

Report on Carcinogens (RoC) Concept: Shift work at night, light at night, and circadian disruption

1 Background and rationale

1.1 Nomination history

Light at night was nominated by several individuals for review for possible listing in the Report on Carcinogens (RoC). One of the reasons cited for the nomination was the 2007 International Agency for Research on Cancer (IARC) Working Group conclusion that “shiftwork that involves circadian disruption” is *probably carcinogenic to humans* (Group 2A) (IARC 2010). IARC’s conclusion was based on (1) limited evidence in humans for the carcinogenicity of shiftwork that involves night work, and (2) sufficient evidence in experimental animals for the carcinogenicity of light during daily dark period (biological night). Considering both the nominee request and the IARC review, the NTP initially defined the nomination as “shiftwork involving light at night” and solicited public comments in January 2012 ([77FR2728](https://www.federalregister.gov/d/2012-01-17)). Three public comments were received (see <http://ntp.niehs.nih.gov/go/37663>), which supported the review of light at night and provided references. The commenters were especially concerned about studies on environmental exposure of people to light at night (“light pollution”), most of which had been published since the IARC review. An overview of the topic, “shift work at night, light at night, and circadian disruption”, and the rationale and challenges in defining the candidate substance(s) associated with this topic are discussed below.

1.2 Shift work at night, light at night, and circadian disruption

The cancer epidemiologic studies of shift workers, including those reviewed by IARC and studies published since that time, were initiated (starting in the mid-1990s) to test the hypothesis that electrical light at night could be a cause of the high rate of breast cancer observed among women in industrial nations. Shift work was considered to be a surrogate for exposure to artificial light at night. The light at night hypothesis was based primarily on experimental data showing that electrical light (depending on the intensity and wavelength) can suppress nighttime melatonin production by the pineal gland and studies suggesting that decreased melatonin levels may play a role in breast cancer development (Stevens *et al.* 1992, Stevens 2011). In addition to the studies among shift workers, the light at night hypothesis has also played a role in stimulating cancer research, both experimental and human epidemiologic studies, on light exposure, melatonin levels and circadian disruption.

Circadian rhythms are daily and predictable variations in biological, physiological, and behavioral processes – such as sleep-wake cycles, body temperature, blood pressure, hormone secretion, metabolism, digestion, glucose homeostasis, and cell-cycle regulation – that are regulated by endogenous clocks. The rhythms are entrained to the external environment by repetitive signals, of which the light-dark cycle is the most important; however, other exposures such as timing of meals can also provide external time cues for coordinating endogenous rhythms. Melatonin plays an important role in transmitting time information (via peak and duration of melatonin production) to many organs and tissues. Circadian disruption occurs when the endogenous circadian rhythms are out of phase with the external environment or with each other (reviewed by Arendt *et al.* 2010, Stevens *et al.* 2011).

Circadian disruption has been proposed to include phase-shifts of the circadian system, displacement of sleep relative to the circadian clock, and/or suppression of nocturnal melatonin

production. Circadian rhythms of individuals who are synchronized to daytime activity and nighttime sleep undergo phase-adjustment after a change in work schedule or travel across multiple time zones. Exposure to light in the latter part of the biological night (such as backward [night to day] rotating shift schedule or traveling eastward) can cause phase advances in circadian rhythms whereas exposure to light in the early part of the night (forward rotating work schedule [day to evening to night] or traveling westward) can cause phase delays. Circadian disruption occurs during the period of adaptation to the new work schedule or time change, and people adapt to the new schedule at different rates. The extent of the disruption depends on many factors such as the direction of the phase, the type of work schedule, and individual susceptibility (Bonde *et al.* 2010, Arendt *et al.* 2010, Erren *et al.* 2010, Stevens *et al.* 2011, Haus and Smolensky 2012). In addition, changes in work schedules affect quality and quantity of sleep and is associated with fatigue.

1.3 Rationale

Numerous studies have evaluated cancer risk among people, who by virtue of the nature of their work, lifestyle choices, or residence, are subjected to interruptions in the natural light-dark cycles, and have the potential for circadian disruption. These include epidemiologic studies among shift workers, aircrew personnel, people exposed to electric light at night via lifestyle choices or geographical residence, and individuals with altered nocturnal melatonin levels (which can be considered a biomarker of both exposure and effect of circadian disruption). In addition there are experimental studies of carcinogenicity related to exposure to light at night, melatonin production, and the circadian system. The potential for circadian disruption among people living in the United States is widespread given the ubiquitous use of artificial lighting at night and large numbers of employees working shifts. Since it has now been accepted as a candidate topic, the ORoC plans to evaluate exposure scenarios that have been associated with circadian disruption for possible listing in the ORoC, but recognizes the challenges in defining a nomination(s) that is based on studies of different types of exposure surrogates associated with circadian disruption and/or light at night. In addition, these exposures are common, so it is important that the candidate substances(s) be defined in a meaningful way that can be communicated to the public and provide information useful for making public health decisions. Therefore, ORoC intends to obtain external scientific and public inputs regarding environmental exposure surrogates (e.g., night shift work, time zone travel) and light at night and/or circadian disruption prior to characterizing the specific candidate substance(s) for RoC evaluation. The proposed ORoC approach is described below and the approach for conducting the preliminary literature search strategy is described in Appendix A.

2 Overview of data related to human exposure

A significant number of people living in the United States are exposed to light at night or other exposures that may cause circadian disruption. People who are exposed to changes in light-dark and/or sleep cycles include night shift workers, aircrew personnel, and individuals living in areas of ambient light pollution or exposed to evening light in their homes as a result of lifestyle choices.

Several lines of evidence indicate that millions of people in the United States work schedules outside normal daylight hours (i.e., 7-8 am to 5-6 pm) either consistently or as part of flexible or rotating work shifts (IARC 2010, Presser and Ward 2011). The most recent estimates of the numbers of Americans who work alternative shifts were compiled by the Bureau of Labor Statistics (BLS) of the U.S. Department of Labor for 2004 (BLS 2005). In that report, almost 15% of full-time workers were reported to have worked an alternative shift (defined as evening, night, irregular, or rotating shifts), with approximately 3.2% of the population identified as working night shifts (BLS 2005). According to the Bureau of Labor Statistics (BLS) data there were approximately 114.8

million full-time workers in the United States in March 2013 (Statista 2013), and an estimated 17 million (14.8%) of them work non-daytime shifts. Occupations and industries with the highest percentages of individuals working night shifts included protective services (e.g., police and fire fighters), leisure and hospitality (e.g., food service and hotel workers), healthcare practitioners and healthcare support, transportation and warehousing, manufacturing, and mining (BLS 2005). Night shift workers included individuals of all ages, genders, and races, although younger people (< 55 years), men, and non-white workers were somewhat more likely to work night shifts. The percentages of workers working any type of alternative shifts in the occupations listed above ranged from 20% to 50%. The exposure of Americans to alternative shifts (defined as “nonday” schedules falling outside 9 am to 4 pm), including working at night, at any time in their employment up to age 39 was estimated by Presser and Ward (2011) to exceed 70% for almost all categories of gender, race, and education.

Individuals who travel frequently across multiple time zones include employees in the airline industry. In addition, these employees are also shift workers. In 2010, there were over 100,000 airline and commercial pilots and over 90,000 flight attendants.

The exposure of people to light at night in the United States goes well beyond occupational exposure. Studies using satellite data (U.S. Air Force Defense Meteorological Satellite Program) identified nighttime illumination (light pollution) for 99% of the U.S. population that exceeded a threshold of 10% above natural sky brightness at 45° of elevation; 83% were exposed to at least 3 times the natural sky brightness, 62% to 9 times, and 30% to 27 times that light level (Cinzano *et al.* 2001). In addition there are numerous individuals (such as college students and parents of infants) who are potentially exposed to evening light in their homes from life-style choices.

3 Overview of the scientific information regarding carcinogenicity

3.1 Human cancer studies

The IARC working group concluded that there was limited evidence of increased breast cancer among women working a night shift. Their review focused primarily on cohort (prospective and retrospective) and case-control studies (nested and retrospective) among shift workers or aircrew personnel that evaluated breast or prostate cancer risk, although a few studies reported risk estimates for cancer at other tissue sites. The review also included a few nested case-control studies of breast cancer and urinary melatonin levels. The studies on shift workers were among nurses, workers of mixed occupations identified from the general population, and radiotelegraph operators. The most common exposure metrics for shift work were: ever working or duration of working shifts, night shifts, or rotating night shifts. Shift work was assessed via questionnaire or interviews (self-reported), employment records, or job exposure metric (e.g., linking occupational histories with survey data linking occupations to night work). Many of the studies were able to evaluate potential confounders for breast cancer. Most of the studies on flight crew personnel (time zone travel and shift work) had relatively cruder exposure measures related to exposure to light at night or circadian disruption (most based on job title) and lacked information on potential confounders; many studies were originally conducted because of concerns of exposure to cosmic radiation (IARC 2010).

Since the IARC evaluation, over 20 epidemiologic studies¹ were identified (via a preliminary, limited literature search) that evaluated shift work, time zone travel, environmental exposure to light at night, and urinary melatonin levels and cancer risk. In general, the newer studies attempted

¹ See References, “Recent epidemiologic studies”

to assess more detailed information about shift work and potential effect modifiers related to circadian disruption. For example, they collected information on the type of shift work (rotating versus permanent, day-evening vs. day-night), direction of shift (forward or backward), consecutive number of shifts, exposure window (age at first shift work, before or after full-term pregnancy, timing of shift work (age), diurnal preference (morning vs. evening), and genetic susceptibility (polymorphisms in circadian genes). In addition, more studies evaluated cancer at sites other than breast, in broader occupational groups, and in different ethnic groups. The environmental studies of light at night exposure included a case-control study on exposure to evening light (Li *et al.* 2010) using self-reported data and several ecological studies assessing exposure to ambient light using meteorological satellite data (Kloog *et al.* 2008, 2009, 2010, Bauer *et al.* 2013). The studies on urinary melatonin levels evaluated breast cancer.

3.2 *Biomonitoring studies*

Numerous studies using urine or blood from shift and day workers have evaluated the effects of non-day shift work on circadian biomarkers (such as melatonin profiles) and circadian gene expression (e.g., promoter methylation) (Stevens 2009, Bollati *et al.* 2010, Zhu *et al.* 2011, Davis *et al.* 2012, Jacobs *et al.* 2013). In addition to evaluating the effects of non-day shift work on melatonin levels, some studies have also looked at associations between urinary melatonin levels and other factors such as ethnicity (Bhatti *et al.* 2013), sleep strategies or sleep duration (Gamble *et al.* 2011, Grundy *et al.* 2009, Wu *et al.* 2008), chronotype (Gamble *et al.* 2011), light exposure (Grundy *et al.* 2009, 2011, Dumont 2011), reproductive hormones (Nagata *et al.* 2008, Grundy *et al.* 2009), genetic polymorphisms (Gamble *et al.* 2011), or job-exposure matrix (Ji *et al.* 2012). These studies may provide information useful for assessing the cancer epidemiologic studies or evaluating potential mechanisms of carcinogenicity.

3.3 *Cancer studies in experimental animals*

The IARC Working Group concluded that there was sufficient evidence in experimental animals for the carcinogenicity of light during daily periods of dark (biological night). Experimental animal models used to evaluate circadian disruption on cancer development or tumor growth included: (1) exposure of animals to chronic alterations in the light-dark environment (e.g., constant light at night or constant darkness, altered light-dark schedules, intermittent light during darkness), (2) experimental phase shifting of circadian activity (simulated jet lag), (3) suppression of nocturnal circadian melatonin (removal of the pineal gland or exposure to dim light during darkness), (4) ablation of central circadian activity (SCN lesions), (5) clock gene mutations, and (6) impact of carcinogen administration at different circadian times (IARC 2010).

3.4 *Mechanistic and other relevant data*

There is a plethora of studies evaluating potential mechanisms related to the disruption of circadian rhythm, light at night, and sleep deprivation (reviewed by IARC 2010, Haus and Smolensky 2012, Fritschi *et al.* 2011). An overview on the circadian system, melatonin suppression, and sleep deprivation is briefly described below.

As mentioned in the background and rationale (Section 1.2), circadian rhythms are entrained to the external environment by repetitive signals, of which the light-dark cycle is the most important. Approximately 10% of genes are under circadian regulation. Light exposure transmits time information (time of day, duration of the day, and day of the year) from the retinal cells in the eye (via the photopigment melanopsin) to the master clocks (or central pacemaker) located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN regulates the numerous peripheral clocks (oscillators) via humoral, endocrine or neural signals. One of the most important circadian

humoral factors is the pineal hormone melatonin, which transmits time information (via peak and duration of melatonin production) to many organs and tissues (Stevens *et al.* 2007, Erren and Ritter 2009, IARC 2010).

The circadian system, which is similar at the molecular level in the SCN and peripheral tissues, comprises a network of genes that interact through positive and negative feedback loops (Hus *et al.* 2012). Exposure to light can cause changes in circadian clock gene expression. The clock genes can act as tumor suppressors and may regulate cell cycle, apoptosis, estrogen signaling systems, and DNA damage response (Fritschi *et al.* 2011). There is a large body of literature that has evaluated effects of circadian genes in tumor progression, including but not limited to experimental studies of tumor promotion in circadian gene knockout mice and studies in humans evaluating genetic polymorphisms in circadian genes and human cancer (IARC 2010).

The pineal gland secretes melatonin in response to the light-dark cycle, which peaks at the biological night. Light (depending on the intensity and spectrum) suppresses melatonin production at night. Melatonin may also be suppressed by repeated phase changes or SCN damage (Haus and Smolensky 2012). Melatonin is proposed to have anti-carcinogenic effects via various mechanisms such as reducing levels of reproductive hormones, enhancing the immune system, and protecting against oxidative damage (Fritschi 2011).

Some studies of shift workers suggest that their length of sleep is 2 to 4 hours less than that of daytime workers. Sleep deprivation may lead to alterations in immune function, inflammation due to metabolic disturbances, oxidative stress, and DNA damage. Sleep deprivation may in part be due to circadian disruption (Haus and Smolensky 2012).

4 Issues and Key Scientific Questions Relevant for the Cancer Evaluation

Based on an initial review of the literature, ORoC has identified several underlying issues or key questions concerning the review of exposures associated with light at night and/or circadian disruption; however, it is anticipated that as these issues or key questions are addressed, additional issues may be identified during the monograph's development. The issues, presented below, are grouped according to the major steps in the evaluation process.

Defining the candidate substance and identifying the types of studies included in the evaluation

- How should the candidate substance(s) be defined so that it accurately reflects the underlying exposure? Is “light at night,” “circadian disruption,” “environmental exposures that induce circadian disruption” best or is something else more appropriate? Is there more than one candidate substance?
 - As mentioned previously, light at night has been indirectly assessed in the human cancer studies using exposure surrogates such as shift work. Shift work is also associated with other factors, of which changes in sleeping patterns leading to sleep deprivation is a particular concern. Sleep deprivation may in part be due to circadian disruption caused by light at night.
 - Defining common exposures or exposure surrogates (such as shift work at night) that is partly defined by an effect (circadian disruption) provides a challenge for communicating useful information to the public. In addition, defining the specific factors or underlying exposure (light at night, circadian disruption) that may increase cancer risk may be more useful for cancer prevention than studying cancer risks associated with specific populations (e.g., shift workers or aircrew personnel).

- Are there other study populations or exposure scenarios that are surrogates for light at night or circadian disruption that should be included in the monograph? Should studies of sleep duration be included in the monograph?

Developing protocols to assess the human cancer studies

- Epidemiologic studies do not have clear and uniform definitions of shift work; e.g., non-day work varies geographically and has not been defined consistently in the epidemiologic studies. In addition, individuals vary considerably in sensitivity to light at night and their ability to adapt to changes in time zones or work schedules. What are the exposure metrics of shift work that are the best surrogates for circadian disruption or light at night? What are the important effect modifiers (e.g., chronotype, genetic susceptibility)?
- Depending on the proposed causal pathways, other characteristics (such as sleep duration) of the study populations (shift workers, aircrew personnel) could be considered as potential confounders or intermediate variables. How should mechanistic data be used to inform interpretation of the epidemiologic studies? Which variables should be considered as confounders, effect modifiers, or part of a causal pathway?

Evaluating the human, animals, and mechanistic studies

- What is the level of evidence (sufficient, limited) for the carcinogenicity of the topic?² What are the cancer sites of interest? Can bias, chance, or confounding be ruled out with reasonable confidence?
- Does the level of evidence vary for the different exposure surrogates or scenarios in the human cancer studies?
- What is the level of evidence (sufficient, not sufficient) of the carcinogenicity of the topic from studies in experimental animals? What are the tumor sites of interest?
- Does the level of evidence vary for different exposure scenarios in the animal cancer studies?
- Many of the studies evaluate tumor promotion or growth rather than tumor incidence. How should that data be considered in the evaluation?
- What are the potential mechanisms by which the topic may cause breast or prostate cancer?
- What are the potential mechanisms by which the topic may cause cancer at other cancer sites?
- Are the findings from studies in humans consistent with the findings from experimental animals?

5 Proposed Approach for Conducting the Cancer Evaluation

5.1 Scope and focus of the draft RoC monograph

The draft RoC monograph for light at night, shift work at night and circadian disruption will consist of two parts: (1) the cancer evaluation component, which reviews and assesses the scientific literature, and applies the RoC listing criteria to reach a preliminary listing recommendation for exposure(s) related to this topic and (2) the substance profile, which provides a concise summary of the scientific information considered key for reaching the listing recommendation. Details on the

² Because the language of the candidate substance(s) involving environmental exposures associated with circadian disruption has not yet been crafted, the term topic is used in asking these questions.

methods for writing the draft RoC monograph and topics typically covered in the monograph are outlined in the NTP process for the preparation of the RoC (<http://ntp.niehs.nih.gov/go/rocprocess>).

The goal of the cancer evaluation component of the draft monograph is to initially review studies of different types of exposure surrogates for circadian disruption and/or light at night, recognizing that during the course of the development of the monograph, the evidence for each type of exposure may be evaluated separately. Because of the complexity of the topic, it is expected that the monograph structure may differ from the typical organization of RoC monographs. The monograph will provide an independent assessment of the cancer studies in humans and experimental animals and mechanistic data. Many of the proposed mechanisms have been described in the IARC monograph and numerous reviews, which will serve as a resource for identifying key topics and writing the mechanistic section of the monograph. In addition, the OROc will seek public and scientific input on the extent and scope of additional information that should be included in the monograph.

5.2 Proposed approaches for obtaining scientific and public input

The OROc has created a web page for the review of shift work at night, light at night and circadian disruption (similar to that developed for other candidate substances), which includes RoC documents related to the review of the nomination, information on webinars or other meetings, and an input box for receiving information or comment from the public.

The first step the OROc will take in obtaining scientific input is to identify a team of appropriate technical advisors, external or internal to the government, with expertise in light at night, circadian disruption, breast cancer and occupational epidemiologic studies to serve as consultants in helping define the candidate substance(s) and/or developing the monograph. Sources for identification of these experts include, but are not limited to, peer-reviewed literature databases and recommendations from the scientific community and the public. For some issues, advisors will be consulted on an individual basis related to their expertise. For other issues, such as those that involve cross-disciplines, the advisors will meet as a group (either in person or by virtual technology) to share information. Some of these meetings to share information will be open to the public.

The technical advisors will provide input at various stages of the development of the cancer evaluation component of the draft monograph and on the key issues and questions largely defined in Section 5 including (1) defining the candidate substance(s) more clearly, and the types of studies to be included in the monograph, (2) developing the protocols used to evaluate the studies, (3) outlining the monograph structure, and (4) reviewing OROc's assessment of the studies.

OROC will seek public input on the first two stages of the monograph development by sharing information on its website including (1) the definition of the candidate substance(s), (2) the detailed literature search strategy, outline of monographs topics and preliminary list of references of the cancer studies in humans and experimental animals and (3) the protocols for evaluating the cancer studies in humans and experimental animals, and (4) the monograph structure.

The NTP may host scientific webinar(s) that allow the technical advisors and public to share scientific information. Topics of the webinar(s) may focus on the issues and questions noted above such as how best to define the underlying exposure(s), the most informative exposure metrics, the proposed causal models, and how mechanistic data can help inform the interpretations of the human cancer studies.

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Approach for Literature Search Strategy: Shift work at night, light at night, and circadian disruption

This document summarizes the approach for identifying literature for the draft Report on Carcinogens (RoC) monograph on “shift work at night, light at night, and circadian disruption.” If this topic is selected to move forward, a more detailed strategy for identifying and reviewing citations will be posted on the ORoC website. The goal of the literature search strategy is to identify information on environmental exposures associated with circadian disruption and/or light at night for the broad range of subjects covered by a RoC monograph, as listed below

- Properties and Human Exposure (focusing on the U.S. population)
- Disposition (ADME) and Toxicokinetics
- Human Cancer Studies (if available)
- Studies of Cancer in Experimental Animals
- Mechanisms and Other Relevant Effects

In general, literature will be identified from the following sources or methods:

1. **General and exposure-related data search:** This search covers a broad range of general data sources such as authoritative reviews (e.g., IARC monographs, U.S. federal, state, and international evaluations) and sources for general exposure information (e.g., Bureau of Labor Statistics, or other sources of data on occupational exposure or information on light pollution).
2. **Database searches in PubMed, Scopus, and Web of Science:** The majority of the primary literature will be identified from these three databases using search strategies that combine terms for the exposure with terms for the monograph subject. Additional biomedical literature database (such as Embase) may also be searched. Technical advisors will be consulted regarding exposure scenarios that disrupt circadian rhythm, and a librarian will be consulted to identify the appropriate search terms for those exposures in the different literature databases. The table below outlines the general approach for identifying studies for the major subject. In addition, IARC has shared its search strategy, which will inform the detailed literature searches.

Subject ^a	Exposures or topics	Approach
Human cancer studies	Identify search terms for the following types of exposure: shift/night work, circadian disruption, light at night or electrical (evening, ambient) light, aircrews and jet lag, melatonin, sleep duration or disruption	Combined search terms for exposure with search terms for human epidemiologic studies and cancer
Studies in experimental animals	Identify search terms for melatonin, circadian disruption, light-dark cycles, jet-lag, biological clocks	Combined search terms for exposure with search terms experimental animal studies and cancer
Mechanistic studies	Identify search terms related to biological clock genes (including specific clock genes) melatonin (including its metabolites and analogues), circadian rhythms, sleep deprivation	Combined search terms for topic with search terms for cancer or other endpoints when relevant

Appendix A

3. **QUOSA library.** A number of QUOSA libraries will be (or have been) created including libraries of occupational case-control studies, cohort studies of occupations associated with high percentage of shift workers (such as nurses and emergency personnel). Full-text searches of the libraries will be conducted using search terms related to non-day work and circadian disruption. The advantage of using this approach is to identify relevant studies that would not be picked up in the database searches because shift work (or other key search terms) is not mentioned in the abstract or key words.
4. **Special topic-focused searches:** Searches on special topics or specific issues identified in the monograph development. Specific topics initially identified include:
 - Biomonitoring studies of melatonin, hormones, epigenetic effects, and other relevant biomarkers of effect or exposure
 - Cancer studies of blind people
 - Genetic susceptibility studies of polymorphisms in clock genes and other genes in the proposed cancer pathways
 - Vitamin D studies
 - Potential confounders
5. **Secondary sources:** Citations identified from authoritative reviews or from primary references located by literature search, together with publications citing key papers identified using the Web of Science “Cited Reference Search,” will be added.

Citations retrieved from literature searches will be uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature are conducted, with initial screening based on titles and abstracts only, followed by full-text screening.