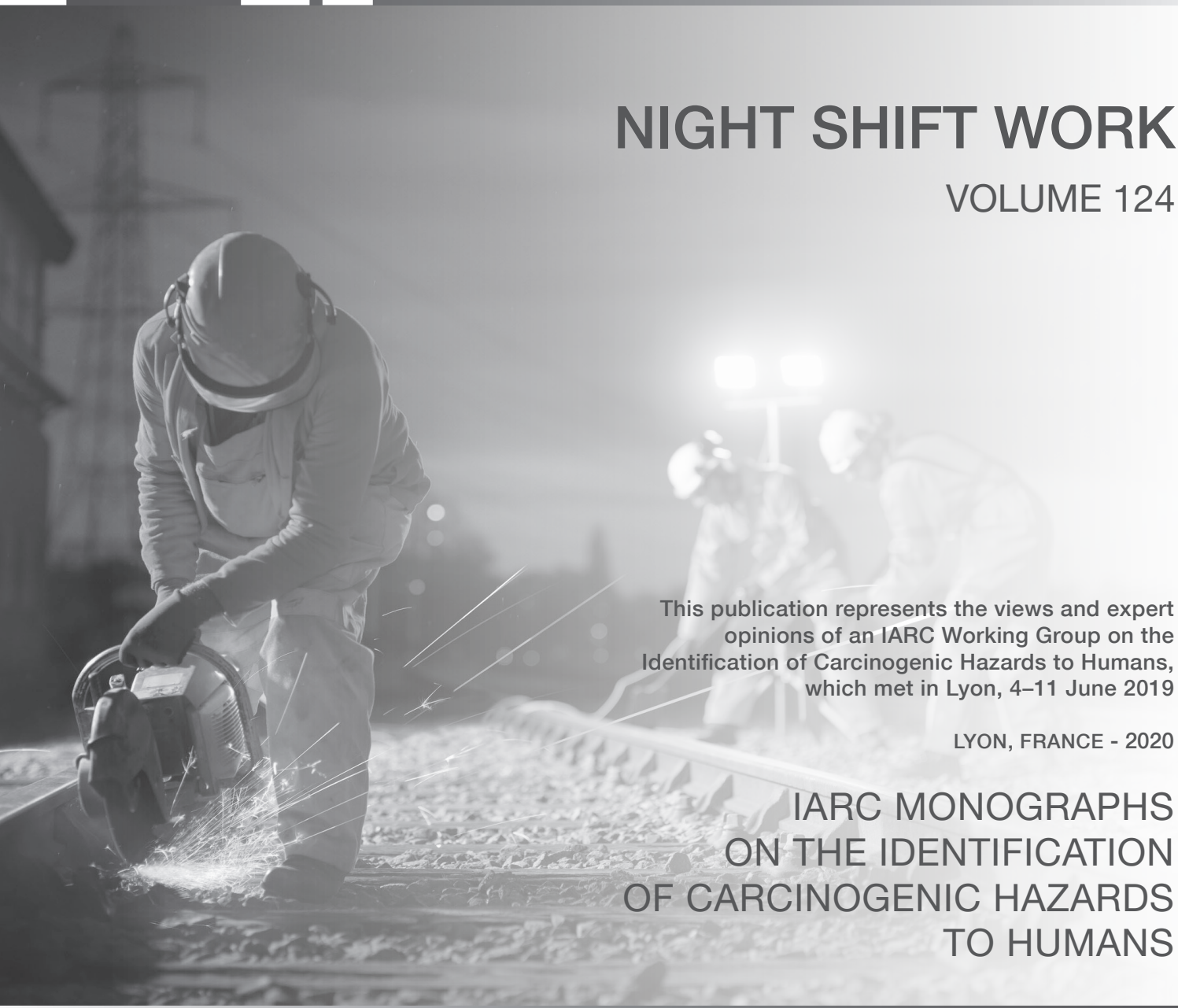
IARC MONOGRAPHS



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

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

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GENERAL REMARKS

This one-hundred-and-twenty-fourth volume of the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans* contains evaluations of the carcinogenic hazard to humans of night shift work.

This agent was considered previously by a Working Group as "shift work that involves circadian disruption" in Volume 98 (IARC, 2010) and was evaluated as "*probably carcinogenic to humans* (Group 2A)". A substantial proportion of the working population is exposed to night shift work. In Volume 98 of the *IARC Monographs* (IARC, 2010), evidence related to cancer in humans and cancer in experimental animals formed the basis of the Working Group's evaluation of "shift work that involves circadian disruption" as Group 2A. Since the previous evaluation, new data have become available for these areas and for carcinogen mechanisms, and these data have been included and considered in the present volume.

A summary of the findings of this volume appears in *The Lancet Oncology* (Ward et al., 2019).

Scope of systematic review

Volume 124 of the *IARC Monographs* represents a milestone for the *IARC Monographs* programme, as the first volume to be published under the amended Preamble to the *IARC Monographs* adopted in 2019 (IARC, 2019; Samet et al., 2020; available from: https://monographs.iarc.fr/iarc-monographs-preamble-preamble-to-the-iarc-monographs/). An important aspect of the Preamble is the enhanced documentation of systematic review practices to identify, screen, and select the studies related to cancer in humans, cancer in experimental animals, and mechanistic evidence for each agent. For Volume 124, the scope of the systematic review encompassed a comprehensive search of the literature, focusing on an agent name reflecting variations on "night shift work", "transmeridian travel", or "circadian disruption", and standardized terms for each of the relevant outcomes (cancer and mechanisms). As a result of the sparse and inconsistent evidence regarding cancer risk associated with variations in melatonin secretion (see "Melatonin in humans" below), the Working Group elected not to evaluate melatonin as part of the agent name in relation to cancer risk in humans. The literature tree, including the full set of search terms for the agent name and each outcome type, is available at: https://hawcproject.iarc.who.int/assessment/605/.

Agent name

For Volume 124, the Working Group re-evaluated an agent previously considered in Volume 98 (IARC, 2010) and entitled "shift work that involves circadian disruption". For the current evaluation, the Working Group elected to change the agent name to "night shift work" in order to better reflect the main evidence base for the studies of cancer in humans, and to avoid mixing the exposure with the potential health effects or mechanisms. Furthermore, as noted in Section 1 of the monograph, measuring circadian disruption itself proves challenging, which argued against invoking it as part of the agent name. The Working Group was careful to note that this new agent name encompasses workers in fixed locations (e.g. hospital, call centre, or factory) as well as those involved in transmeridian air travel (e.g. aircrew).

Working at night involves work during the regular sleeping hours of the general population. This alters exposure to the regular photoperiod and may disrupt circadian rhythms in humans. Working at night is connected to the perturbation of the natural cycle of sleep and wakefulness, and related patterns of activity and rest (e.g. mealtimes, social life), as staying awake at night and trying to sleep during the day is not a physiological condition for "diurnal" creatures like humans.

Trends in night shift work

The nature of night shift work is changing, with decreases in traditional work arrangements, but also increases in irregular and temporary work arrangements. This is likely to have an impact on researchers' ability to accurately assess exposures over the lifespan, and on the development of evidence-based recommendations to support worker health. This further supports the need for strong methodological approaches to assess exposure to night shift work in epidemiological studies.

Regulation with respect to cancer patients

Regulations on shift work are in place in many countries. These regulations do not address explicitly the question regarding return to shift work for cancer patients after treatment. Particularly considering increasing survival rates (e.g. for cancers of the breast and prostate), evidence-based research on this topic was a notable gap.

Exposure assessment quality

The Working Group has noted improvements in exposure assessment methods in epidemiological studies of night shift work and cancer since Volume 98 and the subsequent IARC workshop on exposure assessment of shift work (Stevens et al., 2011). The recommendations made in Stevens et al. (2011) have been incorporated in several case–control studies, allowing assessment of aspects of shift work (e.g. number of consecutive shifts, number of shifts per week or month) that may have an impact on health. The recommendations made by Stevens and colleagues have not been adopted to the same extent in cohort studies, with some exceptions (e.g. Pijpe et al., 2014). Therefore, it remains unclear whether the observed differences in associations between night shift work and breast cancer in case–control versus cohort studies are related to differences in exposure assessment quality across these study designs. In addition to continuing research using case–control studies, the quality of exposure assessment in cohort studies should be improved through implementation

of the recommendations made by Stevens et al. (2011). This is important to reduce heterogeneity in results between studies, allowing for better comparisons of evidence, and facilitating the development of effective public health interventions. To advise on work schedules that may be more or less detrimental for health, evidence-based insight into the most important aspects of night shift work is imperative.

Harmonization of terminology for aircrew studies

The Working Group noted the wide variation in terminology describing aircraft cockpit and cabin crew occupations. To better harmonize this terminology throughout the monograph, the Working Group adopted the following terms throughout (except where giving more specific description of the studied group): "aircrew" was used to designate cockpit and cabin crew, when used collectively; "cockpit crew" was used to designate pilots and flight engineers; and "cabin crew" was used to designate flight attendants and other airborne workers not in the cockpit.

Considerations regarding studies of cancer in humans

The Working Group considered but ultimately decided not to conduct a new meta-analysis of breast or other cancers for the present monograph, despite the existence of a relatively large number of studies for some cancer sites. The rationale was 2-fold: (1) the existence of a recent, large pooled case–control study that combined the most informative studies on breast cancer; and (2) the heterogeneity of the exposure methods used in the cohort studies, which presented a considerable challenge when pooling effect estimates.

The Working Group noted that differentiating the effects of age at exposure from age at risk is very difficult (if not impossible) in the studies of cancer in humans, hampering interpretation of some of the animal bioassay evidence and its relevance to humans (e.g. stronger effects were seen in some animal bioassays after exposures before or near puberty). Health effects of night shift work may differ across latitude and season. Similarly, factors related to night shift work (and also, potentially, to cancer) such as sunlight exposure and physical activity may also differ across latitude and season.

General comments on experimental systems

Studies in a variety of experimental systems were available to the Working Group, including the traditional experimental rodent species – rats (usually *Rattus norvegicus*), mice (usually *Mus musculus*), and hamsters (usually *Mesocricetus auratus*). These species are considered nocturnal (National Research Council, 2011). Certain strains of mice (e.g. BALB/c, C57BL/6J) do not synthesize endogenous melatonin because of a mutation in the *Aanat* gene, resulting in non-functional arylalkylamine *N*-acetyltransferase (AANAT), an enzyme involved in melatonin synthesis (Roseboom et al., 1998; Kasahara et al., 2010). A limited number of studies have used nonhuman primates including capuchin monkey (*Cebus apella*) and rhesus macaques (*Macaca mulatta*). Monkeys demonstrate diurnal behaviour patterns. Several studies also used diurnal rodents (e.g. fat sand rats, *Psammomys obesus*; Sudanian grass rats, *Arvicanthis ansorgei*) and one nocturnal marsupial species (tammar wallaby, *Macropus eugenii*). Some inconsistencies were seen between these various model systems and traditional laboratory animals.

The Working Group also noted that direct experimental evidence for night shift work in experimental models is incomplete since the experimental systems rely instead on alterations in the light–dark schedule as a proxy for night shift work. Experimental designs used with experimental systems can vary significantly from short-term alterations in the light–dark schedule to continuous light or continuous darkness over one or more days. Exposure in animal models can involve the following experimental conditions:

- Light exposure involving visible light intensity for a variable time duration that occurs during the period of darkness in animals kept under artificial schedules consisting of 12 hours of light followed by 12 hours of darkness (LD12:12), such as those in current use in research animal facilities.
- Light exposure can occur repeatedly during the period of darkness or can be repeated during multiple periods of darkness at any frequency.
- Continuous light exposure, as part of the light-at-night paradigm
- The suppression of melatonin secretion by the pineal gland (includes pinealectomy)
- Phase shift of physiological and molecular circadian rhythms in the whole organism
- Disruption of the circadian timing system, as defined by the suppression and/or the internal desynchronization of circadian rhythms in behaviour, physiology, expression of clock genes, or other molecular or biochemical parameters in various tissues.

Experimental details concerning light intensity during animal husbandry procedures were sometimes lacking in the reviewed studies. Increases in daytime room illumination for maintenance purposes have been shown to change photoreceptor physiology and can alter circadian regulation (Remé et al., 1991; Terman et al., 1991; National Research Council, 1996). In addition, many studies used a light–dark schedule consisting of 12 hours of light followed by 12 hours of darkness as the control situation. Abrupt light and dark transitions are common in animal housing facilities, and do not reflect natural lighting conditions.

Circadian rhythm and clock genes

Hormone secretion, cellular function, and metabolism fluctuate throughout the day (Gamble et al., 2014; Tsang et al., 2016; Neumann et al., 2019). Circadian rhythm is generated through circadian variation in the expression of clock genes. Light and related melatonin production is one of several factors affecting circadian rhythm. Light signals detected by the eyes can synchronize through the retinohypothalamic tract the phase of the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN sends synchronization signals to other cells putatively by hormone secretion, sympathetic innervation, and indirect cues including body temperature, feeding time, and activity (Herzog, 2007). While the light–dark information is not critical for the SCN to orchestrate behavioural and physiological rhythms, the photic inputs are essential for the resetting the circadian phase in the SCN pacemaker, and, hence, synchronization of the peripheral clocks (Dallmann et al., 2016).

The first mammalian clock gene, clock circadian regulator, *Clock*, was cloned in 1997 (King et al., 1997). Since then at least 14 core clock genes have been reported, including *Per1*, *Per2*, *Per3*, *Cry1*, *Cry2*, *Bmal1*, *Tim, Ck1ε*, *Npas2*, *Rev-Erbs*, *Dec1*, *Dec2*, and *Rors*. These genes demonstrate oscillating expression with a rhythmicity of 24 hours (e.g. Hamada et al., 2016). Clock genes help coordinate and synchronize different physiological processes. Interdependent transcriptional–translational feedback loops exist

in cells that contribute to circadian cycles (Bozek et al., 2009). For example, the transcription factor heterodimer Clock:Bmal1 activates the expression of period circadian regulator genes (*Per1*, *Per2,* and *Per3*), cryptochrome genes (*Cry1* and *Cry2*), and nuclear receptors (*Rev-erbα*, *Rorα*). Per and Cry proteins form complexes and repress their own expression by interacting with the Clock:Bmal1 dimer. Rev-erbα and Rorα regulate the transcription of *Bmal1* in a separate feedback loop through retinoic acid receptor-related orphan receptor (ROR) regulatory elements (Solt et al., 2011). Clock output genes (e.g. *Dbp*, *Hlf*, *Tef*, *E4bp4*) regulate clock-controlled genes. Other cell cycle genes are under the direct influence of the circadian clock and include *Wee1*, *Myc*, cyclin D1, and *Tp53* (Hassan et al., 2018). Circadian genes are involved in the regulation of cell division (Hunt & Sassone-Corsi, 2007; Li et al., 2016). Mutant mice deficient in a second clock gene, *Per2*, results in disrupted circadian rhythms, alterations in the expression of genes (e.g. cyclin D1, cyclin A, *Mdm2*, and *GADD45a*) involved in cell proliferation and tumour suppression, and increased tumour incidence (Fu et al., 2002; Matsuo et al., 2003). Mutations in clock genes, such as *Per, Cry,* or *Bmal1,* or chronic disruption of circadian homeostasis, promote genomic instability, induce immune suppression and metabolic dysfunction, and increase the risk of cancer in experimental animals (Fu et al., 2002; Anisimov et al., 2004; Yang et al., 2009; Lee et al., 2010; Anisimov et al., 2012; Geyfman et al., 2012; Kettner et al., 2016; Papagiannakopoulos et al., 2016).

Melatonin in humans

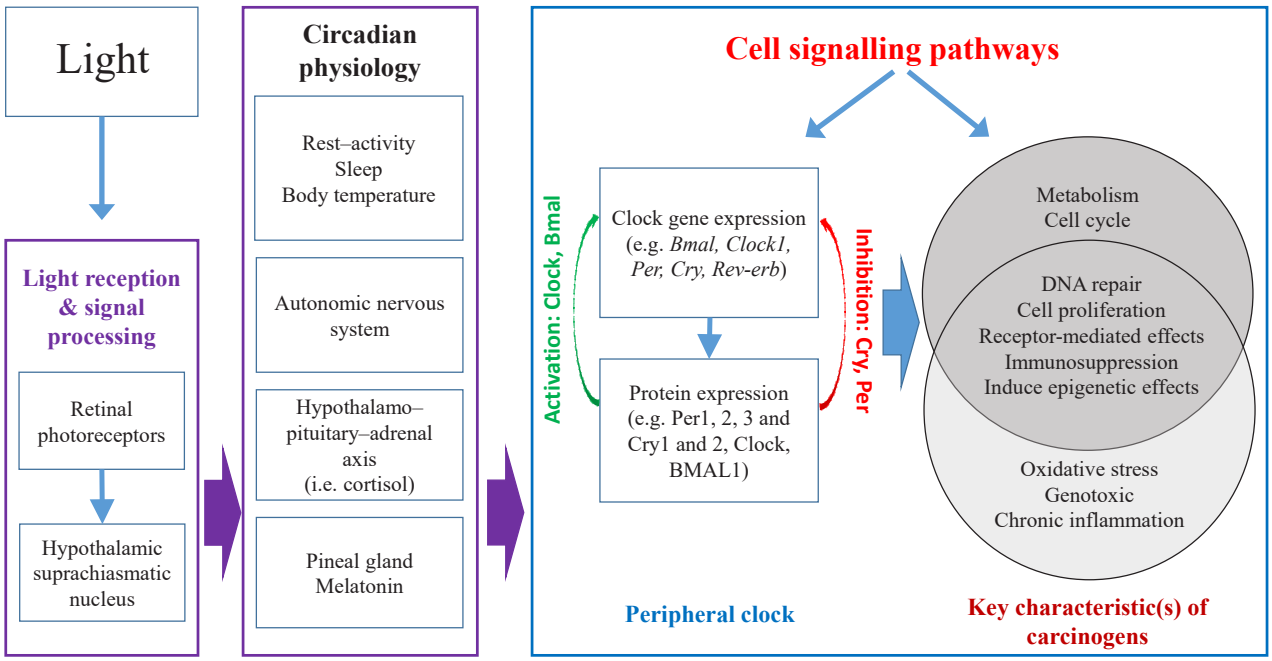
Production of melatonin (*N*-acetyl-5-methoxytryptamine), a hormone secreted by the pineal gland, is rhythmically regulated by the SCN in the hypothalamus. Under the regular alterations of light and darkness over 24 hours, melatonin is the main synchronizer of circadian rhythms. Melatonin secretion increases at night and reaches highest plasma concentrations near 02:00 on average in humans. Melatonin secretion is generally suppressed in the presence of light at night (Bojkowski et al., 1987; Lewy et al., 1980). Even brief (i.e. minutes) exposure to light during hours of natural darkness can alter melatonin production in mammals. Light exposure can also shift the phase of the melatonin rhythm, with exposure to bright light intensities during morning hours being associated with a phase advance, while exposure during evening hours is associated with a phase delay (Duffy & Wright, 2005). Recent data highlight the critical role of blue light in eliciting melatonin responses (e.g. Tanito et al., 2018).

Melatonin metabolism occurs mainly in the liver, where it is hydroxylated and then conjugated as sulfate and excreted mainly as 6-sulfatoxymelatonin (Claustrat et al., 2005). Urinary and salivary 6-sulfatoxymelatonin excretion has been used as a means of monitoring melatonin circadian rhythmicity (Nowak et al., 1987).

Melatonin has diverse pharmacological effects, many of which are mediated through melatonin receptors found in multiple tissues and organs (Reiter et al., 2017; Bondy & Campbell, 2018; Favero et al., 2018). Melatonin also has antioxidant properties secondary to its action as a free-radical scavenger (Tan et al., 2003; Tosini et al., 2014).

Studies linking melatonin secretion to cancer risk are few, and results are inconsistent. For example, a pooled analysis of six independent studies of breast cancer indicated that urinary concentration of 6-hydroxymelatonin sulfate (aMT6s) in the morning hours was not associated with risk of breast cancer (relative risk, 0.97; 95% confidence interval, CI, 0.88–1.08). This result did not vary by menopausal status, estrogen receptor status, or when using 12-hour overnight urine sampling. Time lag between measurement

Fig. 1 Effects of light on circadian physiology and key characteristics of carcinogens



and degree of invasiveness did not affect the results, and no publication bias was detected (Xu et al., 2017); however, in the majority of studies, melatonin measurement followed diagnosis, which might have induced bias.

Fig. 1 illustrates some of the effects of light on circadian physiology, including alterations in sleep, rest, and eating patterns, impacts on the autonomic nervous system and behaviour, disruption of the circadian timing system, as well as changes in body temperature and in melatonin secretion by the pineal gland. The effects on expression of clock genes and other molecular or biochemical parameters are shown as an illustration of the association with key characteristics of carcinogens.

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