	Romania
EE	Estonia	SK	Slovakia
FI	Finland	SI	Slovenia
FR	France	ES	Spain
DE	Germany	SE	Sweden
EL	Greece	UK	United Kingdom
HU	Hungary	HR	Croatia
IE	Ireland	NO	Norway
IT	Italy	CH	Switzerland
LV	Latvia	TR	Turkey
LT	Lithuania		

Country groups
Continental countries: AT, BE, DE, FR, LU
Ireland and the United Kingdom: IE, UK
Eastern European countries,: CZ, EE, HU, LT, LV, Pl, SI, SK
Southern European countries: CY, EL, ES, IT, MT, PT
Scandinavian countries and the Netherlands: DK, FI, NL, SE
Acceding countries: BG, RO
Candidate countries: HR, TR
EFTA (European Free Trade Association): CH, NO
Typology adapted from Esping-Andersen

Figure 1.3. Prevalence of evening and night work by work sector in Europe in 2005 (4th EU Survey on working conditions)

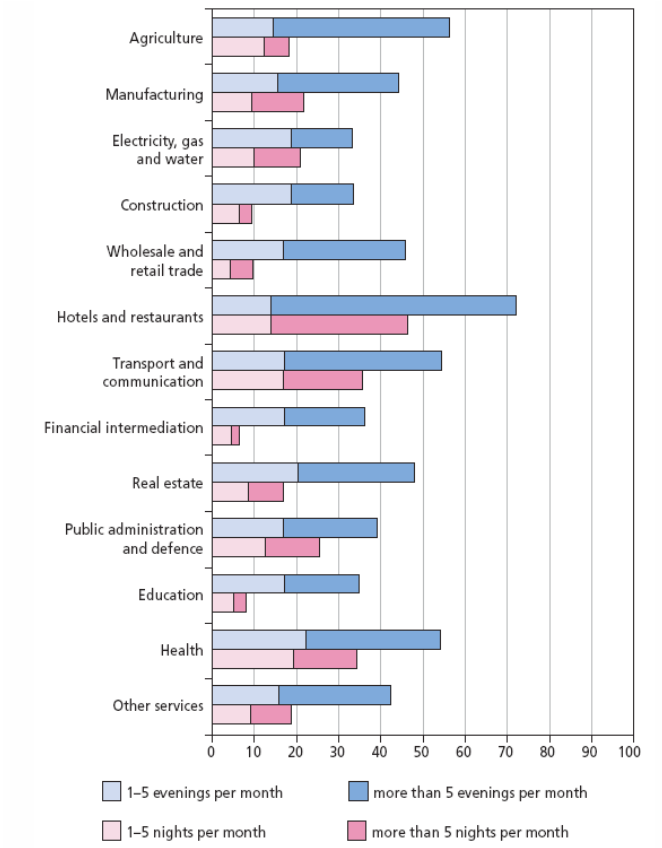


Table 1.3. Prevalence (%) of shiftwork that includes night work, by work activity in Europe in 2005 (4th EU Survey on working conditions)

Agriculture and fisheries	4.5
Armed forces	19.2
Clerks	13.4
Construction	5.3
Craft and related trades	17.6
Education	8
Electricity, gas and water supply	17.4
Elementary occupations	19.2
Financial intermediation	6.2
Health	35.5
Hotels and restaurants	29.9
Legislators, senior officials and managers	8.8
Manufacture and mining	25.8
Plant and machine operators and assemblers	34.5
Professionals	11.6
Public administration and defence	17.7
Real estate	9.5
Service, shop and market sales workers	26.9
Skilled agricultural and fishery workers	2.6
Technicians and associate professionals	14.3
Transport and communications	24.1
Wholesale and retail trade	16.3
Self-employed	5.7
Employee	19.8

Table 1.4. Prevalence (%) of shiftwork, including night work, by gender and age, in Europe in 2005 (4th EU Survey on working conditions)

Gender	Men	17.2
	Women	17.4
Age (years)	≤24	20.7
	25–39	19.1
	40–54	16.7
	≥55	10.5

Table 1.5. Percent distribution of shiftwork in full-time wage and salary workers by sex, race and ethnicity, in the USA in 2004 (US Bureau of Labor Statistics)

Total (>16 years)	14.8
Men	16.7
Women	12.4
White	13.7
Black or african american	20.8
Asian	15.7
Hispanic or latin ethnicity	16

Table 1.5 (contd)

20–24 years	22.3
25–34 years	15.2
35–44 years	14.1
45–54 years	12.8
55–64 years	12.5
≥65 years	10.3

Table 1.6 Percent distribution of shiftwork in full-time wage and salary workers, by occupation and industry, in the USA in 2004 (US Bureau of Labor Statistics)

Occupation	
Management professionals	8.7
Service occupations	36.1
Sales and office occupations	16.4
Natural resources, construction and maintenance	7.6
Production, transportation and material-moving occupations	26.4
Industry	
Private sector	15.4
Agriculture and related industries	9.5
Mining	31.5
Construction	2.8
Manufacturing	17.7
Wholesale and retail trade	22.0
Transportation and utilities	27.8
Information	15
Financial activities	7.0
Professionals and business services	9.4
Education and health services	12.8
Leisure and hospitality	45.8
Other services	13.0
Public sector	11.9
Federal government	14.7
State government	11.5
Local government	11.3

1.3.1 *Exposure assessment*

It is difficult to assess the effective "exposure" and the consequent "risk" of shiftwork with the common methods used (i.e. in toxicology) as the "dose" can widely differ not only in terms of quantitative load, i.e. in relation to the time spent in shiftwork, but mainly in terms of qualitative aspects, i.e. in relation to the interference that different shift

systems may have on biological and psychosocial functions, also taking into account several concurrent individual, social, and working factors.

The various combinations of these aspects can cause a different amount of stress and also different stress-related effects, thus making it difficult to compare groups without adjusting for the amount of "exposure", at least for the type of shift schedule and the years spent in shiftwork.

From a biological perspective, the occurrence and amount of night work is the most important factor to be considered. It is then possible to estimate roughly the effects (more or less severe) the different shift systems may have on health through interference on biological function, and on psychosocial issues.

Several methods have been proposed for assessing working time arrangements to evaluate their potential risk for health and well-being. The criteria most widely used are perturbation of the circadian rhythm, performance at work (ability to work efficiently), health, and social life (Wedderburn, 1994).

The "Rota Risk Profile Analysis," proposed by Jansen and Kroon (1995), describes several risk factors associated with with roster design, related to both physiological and psychosocial aspects, that must be considered. in particular: regularity of shift timetable, periodicity (i.e. the degree to which the "biological clock" is disturbed), shift load (i.e. the average length of shifts) and week load (i.e. the average length of the working week), opportunities for night rest (for sleeping between 11 pm and 7 am) and constancy in night rest (variation in the week), predictability of the shift cycles, opportunities and constancy for household and family tasks, opportunities and constancy for evening recreation (between 7 pm to 11 pm), opportunities and constancy for weekend recreation.

1.3.2 *Factors influencing shiftwork exposure and health*

Many health impairments associated with shiftwork have been reported. These include psychosomatic disorders of the gastrointestinal tract (colitis, gastroduodenitis, and peptic ulcer) and of the cardiovascular system (hypertension, ischaemic heart diseases), as well as metabolic disturbances, that are influenced by other time- and work-related factors and behaviours (Costa, 1996; Knutsson, 2003).

About 20% of all workers have to stop shiftwork altogether after a very brief period because of serious health problems, 10% do not complain about shiftwork during their whole working life, while the remaining 70% withstand shiftwork with different levels of intolerance that can become more or less manifest at different times and with different intensity in terms of discomforts, troubles or diseases (Waterhouse *et al.*, 1992).

1.3.3 *Some lifestyle factors that possibly modify the effects of exposure*

Some personal risk factors can act either as confounders or mediators, and/or modifiers, of the relation between shiftwork and health. Smoking and diet, generally considered as confounders in epidemiological studies, can also be intermediate factors of

the effects of shiftwork (i.e. for cardiovascular and gastrointestinal disorders). Many studies have reported that shiftworkers tend to smoke more (Bøggild and Knutsson, 1999; van Amelsvoort *et al.*, 2006) and/or increase their consumption of caffeinated or alcoholic drinks at night, as well as modify the composition and the caloric distribution of the different meals, i.e. by increasing carbohydrate intake at regular intervals (Reinberg *et al.*, 1979; Romon *et al.*, 1986; Lennernäs *et al.*, 1993). Metabolic disturbances have been found to be prevalent in shiftworkers (Knutsson *et al.*, 1990; Karlsson *et al.*, 2001). Of concern are mainly the risks for cardiovascular disease and obesity (Tenkanen *et al.*, 1998).

1.3.4 *Specificity of exposure to shiftwork for some particular occupations*

(a) Aircraft crew and transmeridian travel over time zones

Aircraft crews operating on long transmeridian flights have to cope with a shift in external time in addition to the shift of the working period. Therefore, the individual biological rhythms have to adjust to abnormal working hours in a changed environmental context. The short-term problems arising from these conflicts are similar to those of normal shiftwork, but are often aggravated by the fatigue due to the extended duty periods, and by a loss of the usual external time cues.

After a long transmeridian flight, the circadian system does not adjust immediately to the new local time, but requires several days in relation to the number of time zones crossed; the greater the number, the longer is the time required, considering that the human circadian system can adjust to no more than 60–90 minutes per day (Wegmann and Klein, 1985).

The adjustment is generally more rapid in westbound (about 1 day per hour of shift) than eastbound flights (about 1.5 day per hour of shift; Ariznavarreta *et al.*, 2002; Gander *et al.,* 1989; Suvanto *et al.,* 1990). In the first case, there is a progressive phase delay of the circadian rhythm in relation to the extended personal day, whereas in the latter there is a phase advance due to the compressed day (*directional asymmetry*). A complete readjustment after transition of six time zones was found to take 13 days and 10 days in eastward and westward flights, respectively (Wegmann and Klein, 1985).

In addition, crews are exposed to many other concurrent risk factors, such as cosmic radiation, electromagnetic fields, lighting, noise, acceleration, vibration, mental stress, fixed postures, and pressurization.

No statistics are currently available on the entire population employed in transmeridian flights, and consequently in related shiftwork, which is generally characterized by very irregular shift schedules. Only in the case of pilots and flight engineers, are there data that can provide a rough idea of the possible number of workers involved, considering that they generally account for about 20% of the total aircraft crew members.

The US Aircraft Owners and Pilots Association (IAOPA 2007) estimated that the civil aviation worldwide during 2004 consisted of approximately 370 000 aircraft and 1.3 million pilots flying some 39 million hours. On balance, roughly 600 000 pilots were employed in commercial air transportation worldwide (including cargo and charter).

The US Bureau of Labor Statistics (2007), reported that civilian aircraft pilots and flight engineers held about 107 000 jobs in the USA in 2006. About 79 000 worked as regular airline pilots, copilots, and flight engineers. The remainder were commercial pilots who worked as flight instructors at local airports or for large businesses that fly company cargo, and executives in their own airplanes or helicopters.

(b) Watchkeeping and driving

Ship's crew members engaged in long distance navigation work on continuous shiftwork, with some differences compare to land-based shiftworkers. For example, they can only take rest time in their place of work after the duty period, and usually have no rest days up until the end of the sea voyage is concluded. Moreover, they also have to cross several time zones (at different speed compared to flight crews), and their leisure time is limited both in terms of space and time. Several different shift systems are used. In merchant fleets, the personnel is generally divided into two or three crews working 12-hour or 8-hour shifts respectively, whereas on warships the crew work more frequently on the "4-hour watch" system, by dividing the 24-hour period into six 4-hour watches, and rotating on a "4-h on/8-h off" schedule, that allows one full night sleep in three. In general, in this shift schedule, the average amount of sleep is nearly the same as that of dayworkers, but the sleep is fragmented into two periods. A further system, the 6-hour on/6-hour off system is becoming more and more common on warships. However, high irregularity and variability of shift duration and rotation are quite frequent due to crew shortage, additional duties and unexpected situations, thus the amount of rest and sleep hours may vary considerably among days and subjects (Eriksen *et al.*, 2006).

The situation is similar for shiftworkers of offshore oil installations, who live in the same environment during both work and leisure time and stay away from home for several weeks, usually working in alternating 12-hour shift schedules (6:00–18:00, 18:00–6:00). In addition, in this occupational setting, the (mal)adjustment of the circadian rhythm may be more or less pronounced and depends on whether the fast or slow rotation is adopted, job characteristics (drilling, maintenance), and working organization (Barnes *et al.*, 1998).

Similar problems can be faced by long-haul truck and train drivers (i.e. coast-to-coast journeys, relay work), in which shiftwork, long working hours and time zone crossing interact in causing circadian disruption of the sleep/wake cycle and biological rhythms, as well as sleep deprivation, and overall fatigue (Jay *et al.*, 2006).

1.4 Biomarkers of circadian regulation and dysregulation

The production and release of nearly all hormones exhibits a circadian timing patterned on approximately a 24-hour cycle (Pandi-Perumal *et al.*, 2007). Agents that disrupt the circadian rhythm may therefore alter hormone levels.

At present, there is no known biomarker of exposure to shiftwork, which is thought to affect circadian regulation. In the past, core body temperature or blood cortisol levels have been used as markers of circadian regulation. However, given the importance of melatonin in the regulation of circadian rhythm, an indicator of melatonin levels is considered a preferable biomarker of circadian regulation and dysregulation, and has been more commonly used in recent studies on the effects of shiftwork in humans. Melatonin levels are comparatively robust in the presence of various external influences (Pandi-Perumal *et al.*, 2007). For example, excessive carbohydrate intake can significantly affect core body temperature and heart rate, whereas melatonin concentration remains relatively unaffected by this factor (Kräuchi *et al.*, 2002). Furthermore, the onset of melatonin production is largely unaffected by biochemical and physiological factors, which further suggests its greater reliability to measure circadian phase position (Lewy, 1999; Lewy *et al.*, 1999).

1.4.1 *Methods of measuring circulating melatonin*

(a) Melatonin in serum and plasma

Plasma melatonin, which has a very short biological half-life and is rapidly metabolized by the liver, reflects the amount of melatonin circulating at the point in time of the sample collection. Thus, measurement of melatonin in plasma at regular intervals (e.g. hourly) will map out a circadian rhythm, enabling identification of the onset of melatonin secretion, the duration of melatonin secretion, peak levels of circulating melatonin, and the time at which peak secretion occurred, and the total amount of melatonin secreted. Although such detailed information may be very useful in identifying the characteristics of the circadian rhythm in an individual, such measurement is possible only in a controlled setting (e.g. sleep laboratory), and is impractical in other applications such as an epidemiological study or other widespread population use.

(b) Melatonin in saliva

Melatonin can also be measured in saliva, using several different laboratory techniques. Salivary testing is a useful method for measuring melatonin in epidemiological studies, given that it is relatively non-invasive and generally acceptable to study participants. With proper training, study subjects can collect their own samples at home, to be later delivered to the laboratory for assay. Several researchers have found a high correlation between serum and salivary melatonin concentrations, and have concluded that salivary melatonin concentrations are reliable indices of serum melatonin

concentrations (Arendt *et al.*, 1985; Laakso *et al.*, 1990; Klante *et al.*, 1997; Davis *et al.*, 2001; Gooneratne *et al.*, 2003). However, Laakso *et al.* (1990) compared salivary and serum melatonin levels and found that saliva and serum measurements were not highly correlated in individuals with low serum melatonin levels, and that the proportion of melatonin found in saliva decreased with increasing serum melatonin levels. They concluded that melatonin concentrations measured in saliva do not always consistently reflect the absolute concentrations in blood. Gooneratne *et al.* (2003) reported similar results in that serum and saliva melatonin levels were less correlated in individuals with low serum melatonin levels. The primary drawback to measuring melatonin in saliva is that, similar to plasma and serum measurements, salivary melatonin reflects the amount of melatonin circulating in the body at a given time-point. To capture details of the rhythm of melatonin secretion, such as the time of onset, peak levels, and cumulative secretion, one has to collect the subject's saliva samples at regular intervals throughout the night.

(c) Melatonin in urine

Arendt *et al.* (1985) suggested that measurement of the primary metabolite of melatonin excreted in urine would allow the non-invasive study of pineal function, useful in a broad range of applications. If appropriately executed, measurement of melatonin in the urine reflects the cumulative amount of circulating melatonin corresponding to the time period between the prior urine void and the collection of the subsequent urine sample. Using this approach to quantify melatonin levels in urine is typically accomplished through the measurement of 6-hydroxymelatonin sulfate (aMT6s), the primary metabolite in urine, although some studies directly measure urinary melatonin. The principal methods for determination of urinary aMT6s include assay by either radioimmunoassay (RIA) or enzyme-linked immunosorbant assay (ELISA); commercial kits are available for both methods. Concentrations of aMT6s are often adjusted by urinary creatinine concentrations to account for differing urine output volume from one individual to the next, and for separate urine collections within individuals (Klante *et al.*, 1997).

The stability of such measurements further promotes the usefulness of this technique, since long-term levels of hormones are often of interest in diseases with long latency periods. Davis *et al.* (2001) evaluated nocturnal aMT6s levels in a group of women 20–74 years of age over 3 consecutive days, then repeated the measurement protocol 3–6 months later. Urinary aMT6s concentrations have been shown to be highly and significantly correlated on consecutive days, as well as between measurements sessions over long time period until 5-year time period in several studies (Levallois *et al.*, 2001; Travis *et al.*, 2003). Levallois *et al.* (2001) measured urinary aMT6s concentrations over 2 consecutive days and a found similarly high correlation.

(d) Comparison between blood and urinary melatonin levels

As melatonin is secreted primarily at night, studies have focused on nocturnal samples when evaluating the correlation between melatonin levels in blood and urine, and found a high degree of correlation between nocturnal measurements of urinary melatonin or urinary aMT6s, and plasma or serum melatonin. Graham *et al.* (1998) found a significant relationship between total nocturnal plasma melatonin and both urinary aMT6s corrected for creatinine and urinary melatonin. Combining the two urinary measures of aMT6s and melatonin accounted for 72% of the variance in total plasma melatonin. Furthermore, peak nocturnal levels of plasma melatonin were significantly related to morning levels of urinary melatonin and aMT6s. Cook *et al.* (2000) assessed the differences in melatonin levels between blood and urine samples collected in a laboratory-based setting with nocturnal urine samples collected in a field study, and found very high correlations ($P < 0.001$) between first morning void melatonin and creatinine-corrected aMT6s and both total nocturnal plasma melatonin output and peak nocturnal plasma melatonin.

Similarly high correlations have been found in studies that compared melatonin in plasma and serum with urinary melatonin and/or urinary aMT6s over a 24-hour period (Markey *et al.*, 1985; Baskett *et al.*, 1998). Bojkowski *et al.* (1987) found that total 24-hour urinary excretion of aMT6s was significantly correlated with the area under the curve of the respective profiles for plasma melatonin ($r = 0.75$), and plasma aMT6s ($r = 0.70$).

In conclusion, both urinary melatonin and urinary aMT6s are good indicators of melatonin secretion in blood with a significantly smaller variation for the former molecule (Pääkkönen *et al.*, 2006). Such measurements in urine samples would provide a suitable tool in epidemiological settings to study the modulation of the circadian rhythm in shiftworkers.

1.5 Regulations on shiftwork

Some international directives have been issued in the last decades addressing the need for a careful organization of shift and night work and the protection of shiftworkers' health: in particular, the International Labour Office (ILO) "Code of practice on working time" (1995) and Convention no. 171 (C171) on "Night work" (1990), and the European Directive no. 93/104/EC "concerning certain aspects of the organization of working time" (1993), which in European countries has been implemented through national legislation.

1.5.1 *ILO Night Work Convention and Recommendation*

(a) General population

The ILO C171 Night Work Convention (International Labour Organization, 1990a) refers only to *night work*, that is "all work which is performed during a period of not less than seven consecutive hours, including the interval from midnight to 5am," and *night worker*, who is "an employed person whose work requires performance of a substantial number of hours of night work which exceeds a specified limit, fixed by the competent authority. This convention applies to all employed persons except those employed in agriculture, stock raising, fishing, maritime transport and inland navigation."

In addition, the ILO R178 Night Work Recommendation (International Labour Organization, 1990b), supplementing the Night Work Convention C171, points out the following:

"Normal hours of work for night workers should not exceed eight in any 24-hour period in which they perform night work, except in the case of work which includes substantial periods of mere attendance or stand-by, in cases in which alternative working schedules give workers at least equivalent protection over different periods or in cases of exceptional circumstances recognized by collective agreements or failing that by the competent authority.

The normal hours of work of night workers should generally be less on average than and, in any case, not exceed on average those of workers performing the same work to the same requirements by day in the branch of activity or the undertaking concerned.

In occupations involving special hazards or heavy physical or mental strain, no overtime should be performed by night workers before or after a daily period of work which includes night work, except in cases of force majeure or of actual or imminent accident.

Where shift work involves night work: (a) in no case should two consecutive full-time shifts be performed, except in cases of force majeure or of actual or imminent accident; (b) a rest period of at least 11 hours between two shifts should be guaranteed as far as is possible."

(b) Women during pregnancy and around childbirth

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.

Measures shall be taken to ensure that an alternative to night work is available to women workers who would otherwise be called upon to perform such work: (a) before and after childbirth, for a period of at least 16 weeks of which at least 8 weeks shall be before the expected date of childbirth; (b) for additional periods in respect of which a medical certificate is produced stating that it is necessary for the health of the mother or child: (i) during pregnancy; (ii) during a specified time beyond the period after childbirth fixed pursuant to subparagraph (a) above, the length of which shall be determined by the

competent authority after consulting the most representative organizations of employers and workers. These measures may include transfer to day work where this is possible, the provision of social security benefits or an extension of maternity leave. During those periods, a woman worker shall not be dismissed or given notice of dismissal, except for justifiable reasons not connected with pregnancy or childbirth, and shall not lose the benefits regarding status, income, seniority and access to promotion which may attach to her regular night work position (ILO C171, 1990).

(c) Young people

With regard to young people, following the first Night Work of Young Persons (Industry) Convention (1919), the ILO Night Work of Young Persons (Industry) Convention (Revised) (1948), stated that: "young persons under eighteen years of age shall not be employed or work during the night in any public or private industrial undertaking (i.e. mines, quarries, manufactures, construction, transports, electrical-gas works, etc.). "Night" means a period of at least twelve consecutive hours. In the case of young persons under sixteen years of age, this period shall include the interval between ten o'clock in the evening and six o'clock in the morning. Moreover, in the case of young persons who have reached the age of sixteen years but are under the age of eighteen years, this period shall include an interval prescribed by the competent authority of at least seven consecutive hours falling between ten o'clock in the evening and seven o'clock in the morning. For purposes of apprenticeship or vocational training in specified industries or occupations which are required to be carried on continuously, the Convention stated that the competent authority may, after consultation with the employers' and workers' organizations concerned, authorise the employment in night work of young persons who have reached the age of sixteen years but are under the age of eighteen years."

(d) Seafarers

For specific groups of workers, the ILO Convention No. 180 "Concerning Seafarers' Hours of Work and the Manning of Ships" (1996) states limits on hours of work or rest, in particular: "a) maximum hours of work shall not exceed 14 hours in any 24-hour period, and 72 hours in any seven-day period; b) minimum hours of rest shall not be less than ten hours in any 24-hour period, and 77 hours in any seven-day period; c) hours of rest may be divided into no more than two periods, one of which shall be at least six hours in length, and the interval between consecutive periods of rest shall not exceed 14 hours. Moreover, no seafarer under 18 years of age shall work at night (which means a period of at least nine consecutive hours, including the interval from midnight to five a.m.)."

(e) Long-distance drivers

According to the US Bureau of Labor Statistics (2007) long-distance drivers may drive for 11 hours and work for up to 14 hours – including driving and non-driving duties – after having 10 hours off-duty. Moreover, they may not drive after having worked for

60 hours in the past 7 days or 70 hours in the past 8 days unless they have taken at least 34 consecutive hours off-duty.

(f) Airline pilots

According to the National Aeronautics and Space Administration guidelines (Dinges *et al.* 1996), for standard operations including day and night flying, the duty period for air pilots should not exceed 10 hours within a 24-hour period; in case of extended flight duty periods, the limit should be fixed at 12 hours, and accompanied by additional restrictions and compensatory off-duty periods. It is also recommended that in any 7-day period, there be no extended flight duty period that encroaches on any portion of the window of circadian low (i.e. period between 2–6 am for an individual's normal day–wake/night–sleep schedule).

Because of Federal Aviation Administration regulations, airline pilots flying large aircraft, cannot fly more than 100 hours a month or more than 1000 hours a year. Most airline pilots fly an average of 75 hours a month and work an additional 75 hours a month performing non-flying duties. To guard against pilot fatigue, which could result in unsafe flying conditions, the Federal Aviation Administration requires airlines to allow pilots at least 8 hours of uninterrupted rest in the 24 hours before finishing their flight duty.

Many countries in the world have national laws regulating night work according to ILO recommendations, whereas in many others this topic is regulated by means of collective or local agreements between parties (International Labour Organization, 1995).

1.5.2 *European Directive on Working Time*

(a) General population

In Europe, the EU Council Directive No 93/104/EC (European Council Directive, 1993) "concerning certain aspects of the organization of working time" (re-confirmed by EU Directive 2003/88/EC):

– defined "night time" as "any period of not less than seven hours, as defined by national law, and which must include in any case the period between midnight and 5 am"; and "night worker" as (a) any worker who, during night time, works at least three hours of his/her daily working time as a normal course, and (b) any worker who is likely during night time to work a certain proportion of his/her annual working time, as defined at the choice of the Member State concerned either by national legislation or by collective agreements. On the other hand, 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; consequently, "shift worker shall mean any worker whose work schedule is part of shift work."

– forced Member States to take the measures necessary to ensure that: normal hours of work for night workers do not exceed an average of 8 hours in any 24-hour period for normal work activities, but not more than 8 hours in any 24-hour period in case of work involving special hazards or heavy physical or mental strain; every worker is entitled to a minimum daily rest period of 11 consecutive hours per 24-hour period; where the working day is longer than 6 hours, every worker is entitled to a rest break; per each seven-day period, every worker is entitled to a minimum uninterrupted rest period of 24 hours plus the 11 hours daily rest; and it should preferably include Sunday; the average working time for each seven-day period, including overtime, does not exceed 48 hours; every worker is entitled to paid annual leave of at least four weeks in accordance with the conditions for entitlement to, and granting of, such leave laid down by national legislation and/or practice; the minimum period of paid annual leave may not be replaced by an allowance in lieu, except where the employment relationship is terminated.

Implementing such directive at national level, some European countries added the quantitative criterium of 80 night shifts worked per years as minimum level for establishing the compulsory periodical medical surveillance for night workers: this limit appears as a mere technical compromise among social parties (i.e. one third of the total working days), being not supported by any evidence based on the scientific literature.

There are also some differences among countries in the definition of both "night work" and "night worker" (see Table 1.7).

Table 1.7. Legislation on night work in 15 EU[a] countries

Country	Max. length of night work in hours	Legislation
AUSTRIA	–	Nachtschwerarbeitsgesetz nr. 354/1981 (rev. 1993)– "Night work": period of at least 6 hours between 22:00 and 06:00 for at least six nights a month. Additional breaks: 10 min paid break during the night shift. Additional vacations: 60 nightshifts per year, 2 work days, after 5 years on shift, 4 work days, after 15 years on shift, 6 work days. Health service, possibility of early retirement.
BELGIUM	**8**	Loi du 17/02/1997 et Loi du 04/12/1998: "Night time": a period, generally of 8 hours, between 20:00 and 06:00. "Night work": in principle, prohibited, but various derogations are possible.
DENMARK	–	The notions of night time and night worker have been defined generally in collective agreements**.**

Table 1.7 (contd)

Country	Max. length of night work in hours	Legislation
FINLAND	**–**	Working Hours Act 605/1996: "Night work": work of at least 3 hours between 23.00 and 06.00. An employer must notify the labour protection authorities of regular night work, when the said authorities so request.
FRANCE	**–**	Loi 461/1998: "Night time": period between 22:00 and 05:00 or whichever night work period between midnight and 05:00. "Night workers": any employee working usually at least 2 times per week at least 3 hours on the period defined as night work.
GERMANY	**8/10**	Arbeitszeitgesetz 1994: "Night time": a period which includes the time between 23.00 and 06.00, in the case of bakers between 22.00 and 05.00. "Night work": every kind of work which includes more than 2 hours of night time. The working time of a night worker and shiftworker shall not exceed 8 hours, or 10 hours if within a month or a 4-weeks period where the average working hours are 8 hours per day. The night workers are entitled to a health assessment before they take up the assignment and after that, every 3 years. After the age of 50, the time is reduced to 1 year. "Night worker": a worker who works at least 2 hours during night time. "Night workers" are those workers who usually work nights in rotating shifts system or works at night on not less than 48 days during a year. The working time of a night worker and shiftworker shall be laid out according to evidence based knowledge about human centred design of working hours from ergonomics.
GREECE	**8**	Presidential Decree no. 88/1999: "Night time": period of 8 hours which includes the period between 22:00 and 06:00. "Night worker": a worker who during night time works at least 3 hours of his daily working time or a worker who has to perform night work for at least 726 hours of his annual working time.
IRELAND	**9**	Statutory Instruments no. 485/1998: "Night time": period between midnight and 07.00. "Night worker": a) an employee who normally works at least 3 hours of his or her daily working time during night time; b) an employee whose working hours during night time, in each year, equals or exceeds 50 per cent of the total number of hours worked during the year.

Table 1.7 (contd)

Country	Max. length of night work in hours	Legislation
ITALY	–	D.Lgs. 66/2003: "Night work": the activity carried out in a period of at least 7 consecutive hours comprising the interval between midnight and 05.00 in the morning. "Night worker": a) any worker who during the night period carries out, in a not exceptional way, at least 3 hours of his daily working time; b) any worker who carries out, during the night, at least a part of his normal working hours. Night work does not have to be done obligatorily by: a) the working mother of a child under 3 years of age or, alternatively, by the cohabiting father; b) the worker who is the only entrusted parent of a cohabiting child of less than 12 years of age; c) the worker who takes care of a disabled subject. Women are forbidden to work from 24.00 to 06.00, from the assessment of state of pregnancy until the first year of age of the child. Thereafter their assignment to night work is on voluntary basis until the third year of age of the child.
LUXEMBOURG	–	There is no general legislation on night work or night worker.
NETHERLANDS	–	Wet van 23/11/1995: "Night work": work which covers all or part of the period from midnight to 06:00.
PORTUGAL	**8**	Decreto Lei 259/98: "Night time": a period between 20:00 and 07:00 L.73/98: "Night work": shall not exceed 8 hours. The night workers with risks shall not work more than 8 hours in a period of 24 hours. The employer ensures the worker the opportunity of a free health assessment before he takes up the assignment and during the period of work.
SPAIN	**8**	Real Decreto Lei 1/1995: "Night time": the period which includes the interval between 22.00 and 06.00. "Night work": shall not exceed the 8 hours in a work period of 15 days. The employer, who usually utilizes night work, has to inform the authority. "Night worker": the worker who at night carries out at least 3 hours of its daily working time".

Table 1.7 (contd)

Country	Max. length of night work in hours	Legislation
SWEDEN	–	Working Hours Act 1982: All employees shall be afforded free time for nightly rest. Such free time shall include the hours between midnight and 05:00. Exception could be made depending on the nature of the work. "Night worker": a worker that works at least 3 hours of his daily work during night time, or a worker that most likely will work at least 38% of his annual work during the night.
UK	**8**	Statutory Instruments.1833/1998: "Night time": a period the duration of which is not less than 7 hours, and which includes the period between midnight and 05:00. A nightworker's normal hours of work, in any reference period which is applicable in his case, shall not exceed an average of 8 hours for each 24 hours. "Night worker": a worker who, as a normal course, works at least 3 hours of his daily working time during night time, or who is likely, during night time, to work at least such proportion of his annual working time as may be specified for the purposes of these regulations in a collective agreement or a workforce agreement. An employer shall not assign an adult worker to work which is to be undertaken during periods such that the worker will become a night worker unless the employer has ensured that the worker will have the opportunity of a free health assessment before he takes up the assignment; or the worker had a health assessment before being assigned to work to be undertaken during such periods on an earlier occasion, and the employer has no reason to believe that that assessment is no longer valid.

[a] Council Directive 93/104/EC of 23 November 1993 concerning certain aspects of the organization of working time.
Compiled by the Working Group

(b) Women during pregnancy and around childbirth

For women, the EU Council Directive 92/85/EEC (European Council Directive, 1992), "on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding," forced Member States to take the necessary measures to ensure that such workers are not obliged to perform night work during their pregnancy and for a period following childbirth which shall be determined by the national authority competent for safety and health. These measures must entail the possibility, in accordance with national

legislation and/or national practice, of transfer to daytime work, or leave from work or extension of maternity leave where such a transfer is not technically and/or objectively feasible.

In most legislations of European countries, women are prohibited to work at night from the assessment of state of pregnancy until the first year of age of the child. Thereafter, in many cases, assignment to night work is on voluntary basis until the third year of the child.

(c) Young people

For young people, the European Council Directive 94/33/EC (1994) on the protection of young people at work states that: "Member States shall adopt the measures necessary to prohibit work by children (less than 15 years of age) between 8 pm and 6 am (in case of cultural or similar activities allowed to children), and by adolescents (15–18 years of age) either between 10 pm and 6 am or between 11 pm and 7 am. For adolescents, there may be some exceptions in specific areas provided that they are supervised by an adult, but work between midnight and 4 am continues to be prohibited.

1.5.3 *Scientific guidelines*

The main indications for the design of better shift systems according to ergonomic criteria are (Knauth, 1996; Knauth and Hornberger, 2003; Wedderburn, 1994):

a) Quickly rotating shift systems are better than slowly rotating ones.

b) Clockwise rotation (morning/afternoon/night) is preferable to counter-clockwise (afternoon/morning/night).

c) Early starts for the morning shift should be avoided.

d) Prolonged work shifts (9–12 hour) should only be considered when the workload is suitable, there are adequate breaks, and the shift system is designed to minimize accumulation of fatigue and exposure to toxic substances.

e) Shift systems should be regular and able to guarantee as many free weekends as possible.

f) Permanent night work can be acceptable only for particular working situations which require a complete adjustment to night work to guarantee the highest levels of safety. Be aware that such complete adjustment requires people to maintain the inverted sleep/wake cycle also on rest days and to avoid exposure to bright light after night shifts (i.e. wearing dark sun glasses while commuting home).

g) Adequate time off between shifts should be allowed to compensate for fatigue and sleep as quickly as possible (i.e. two shifts in the same day must be avoided), and rest days should come preferably after the night duty period to allow prompt recovery from sleep deficit and an easier return to the normal sleep/wake cycle.

h) Some flexibility in working times is desirable to give the workers the possibility of combining better work duties with family and social life.

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