Report on Carcinogens Protocol:
Night Shift Work and Light at Night (LAN): Human cancer studies

Running title- Electric Light: RoC Protocol

May 7, 2018

Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

This Page Intentionally Left Blank

Table of Contents

Peer-Review

The ORoC gratefully acknowledges the following individuals for their peer review of the RoC protocol on *Health Consequences of Electric Lighting Practices in the Modern World*:

Richard Stevens, PhD
Community Medicine and Community Health
University of Connecticut
Farmington, Connecticut

Tania Carreón, PhD
National Institute for Occupational Safety and Health (NIOSH)
Centers for Disease Control and Prevention
Cincinnati, Ohio

Introduction

Protocol objective

The objective of this protocol is to provide the methods and guidance that will be used to prepare the cancer hazard evaluation component of the draft Report on Carcinogens (RoC) monograph on Night Shift Work and Light at Night. This monograph will evaluate whether scenarios associated with exposure to modern electrical light practices that lead to circadian disruption, including light at night (LAN), shift work at night, and transmeridian travel, are associated with cancer risk. This protocol applies the general methods outlined in the Handbook for Preparing RoC Monographs (hereinafter referred to as RoC Handbook 2015) to issues specific for these exposure scenarios. The protocol mainly focuses on the systematic review methods for evaluating the human cancer studies.

Background information

The invention of electric light has facilitated a society in which people work, sleep, eat, and play, at all hours of the day, including night. With the expansion of the global economy over the last several decades, exposure to unnatural light has increased to accommodate an increasingly 24/7 culture.

LAN 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 "shift work 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 shift work that involves night work (presumed to be a proxy for LAN) and (2) sufficient evidence in experimental animals for the carcinogenicity of light during daily dark period (biological night). Considering both the nominees' request and the IARC review, the NTP initially defined the nomination as "shift work involving LAN" and solicited public comments in January 2012 (Federal Register 2012). Three public comments voiced concern about environmental exposure to LAN ("light pollution") for the general public. Based on this input, NTP then developed a concept on shift work at night, LAN, and circadian disruption (available at http://ntp.niehs.nih.gov/go/41532.

To obtain input on an approach to the health hazard evaluation and to identify data gaps and research needs, NTP convened a workshop in 2016 with experts in a variety of fields (for more information, see http://ntp.niehs.nih.gov/go/workshop_ALAN). "Health consequences of electric lighting practices in the modern world" was recommended as a unifying theme for the NTP monographs by workshop participants. The rationale for this recommendation was that electric light acts as both an effector (based on direct effects on circadian disruption and melatonin suppression, and animal models and human studies of light pollution and indoor light), and as an enabler, allowing what were once daytime activities to be conducted 24/7. And thus, electric light as both an effector and an enabler of additional activities or behaviors (e.g., shift work), may lead to circadian disruption.

Objective and scope of the monograph

Based on input from the workshop panel and due to the overlapping nature of the exposures, studies of cancer with exposure scenarios related to unnatural light will be included in the hazard evaluation. The two major exposures related to modern lighting practices are LAN and night shift work, thus the monograph title reflects those exposures.

The objective of the monograph is to reach a preliminary listing recommendation for night shift work and exposure to LAN for the RoC and to adequately define these two exposure scenarios as they relate to cancer. Human cancer studies of transmeridian travel will also be reviewed as this involves exposure to both LAN and shift work. The key scientific questions of the monograph are as follows:

- Do a significant number of people residing in the United States work night shifts?
- Are a significant number of people residing in the United States exposed to LAN?
- Should night shift work be listed in the RoC?
  - If so, how should it be defined?
  - Can we define the underlying exposures related to circadian disruption?
- Should LAN be listed in the RoC?
  - If so, how should it be defined?

The preliminary listing recommendations will be reached by applying the RoC listing criteria. Conclusions regarding the carcinogenicity of exposure scenarios associated with electric lighting practices as well as mechanistic and related data are based on scientific judgment with consideration of all relevant data.

Known to be a human carcinogen

- *Sufficient evidence of carcinogenicity from studies in humans**: indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably anticipated to be a human carcinogen

- *Limited evidence of carcinogenicity from studies in humans**: a causal interpretation is credible, but alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded.

- Sufficient evidence of carcinogenicity from studies in experimental animals, OR
- Substance belongs to a structurally related class of substances that are listed in the RoC, OR
- Convincing relevant information that the agent acts through a mechanism indicating it would likely cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

As circadian disruption is a key intermediate in the pathway between exposure and potential cancer, this monograph reviews studies evaluating exposure and circadian disruption and studies on circadian disruption and cancer. The table below summarizes the evidence streams, exposures of interest, and outcomes. This is somewhat analogous to a "population, exposure, comparator, outcome" statement except that population has been replaced by evidence stream (e.g., humans, experimental animals, *in vitro* studies).

Evidence stream[a]	Exposure (intermediate)	Comparison group	Outcome
Main effect			
Human epidemiology studies	Night shift work	Day shift workers	Breast cancer, prostate cancer, colorectal cancer, lung cancer, hormonal cancers
Human epidemiology studies	LAN Outdoor LAN LAN in the sleeping area	Low exposure to LAN	Breast cancer
Human epidemiology studies	Transmeridian travel	Large number of trips vs. lower number of trips	Breast cancer
Supporting studies			
Experimental animals	LAN proxies: continuous light, dim light at night, interrupted light	Standard lighting, usually 12 hr light and 12 hr dark	Total neoplasms (usually combined) Primarily tumor proliferation, promotion, or latency promotion Cancer site is dependent on type of initiator and xenograft Mammary gland or human breast (xenografts) is most studied site
Experimental animals	Shift work proxies Simulated shift work Chronic jet lag	Standard lighting, usually 12 hr light and 12 hr dark	Spontaneous tumors in cancer-prone mouse model Primarily tumor proliferation, growth or latency; cancer site is dependent on type of initiator and xenograft Mammary gland or human breast (xenografts) is one of the studied sites
Intermediate effects: Exposures and biomarkers of circadian disruption or biological effects			
Human molecular epidemiology	Night shift workers Night shift among rotating shift workers	Day shift workers Day shift among rotating shift workers	Circadian disruption: Primarily melatonin and clock gene expression

Evidence stream[a]	Exposure (intermediate)	Comparison group	Outcome
Human experimental studies	Different types of light (e.g., wavelength, level, duration, timing)	Same individuals or comparisons of other subjects exposed to "control" lighting conditions	Circadian disruption: Primarily melatonin and clock gene expression
Experimental animal studies	LAN proxies	Standard lighting, usually 12 hr light and 12 hr dark	Circadian disruption: Primarily melatonin and clock gene expression
Experimental animal studies	Simulated shift work or chronic jet lag	Standard lighting, usually 12 hr light and 12 hr dark	Clock gene expression
Molecular epidemiology studies	Night shift work	Day shift workers	Biological effects related to cancer (e.g., 10 characteristics of carcinogens)
Experimental animal studies	LAN proxies Simulated shift work or jet lag	Standard lighting, usually 12 hr light and 12 hr dark	Biological effects related to cancer
Circadian disruption biomarkers to biological effects or cancer			
Human epidemiology studies	Circadian disruption Melatonin or melatonin proxies (blind people)	General population (for blind people) or sighted people Low vs. high levels	Breast cancer
Human epidemiology studies	Circadian disruption Clock gene polymorphisms	Clock gene polymorphisms	Breast cancer susceptibility
Review (human, animal, & *in vitro*)	Melatonin, clock gene expression	Not relevant	Cancer and biological effects related to cancer

[a]Evidence stream replaces population.

The monograph will conduct a systematic review of the individual human cancer studies as part of its cancer hazard assessment (see Part 2 for methods). For the supporting and intermediate endpoints, the monograph will assess scientific information from a combination of primary studies, and authoritative and other reviews but will not conduct a systematic review of individual studies (e.g., normal quality evaluation) (see Part 3 for methods). Experimental animal studies play a key role in understanding specific exposures and mechanisms, and provide input for interventions; however, animal studies will not be systematically reviewed and no level of evidence conclusion will be made based on this literature. Studies of light in animals do not fully replicate the complex and overlapping exposure scenarios in humans.

Protocol components

This protocol discusses the methods that will be used to prepare the cancer evaluation component of the draft monograph on *Health consequences of electric lighting practice in the modern world.*

- Part 1: Outline of the Draft RoC Monograph
- Part 2: Systematic Review Methods for Evaluating Human Cancer Studies
- Part 3: Scope and Methods to Review Supporting Information

Appendix A provides the literature search strings that are specific for electric lighting practices.

This Page Intentionally Left Blank

1 Outline of the Draft RoC Monograph

The major sections in the monograph are as follows:

- Section 1: Circadian regulation and modern electric lighting practices
- Section 2: LAN and night shift work-induced circadian disruption
- Section 3: Human breast cancer studies: Night shift work, LAN, and transmeridian travel
- Section 4: Other types of human cancer
- Section 5: Cancer studies in experimental animals
- Section 6: Mechanisms and other relevant data
- Section 7: Evidence integration and preliminary listing recommendations
- References
- Appendices

The appendices in the Draft RoC Monograph will contain important supplementary information such as the literature search strategy, study quality tables for human cancer, and results from supporting studies.

This Page Intentionally Left Blank

2 Methods for Evaluating Human Cancer

The human cancer evaluation component of the draft monograph separately evaluates the relationship of breast and other cancers and the three exposure scenarios related to exposure to electric lighting practices: primarily (1) shift work, (2) LAN *per se*, and (3) transmeridian travel or jet lag. If literature searches yield cancer studies on social jet lag or use of consumer electronics (i.e., parents with infants, weekend/weekday differences in sleep schedules, adolescent sleep schedules, use of electronics at night, etc.), these will also be evaluated.

Key questions for each exposure scenario

- What are the methodological strengths and limitations of studies related to exposure scenarios (e.g., shift work, LAN, or transmeridian travel) associated with modern electric lighting practices?
- What are the potential confounders and effect modifiers for cancer risk for the tumor sites of interest in these studies?
- Is there a credible association between these exposure scenarios related to electric lighting practices and cancer?
- If so, can the relationship between cancer endpoints and each of these exposure scenarios be explained by chance, bias, or confounding?

The four steps for conducting the human cancer hazard evaluation are outlined below. The procedures and guidelines for conducting each step are described in Sections 2.1 through 2.4 of this protocol.

1. Identification and selection of human studies of electric lighting exposure practices to be included in the cancer hazard evaluation from the literature (Section 2.1)
2. Systematic extraction of data from the epidemiologic studies of cancer (Section 2.2)
3. Assessment of the utility of individual epidemiologic studies for each exposure scenario (Section 2.3)
4. Cancer hazard assessment which includes an evaluation of the evidence from each study, evaluation of the individual studies including the evidence from each study, and a synthesis of the evidence across studies (Section 2.4)

No human cancer studies have adequately evaluated shift work associated with circadian disruption *per se*. We hypothesized that working extreme conditions of night shift work may be a possible proxy for circadian disruption. Extreme conditions refer to longer duration, higher frequency, or younger age (which is the susceptible time period for exposure to breast cancer carcinogens). In addition, risk may vary by the type of breast cancer or effect modifier. These factors informed the systematic review of the study quality (e.g., studies that were able to evaluate these factors were considered to be more informative) and in the cancer hazard assessment (e.g., the evidence for each of these metrics across studies was systematically evaluated).

2.1 Identification and selection of relevant literature

Citation databases, including PubMed, Scopus, or Web of Science, will be searched for epidemiological studies evaluating cancer and shift work, LAN, or transmeridian travel using the strategy outlined in the table below. In addition, searches will be conducted to identify other types of unnatural light exposures (such as the use of consumer electronics or exposure scenarios associated with social jet lag). Because this exposure scenario is less defined than the other exposure scenarios, these search terms will be limited (e.g., combined using the word "and") by terms focused for circadian disruption before being combined with epidemiological and cancer search strings.

Table 2-1. Literature search strategy for human cancer studies on light-related exposures

Type of "exposure"	Search strategy
Night shift work	(Shift work string[a]) and (RoC human epidemiological string[b]) and (RoC cancer string[b])
LAN (e.g., light in the bedroom, outside light)	(LAN string[a]) and (RoC human epidemiological string[b]) and (RoC cancer string[b])
Transmeridian travel	(Transmeridian travel string[a]) and (RoC human epidemiological string[b]) and (RoC cancer string[b])
Other light exposures	(Unnatural light exposure string[a] and focused circadian disruption string[c]) and (RoC human epidemiological string[b]) and (RoC cancer string[b])

[a]See Appendix A, Exposure scenarios for search string terms.
[b]See RoC Handbook Appendix: Standard search strings for databases searches (2015) for search terms for epidemiological studies and cancer.
[c]Search terms for broad categories are combined with focused search terms for circadian disruption to increase specificity of the search, see Appendix A, Intermediate effects for search string terms.

Search results are processed in Endnote and imported into Health Assessment Workplace Collaborative (HAWC) software to identify relevant literature as described (HAWC (https://hawcproject.org/). HAWC is an open-source, modular, content-management system designed to facilitate synthesis of multiple data sources, integrating and documenting workflow from literature search to data extraction, synthesis, and interpretation). Citations are screened for primary epidemiologic studies using general approaches outlined in the RoC Handbook. Studies are initially included in the evaluation if they meet the following inclusion criteria for Levels 1 (titles and abstracts) and 2 (full text):

- Primary studies (including analytical epidemiologic studies, descriptive studies) and pooled analyses.
- Studies providing supporting information for topics that are relevant to the evaluation of the human epidemiologic evidence including but not limited to qualitative reviews or letters to the editor, and information on co-exposures or potential confounders.
- Meta-analyses of studies of shift work, LAN, and transmeridian travel will not be included in this evaluation as these analyses typically combine exposures not strictly comparable. Individual studies in the reviews will be confirmed against primary literature searches.

Primary epidemiologic studies will be included in the review if they meet the following inclusion criteria (Level 3).

- The publication is a peer-reviewed, primary research study on potential exposure to LAN, shift work, transmeridian travel, or social jet lag, or other light-related exposure at the individual level.
- The study reports a risk estimate (or information to calculate a risk estimate) for cancer.
- Country-level environmental studies of light pollution and human cancer using light and sky glow data captured by sensors on satellites and transferred into the U.S. Defense Meteorological Satellite Program's (US-DMSP) database will not be included in the evaluation. In addition to the lack of individual level data in these studies, confounding is often a serious source of bias, as confounders are also not measured at the individual level. Findings of these studies will be briefly discussed in the text. However, studies with exposure measurements based on sky glow database of the U.S. Defense Meteorological Satellite Programs (US-DMSP) for geographically defined areas linked to individual residential address data and individual level cancer data will be included.
- Only those peer-reviewed, primary research studies of transmeridian travel that assess exposure based on metrics measuring time zones crossed or a proxy for the number of time zones crossed will be included in the quality evaluation.

2.2 Systematic extraction of data from the epidemiologic studies

The latest published follow-up or update for each of the cohort, nested case-control, and case-control studies is extracted for each cancer endpoint included in the study. Additional relevant information (such as exposure data or re-analyses) from earlier and related publications on the same or overlapping study population(s) is also included if these publications provide unique or additional data to inform the cancer evaluation of the primary study under review.

Detailed information regarding study data and methods abstraction from individual studies is described in the RoC Handbook, Part D, Section 3. Briefly, data are selected and entered into NTP Table Builder, a database specifically created for entering information from scientific publications in a systematic manner using standardized instructions and questions. The database contains "fields" that are specific for the different types of extracted information (e.g., study population characteristics, exposure and disease assessment, analytical methods, confounders, and results). Questions and guidelines are available to describe the specific type of information that should be summarized or entered into each field; and selected fields are used to populate tables in the monograph.

2.3 Assessment of the utility of the individual epidemiologic studies

Each primary study is systematically evaluated for its ability to inform the cancer hazard evaluation using five domains related to risk of bias (selection and attrition bias, exposure assessment, outcome assessment, potential confounding, and analysis and selective reporting), and one domain related to study sensitivity. General methods used to assess the utility of the individual epidemiologic studies are described in detail in the RoC Handbook, Part D, Section 4. Briefly, this protocol discusses issues specific for studies related to LAN, shift work, and transmeridian travel.

Domain-level judgment terms: Responses for core questions

The evaluation of the potential for bias in each domain is captured by core questions. A series of signaling and follow-up questions are used to address specific issues related to the core question and are used to provide transparency for the domain level judgment provided below; the responses to the questions are captured in the rationale for the response to the core question. These questions are not meant to be a checklist. When adequate information is available, a judgment is made for the direction and distortion of each bias.

- *Low/minimal concern (+++):* Information from the study design and methodology indicate that the study is close to ideal and that the potential for bias is unlikely, recognizing general limitations of observational studies.
- *Some concern (++)*: The study design or methodology is less than ideal, and there are some concerns about potential bias.
- *Major concern (+):* The study design or methodology suggests that the potential for a specific type of bias is likely.
- *Critical concern or inadequate (0):* Distortion of estimates due to bias makes the study unreliable for hazard identification.
- Inadequate information

Our approach will be to evaluate the components of study quality separately for studies on each of the three exposure scenarios (LAN, shift work, and transmeridian travel) using the questions, domain level ratings, and guidelines given below. For some types of bias, the questions and guidelines will be identical for both exposure scenarios and that will be noted.

2.3.1 Selection and attrition bias

Core question, domain level ratings, and guidelines for the domain level ratings are provided below. For more information on selection bias including signaling and follow-up questions, see the RoC Handbook, Part D, Section 4.2.1 and Table D-2.

Core question and ratings

Core question

Is there a concern that selection into the study or out of the study was related to both exposure (e.g., LAN, shift work, or transmeridian travel) and to cancer?

Domain level ratings

Low/minimal concerns: (***) rating

Cases and controls selected from the same population using similar methods and criteria. No evidence that selection of the subjects is related to both exposure (e.g., LAN, shift work, or transmeridian travel) and cancer.

Cohort is clearly defined (e.g., includes groups of those exposed [e.g., to LAN, shift work, or transmeridian travel] or unexposed) for a specific time period/location with no evidence that follow-up differs between the exposed and non-exposed.

There is little evidence of a healthy worker survival effect or left truncation that could materially bias the results.

Critical concerns: Inadequate rating

Strong evidence that selection or attrition of subjects is clearly related to both exposure to LAN, shift work, or transmeridian travel and cancer.

Guidelines for domain level judgments

Cohort studies

In cohort studies, the exposed and unexposed groups should ideally be similar in all respects except for an exposure history of interest. Systematic biases may be introduced if the length and completeness of follow-up differ between exposed and unexposed groups and are related to the outcome of interest (Pearce *et al.* 2007). Ideally, the total loss to follow-up should be less than approximately 5% over the duration of the study observation period, although incidence studies may have greater loss to follow-up than mortality studies. Statistical power may also be reduced in studies having a high percentage of all subjects (regardless of exposure and disease status) lost to follow-up. Depending on the type of cohort and the specific design of the study, concerns about the healthy worker effect (HWE) and its variants – healthy worker survival effect (HWSE) and left truncation (Applebaum *et al.* 2011, Picciotto *et al.* 2013).

Nested case-control studies conducted either within retrospective manufacturing cohorts or within longitudinal cohorts of particular professions or general populations assembled to study a range of endpoints and exposures can avoid HWE, since by definition, cases and comparisons come from the same source population.

Both retrospective and prospective cohort studies of shift work have been conducted. These studies include either cohorts of workers in manufacturing or industrial settings assembled to study occupational exposures, in which shift work is one of multiple exposures examined retrospectively through the review of administrative records; or longitudinal cohorts in which volunteers from the general public or professions in which shift work is common (e.g., nurses, military service members) provide information either prospectively or retrospectively (after cancer determination) about past night shift work. Issues relevant to specific types of cohort studies of shift work are discussed below.

Shift work has an important behavioral element, that is, individuals select themselves into or out of jobs requiring night work or rotations depending on a variety of responses (e.g., economic, social, psychological, physical) to night work. In general, selection in or out of shift work jobs is likely to be highly dependent on an individual's tolerance to shift work (Reinberg *et al.* 1989) (imposed by the employer or self-imposed), which can result in an exposed study group who are different than those who did not remain in the cohort. Those remaining may be more or less susceptible to chronic disruptions caused by shift work. For example, Reinberg *et al.* (1979) showed that individuals with high amplitude circadian rhythms measured by body temperature and cortisol shifted slowly from day to night shift and had more complaints than those with low amplitude rhythms who shifted very quickly. Also, the overlapping concept of left truncation can occur when workers hired prior to the start of the study and still working at baseline are followed over time. Historical or cultural trends in shift work policy vary across populations and across

time, such that prevalent hires may have had different patterns of exposure to shift work than incident hires (workers arriving after the start of the follow-up period). To avoid such selection biases, an ideal cohort would include a significant number of newly hired shift workers. Newer workers could be compared with workers of longer duration on a variety of criteria related to the conditions or patterns of shift work to assess the potential for bias. Alternatively, analyses could be conducted excluding short-term workers and comparing results with those from the full cohort.

In the manufacturing cohorts, selection in and out of the cohorts can result in an exposed study group of shift workers who are different than those who did not remain in the cohort. In the flight studies, bias from HWSE and left truncation are also possible as patterns of flights, length of hours, number of time zones crossed, etc. may have changed over time, and also, individuals susceptible to disruption from such schedules may remove themselves from the cohort (Applebaum *et al.* 2011, Pearce *et al.* 2007, Picciotto *et al.* 2013).

Finally, selection bias in cohort studies may arise from initial selection into the cohort such that current shift workers, or those most susceptible to disruption from shift work may not be as likely to be recruited, or cohorts of older participants, if cancer occurs in the younger individuals with exposures at younger ages, may not be sensitive enough to detect such an effect. Similarly, follow-up time of disease outcomes may differ for shift workers and non-shift workers, as suggested by the findings from Tsai *et al.* (2014), which could bias the results towards the null.

Case-control studies

Cases and controls should be selected from the same underlying population during the same time period using similar methods and criteria. Ideally, diseases other than the outcome of interest related to LAN or shift work would be known and shown not to differ between cases and controls. Also, participation rates should be high and be similar for cases and controls, although it is recognized that participation rates in population-based case-control studies are sometimes lower than those in hospital-based or nested case-control studies.

While the HWE has the most serious impact in cohort studies, population-based case-control studies that seek new recruits may also be susceptible to selection factors, in that fewer current shift workers may participate in a study that may require a significant time commitment. Tsai *et al.* (2014), using data from the National Health Interview Survey, found that women who work alternative shifts (i.e., any shift outside of regular daytime working hours) are less likely to adhere to cancer screening recommendations than their daytime shift counterparts, particularly for breast and colorectal cancer.

2.3.2 Information bias: Potential exposure misclassification

One of the most important aspects of a study is the ability to characterize exposure at the individual level. Core question, domain level ratings and guidelines for the domain level ratings are provided below. For more information on exposure misclassification including signaling and follow-up questions, see the RoC Handbook, Part D, Section 4.2.2 and Table D-3. See the RoC handbook for a more general discussion (such as signaling questions).

Core question and ratings

Core question

Is there a concern that the exposure assessment methods for LAN, shift work, or transmeridian travel do not distinguish between exposed and non-exposed subjects or exposure categories?

Domain level ratings

Low/minimal concerns: (***) rating

Exposure assessment methods of LAN, shift work, or transmeridian travel have good sensitivity and specificity leading to reliable classification (or discrimination) with respect to both ever exposure, exposure level, timing, or other relevant metrics (see guidelines for characteristics of ideal exposure assessments). Alternatively, exposure assessment methods may be less than ideal, but detailed information on exposure assessment allows for discrimination between exposed and non-exposed and exposure category.

Critical concerns: Inadequate rating

Exposure to LAN, shift work, or transmeridian travel is not at the individual level or not likely to reflect relevant individual exposure. Study has poor sensitivity and specificity resulting in poor discrimination between exposed and non-exposed individuals.

Guidelines for reaching domain level rating

LAN

Studies that include a comprehensive evaluation of light exposures and capture the total light emanating both from the indoor and outdoor environments are most useful for assessing exposure to LAN (Hurley *et al.* 2014). An ideal study of LAN would include validated questionnaire data or data from light loggers that would characterize all aspects of light that can lead to circadian disruption including amount (dose, intensity), spectrum (e.g., wavelength), distribution, timing, and duration of exposure. As light exposure during the day influences melatonin suppression (Hebert *et al.* 2002, Rea *et al.* 2008, Rea *et al.* 2010), measures of light exposure during the day would be included as well (see Workshop Report). However, light loggers or spectroradiometers which can quantify the complex photoreceptive inputs to non-visual responses have not been available for use in large epidemiologic studies, and only recently have questionnaires been validated against light loggers (Bajaj *et al.* 2011).

Thus, studies including more detailed assessments aligning light levels with those known to affect circadian rhythms would be assigned higher quality ratings than those with less precise details. For example, questions about the presence of light in the sleeping habitat (e.g., keeping lights on while sleeping, exposure to outside light, sleeping mainly in the daytime, not drawing the curtains/window shades while sleeping at night, turning lights on during sleep hours, falling asleep with TV on, turning the TV off prior to sleep, use of bed lamps or room lamps for reading before sleep, wearing masks during sleep) should capture some information about level of light, timing, and duration of exposure. Questions assessing the subjective level of light in the sleeping habitat, should be asked in such a way as to enable linkage with levels known to affect the circadian system, such as the suppression of melatonin levels. Studies using satellite measurements of light as surrogates for indoor bedroom lighting are likely to misclassify

exposure, even though they may differentiate high and low levels of light pollution on a global level. Rea *et al.* (2011) found that satellite photometry is unrelated to personal light exposures as they might affect melatonin suppression and/or circadian disruption.

The strength of the association between exposure and cancer risk may be stronger in analyses using lagged models that are consistent with knowledge of the latency of a specific type of cancer or other experimental data; in addition, the reference period for light in the sleeping area should align with the known latency for cancer, although questions about lighting 10 or 15 years in the past may be less well remembered than more recent referent periods. Studies using self-reported data from questionnaires ideally would provide some evidence of their validity in the target population either using validated questionnaires or internal validation against a standard. For example, Bajaj *et al.* (2011) validated the Harvard Light Exposure Assessment (H-LEA) questionnaire - a self-administered semi-quantitative questionnaire on current light exposure. They compared photopic scores derived from the questionnaire with circadian measurements from a "real life" 7-day light meter application among rotating night shift workers and day workers in the Nurses Health Study II and found a high correlation (0.72) between the light meter and self-reported light exposure. However, they also found that self-reported LAN in the distant past is likely to be subject to greater error.

Finally, recall bias in case-control studies of cancer can arise from self-reported exposures, particularly when the exposure has received extensive discussion in the popular press. LAN has not been extensively associated with cancer in the popular imagination over the past two decades (that is, during the course of data collection for most existing studies), thus it is unlikely that misclassification of exposure in most studies is differential by case and control status, although this consideration should not be excluded.

Shift work

Shift work is a complex multi-dimensional exposure with a range of associated effects or exposures; and the most relevant exposure metrics for any cancer are unknown. Guidance on measurement issues is provided below.

In general, the potential for bias in exposure assessment in studies of shift work should consider three factors: (1) how night work is defined, (2) the quality of the measurements, and (3) the inclusion of multiple metrics which may differentiate subjects with the most extreme exposures from those with weaker exposures.

Definitions of night shift work. Across studies, definitions of night work should be similar. Garde *et al.* (2016) found the most agreement and least potential misclassification among night work studies by using a definition of night work that specified a minimum number of hours of work during biological night (e.g., between midnight and 5:00 am) or limited the definition of biological night to a narrow range of hours (e.g., any time between 1:00 am and 4:00 am) rather than a broader range, say from 11:00 pm to 7:00 am. Also, in studies with large proportions of women ever performing night work (e.g., nurses), the definition of "unexposed" is important. As most nurses are routinely assigned night shifts during training, the small numbers of "unexposed" women in these studies might not be completely unexposed, which would disproportionately tend to bias the results towards the null.

Quality of exposure assessment. At the most general level, to avoid misclassification and increase the quality of the exposure assessment, in-person interviews are preferred over mailed or phone interviews, and information obtained directly from the subject is preferred over information from proxies. Studies including detailed assessments based on self-report would be assigned higher quality ratings than those with less detail. Details about shifts worked in the past would ideally come from self-reported retrospective questionnaires or interviews that query lifetime job histories. Participants would indicate the approximate number of hours per week worked, their usual hours, the number of shifts per week, and the length of time working these hours for each job they worked. Alternatively, some employer-maintained work histories have reliable information that could be used for this purpose (Fekedulegn *et al.* 2013). As self-reported data can be susceptible to non-differential memory bias, questions about job-by-job histories that provide multiple prompts to help respondents remember can minimize this bias compared to more general questions about night work. Furthermore, the collection of complete job-by-job data enables the examination of multiple exposure windows, including the earliest exposures to night work.

Studies using only job titles which have been probabilistically ranked as likely to include shift work would be assigned a lower quality rating than studies which gather more data about detailed work patterns from individuals or employment records. Potential misclassification of exposure may or may not be reduced in studies using a job-exposure matrix (JEM) or expert assessment of information on tasks and jobs collected via detailed occupational questionnaires and interviews. However, changing shift work patterns over time can introduce misclassification. Ideally, studies would address potential cohort effects as interactions or as effect modifiers, conducting analyses of shift work and cancer within various periods of follow-up. For example, Pijpe *et al.* (2014) report that in the Nightingale study, the mean number of consecutive night shifts has declined over time (1960 to 2011) from 7 nights in a row to mostly 2 to 4 nights in a row; in addition, currently, < 1% of shifts are backward rotating shifts while 77% are variable shift patterns unlike patterns in previous years (Pijpe *et al.* 2014).

Multiple metrics of exposure. Studies that include one or more metrics of exposure which may differentiate the most highly exposed from those with inconsequential exposure could help elucidate the type of exposure with the most impact on risk and should receive higher assessment ratings. For example, shift intensity according to the IARC Working Group Report (Stevens *et al.* 2011) can refer to regular/irregular shift schedules, time schedules of each shift, intensity of night work and intensity of work week (part-time or full-time work), permanent/rotating night shifts, direction and speed of rotation, consecutive night shifts, forward or backward rotations, permanent versus rotating shift work, classifications based on time schedules, and exposure window (age at first shift work, or timing before or after full-term pregnancy, or recency of exposure) as potential metrics to capture those most highly exposed.

Transmeridian travel or social jet lag

When travelers rapidly cross several time zones in one day, their bodies are not synchronized to the day/night cycle at their destination, upsetting normal biological rhythms including sleeping and eating, which further desynchronizes the master and peripheral clocks from each other and the rest of the body (Härmä *et al.* 1994, Tajima *et al.* 1991). Traveling west to east, compared to east to west, for most persons whose inherited circadian period tends to be slightly greater than 24 hours is more difficult due to advancement of time or loss of night, i.e., shortening of the 24

hour "day." Ideally, in studies of transmeridian travel, the most relevant metrics for assessing exposure to circadian disruption are counts of the number of time zones crossed or flight hours worked during the standard sleep interval (SSI, defined as sleep between 10:00 pm and 6:00 am) (Grajewski *et al.* 2011, Waters *et al.* 2009). Studies using such metrics would be assigned a higher quality rating than those using only "international travel," for example, to assess exposure to desynchrony.

Similarly, the effects of desynchrony or what is referred to as social jet lag, are experienced among the vast majority of non-shift working Americans who wake to the alarm clock during the work week and sleep later on the weekends, equivalent to traveling across several time zones (Roenneberg *et al.* 2012). Studies of social jet lag would ideally assess exposure using self-reported lifetime weekly sleep habits.

2.3.3 Informational bias: Potential outcome misclassification

Studies are evaluated for their adequacy in measuring disease outcomes, including missing data and the probability of misclassification of disease. Similar to exposure misclassification, the effects of non-differential misclassification of a binary endpoint will produce bias toward the null, provided that the misclassification is independent of other errors. Also, when the risk of disease is low in both exposed and non-exposed (< 10%), the odds ratio will remain biased towards the null although the bias will be small (Rothman *et al.* 2008). However, when both exposure and disease are non-differentially misclassified but the classification errors are dependent, it is possible to obtain substantial bias away from the null (Chavance *et al.* 1992, Kristensen 1992).

Core questions and domain level ratings are provided below (see Part D, Sections 4.2.3 and Tables D-4 of the RoC Handbook for a discussion of these potential biases and signaling and follow-up questions.

Core question and ratings

Core question

Is there a concern that the outcome measure does not reliably distinguish between the presence or absence (or degree of severity) of the cancer under study?

Domain level ratings

Low/minimal concerns: (***) rating

Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.

Critical concerns: Inadequate rating

There is strong evidence that the methods do not discriminate between diseased and non-diseased subjects and/or that follow-up and diagnoses are likely to be related to exposure status.

Guidelines for reaching domain level rating

Ascertainment of cancer diagnosis in studies of LAN and shift workers would best be based on medical records, and/or cancer registry data. Incidence data from population-based cancer

registry sources or hospital pathology data are generally more detailed and accurate than death certificates, as their source is medical records and cancer registry data. Ideally, cases of cancer should be histologically confirmed and/or undergo independent pathology review (for at least a subset of the cases).

The major cancer sites of interest are breast and prostate. Age-adjusted annual incidence of breast and prostate cancers (per 100,000 males or females) in the United States from 2009 to 2013 (U.S. SEER Statistics - http://seer.cancer.gov/statfacts/html) are breast (125.0 for females) and prostate (129.4 for males). Both cancer sites have relatively long 5-year survival based on SEER age-adjusted data from 2009 to 2013 (breast is 89.7%, prostate is 98.9%) suggesting that incidence data is more informative since mortality analysis would miss cases with longer survival and later death. Non-differential (not related to exposure status) misclassification of cancer would most likely result (if not related to exposure status) in loss of statistical power and an underestimation of the risk estimate.

Some studies of colorectal, ovarian, and lung cancers in relation to shift work have been reported from large cohorts and case-control studies. Age-adjusted annual incidence rates per 100,000 for colorectal cancer are 47.1 (male) and 36.0 (female); 67.9 (male) and 49.4 (female) for lung cancer; and 11.9 for ovarian cancer. Five-year survival rates based on SEER age-adjusted data from 2009 to 2013 vary for these cancers: colorectal, 65.1%; lung, 17.7%; and ovary, 46.2%, suggesting that both mortality and incidence data are informative for lung cancer, while incidence data would be more informative for colorectal and ovarian cancer (SEER 2018).

Finally, very few studies of shift work are available in relation to leukemia, endometrial, esophageal, pancreatic, bladder, kidney, and stomach cancers.

Cancers are often heterogeneous (e.g., breast cancer) and grouping together all subtypes can dilute the estimate of effect towards the null. Ideally, risks of breast cancer subtypes defined by tumor status (hormone receptor positive or negative) would be reported.

2.3.4 Potential confounding bias

The evaluation of confounding is a multi-step process and involves consideration both of study methods and study findings. This section discusses (a) methods for evaluating how authors assessed confounding in the study and/or provided information to inform the evaluation of confounding; and (b) the potential confounders which would ideally be considered in studies of common cancers and LAN, shift work, and transmeridian travel. Methods for assessing the impact of potential confounders on study findings is discussed in Section 2.4.

Core questions and ratings

Core question, domain level ratings, and guidelines for reaching the domain level ratings are provided below. For more information on evaluating how studies assessed confounding, including signaling and follow up questions, see the RoC Handbook, Part D, Section 4.2.4 and Table D-5; for information on evaluating whether confounding exists in the study, see Part D, Section 5.1.1.

Core question

Is there a concern that either the methods are inadequate or there is inadequate information to evaluate potential confounding in studies of LAN or shift work?

Domain level ratings

Low/minimal concerns: (***) rating

Studies measured all relevant potential confounders and/or used appropriate statistical analyses or designs to address them. Final statistical models should, however, only include "actual" confounders and not variables that have minimal effect on the risk estimate.

Critical concerns: Inadequate rating

Strong evidence that the effects of the exposure cannot be distinguished from potential confounders.

Guidelines for reaching domain level ratings

In general, candidates for evaluation as potential confounders include (1) occupational co-exposures, (2) reproductive and family history factors, (2) diet, lifestyle, and pharmacologic factors, and (3) demographics known to be related to the particular cancer of interest.

Table 2-2 shows potential risk factors and the critical confounders for commonly studied cancers in relation to shift work, LAN, and transmeridian travel literature. Critical common confounders are defined as factors associated with exposure and strongly associated with disease, are not in the causal pathway, and are not correlated with other risk factors. In addition, it may not be possible to identify common confounders across studies because the relationship between the activity (such as diet or physical activity) and exposure (such as shift work) may vary by population (e.g., nurses versus other industrial workers) and the comparison group.

Occupational co-exposures

Ideally, studies should provide quantitative exposure data for any occupational co-exposure as part of a job-exposure matrix or expert assessment for each worker. However, some studies provide quantitative or qualitative data on co-exposures for subsets of workers in particular fields of work or industries, which may be used to evaluate potential confounding.

Many studies of shift work and LAN have been conducted among nurses and medical care workers, most of whom are exposed to chemotherapeutic drugs, radiation, and disinfecting and sterilizing agents, risk factors for the cancer sites of concern (Snedeker 2006). Employment in particular nursing specialties in which exposure to ethylene oxide or x-rays are common, both known risk factors for breast cancer, may be helpful in understanding whether such co-exposures may have been considered in such studies. However, in order to evaluate whether the co-exposure could confound the association between shiftwork and cancer, information about occupational co-exposures of both night and day workers should be known.

Flight crews are routinely exposed to high radiation exposure which is a complex function of latitude, altitude, and duration of the flight (Pukkala *et al.* 1995, Waters *et al.* 2000). Among those flying in the 1950s and 1960s, exposure to organochlorine pesticides was also common (Wartenberg and Stapleton 1998).

In manufacturing cohorts, multiple co-exposures are likely depending on the setting. For example, workers in the textile industry may be exposed to a variety of carcinogenic agents including formaldehyde, flame retardants including organophosphorus and organobromine compounds, and dyes including azo dyes which are aromatic hydrocarbon derivatives of benzene, toluene, naphthalene, phenol, and aniline (IARC 1990). Among radio and telegraph operators, exposure to magnetic fields is common (Tynes *et al.* 1996).

Finally, in general population studies, subjects will report many different occupations, and it is unlikely that there will be enough exposure to any particular carcinogenic co-exposure to warrant concern about confounding from co-exposures.

Non-occupational factors

Ideally, quantitative information on non-occupational exposures or lifestyle factors should be assessed by in-person interview by interviewers blinded to the status of the respondent in cancer incidence studies, rather than via proxy respondents or work records.

Residual confounding is more likely when only limited qualitative information on a given risk factor (dichotomous yes/no) is available. Studies should provide, at minimum, data on the distribution of potential confounders among the exposed and unexposed in cohort studies, or among the cases and controls in case-control studies. In some cases, data may be available on potential confounders in sub-samples, which can help provide interpretation of the prevalence of the potential confounder in the exposed and unexposed or cases and controls. In addition, data on diseases associated with LAN or shift work (e.g., obesity or metabolic syndrome) may provide indirect information about risk factors for specific cancer endpoints of concern. While early studies of LAN sought to assess exposure by studying populations working outside of a standard daytime shift schedule in order to constitute the most extreme exposure to LAN, shift work is now recognized as a complex exposure scenario (Figure 2-1) and not a simple surrogate for LAN. Thus, in addition to exposure to LAN, shift workers are exposed to a wide array of exposures that have the ability to disrupt their circadian rhythms including disturbed social patterns and sleep, behavioral changes, eating at night, and sun exposure. Several of these exposures are also risk factors for various cancers (Table 2-2).

Finally, care should be taken to assess whether models are over-controlled – that is, when many variables that are not associated with both exposure and disease are included in the models, results can be biased towards the null.

Reproductive and family history

Some risk factors may be highly correlated (e.g., age at first full-term pregnancy and parity, with age at first full-term pregnancy being more specific for breast and ovarian cancers) and thus controlling for one variable also partly controls for the correlated risk factor. Other risk factors may be in the causal pathway and controlling for these factors tends to bias risk estimates towards the null. For example, early age at menarche may be related to exposure to light at an early age, and early menarche is a risk factor for breast cancer, putting it in the causal pathway to breast cancer. Some risk factors may be protective and therefore lack of control will not produce a biased elevated risk (e.g., breastfeeding duration). Strong risk factors for breast cancer, such as family history in first degree relatives, are unlikely to be strongly related to shift work or LAN, if at all. Thus, failing to control for family history would not reduce the quality rating for such a

study. Other factors, such as menopausal status, are more likely to be considered in the analysis as effect modifiers. Flight crew may have unique characteristics that put them at higher or lower risk of various cancers than other women. A study of German cabin crews reported differences in anthropometric, gynecological, reproductive and lifestyle factors including higher nulliparity, longer oral contraceptive use, and lower hormone replacement therapy use (Winter *et al.* 2014) than the general population of German women.

Demographics, diet, lifestyle, and pharmacologic factors

In one large population-based cohort study, the Million Women Cohort in the United Kingdom, Wang *et al.* (2012) reported that two thirds of the sociodemographic, behavioral, reproductive, and hormonal factors examined showed highly significant differences between "ever" and "never" night workers, and 12 showed significant trends by duration of night work ($P < 0.01$). In particular, compared to women who had never worked at night, women who had ever worked at night were more likely to be of lower socioeconomic status, be current smokers, and be obese; while those who had worked at night for ≥ 20 years were more likely to be of lower socioeconomic status, nulliparous, current smokers, and obese compared to never night workers. Other studies have reported that shift workers tend to smoke more (Bøggild and Knutsson 1999, van Amelsvoort *et al.* 2006), or increase their consumption of alcoholic drinks at night, as well as modify the composition and the caloric distribution of the different meals (Lennernas *et al.* 1993, Reinberg *et al.* 1979, Romon *et al.* 1986), although in some populations, shift workers tend to have a lower consumption of alcohol.

Alcohol is a consistent and moderately strong risk factor with almost any level of alcohol use consistently related to breast cancer and also to colorectal cancer and should be considered a major confounder for these cancers. On the other hand, alcohol consumption is not a risk factor for prostate, ovarian, or lung cancer, and does not need to be controlled as it is unlikely to bias the relative risks for the exposures of interest. Smoking is a weak risk factor for breast, colorectal, prostate cancer, and it may not be necessary to control for these cancers. However, tobacco smoking should be considered a major confounder for lung cancer and ovarian cancer. Recent studies of ovarian cancer indicate that smoking is related to mucinous ovarian cancer with the risk increasing with increased amount of smoking, and decreasing over time after quitting (Licaj *et al.* 2017, Praestegaard *et al.* 2017). Winter *et al.* (2014) reported higher alcohol consumption among German cabin crew which is relevant for breast and colorectal cancers in this population of women exposed to transmeridian travel and jet lag; they also reported lower rates of smoking which is relevant to ovarian and lung cancers.

Some studies have found that dietary patterns (such as consumption of meat or fat intake) differ between shift workers and non-shift workers or between flight attendants and the general population (Hemiö *et al.* 2015, Winter *et al.* 2014). Hulsegge *et al.* (2016) reported that night shift workers had higher energy intake but had a similar diet quality as day workers. Studies have also suggested that shift workers are less likely to exercise (Bushnell *et al.* 2010). Obesity is a risk for post-menopausal but not pre-menopausal breast cancer, but it is impacted by circadian factors, placing it in the causal pathway to breast cancer.

Oral contraceptive (OC) use has been implicated as a weak risk factor for breast cancer, thus lack of control is not likely to introduce bias; for ovarian cancer, OC use is considered protective, thus lack of control will not produce a biased elevated risk. Both OC use and hormone replacement

therapy are population dependent, but like OC use, hormone replacement therapy is a weak risk factor for breast cancer and lack of control is unlikely to introduce bias.

Education, which is an imperfect surrogate for socioeconomic status, is consistently related to breast cancer and should be controlled.

Table 2-2. Potential confounders for cancers of the breast, prostate, colorectum, ovary, and lung cancer

Cancer site	Cancer risk factors	Potential major confounder (i.e., possibly associated with exposure scenario and disease)
Breast	*Reproductive and family history factors:* early age at menarche, late age at first full pregnancy, nulliparity, menopausal status, no breastfeeding, family history of breast cancer *Diet, lifestyle, and pharmacologic factors:* Diethylstilbestrol (DES), estrogen-progestogen contraceptives, hormone menopausal therapy (estrogen-progestogen or estrogen only), digoxin, lack of physical activity (primarily postmenopausal breast cancer), obesity (high body mass index [BMI]), waist circumference or waist-hip ratio (increases risk in postmenopausal women; decreases risk in premenopausal women), consumption of alcoholic beverages, tobacco smoking *Demographics:* Age, socioeconomic status/education, population-specific characteristics *Occupational agents:* X-radiation,[a] gamma-radiation,[a] ethylene oxide, polychlorinated biphenyls	**Shift work studies** *Reproductive and family history factors:* Age at first full-term pregnancy and/or parity *Diet, lifestyle factors:* Alcohol consumption *Demographics:* Socioeconomic status/education, population-specific characteristics *Occupational co-exposures:* depends on comparison group (e.g., day workers or non-workers) and study population **LAN studies** *Reproductive and family history factors:* Age of first full-term pregnancy and/or parity *Diet, lifestyle factors:* Alcohol consumption *Demographics:* Socioeconomic status/education, population-specific characteristics *Occupational co-exposures:* depends on comparison group (e.g., day workers or non-workers) and study population **Transmeridian travel** *Reproductive and family history factors:* Age at first full-term pregnancy and/or parity *Diet, lifestyle factors:* Alcohol consumption *Occupational co-exposures:* Cosmic/ionizing radiation
Prostate	*Diet, lifestyle, and pharmacologic factors:* Androgenic steroids, consumption of red meat *Occupational agents:* Arsenic and inorganic arsenic compounds, cadmium and cadmium compounds, malathion, rubber production, thorium-232, X-radiation,[a] gamma-radiation[a]	**Shift workers** *Diet, lifestyle factors:* May depend on comparison group (e.g., day workers or non-workers) and study population *Occupational co-exposures:* May depend on comparison group (e.g., day workers or non-workers) and study population
Colorectal	*Diet and lifestyle:* Lack of physical activity, obesity (high body mass index [BMI]), and high waist-hip ratio), high consumption of red meat,	**Shift workers**

Cancer site	Cancer risk factors	Potential major confounder (i.e., possibly associated with exposure scenario and disease)
	high consumption of processed meat, high alcohol consumption (men), low fiber diet; *Schistosoma japonicum* *Occupational agents:* X-radiation, [a] gamma-radiation, [a] asbestos	*Diet and lifestyle,* Alcohol consumption and other such factors as diet (red meat consumption) may depend on population and comparison group *Occupational co-exposures:* May depend on comparison group (e.g., day workers or non-workers) and study population **Transmeridian travel** *Diet, lifestyle:* Alcohol consumption and other such factors as diet (red meat consumption) may depend on population and comparison group *Occupational co-exposures:* Cosmic/ionizing radiation
Ovarian	*Reproductive and family history factors:* Age at first full-term pregnancy *Diet, lifestyle, and pharmacologic factors:* Obesity (high body mass index [BMI], depending on tumor type, menopausal status and HRT use), estrogen menopausal therapy, tobacco smoking, talc-based body powder (perineal use), oral contraceptive use *Occupational agents*: asbestos, x-radiation[a], gamma-radiation[a]	**Shift workers** *Reproductive and family history factors:* Age at first full-term pregnancy, oral contraceptive use *Diet and lifestyle:* Tobacco smoking; others depend on comparison group and study population and subtype of cancer *Occupational co-exposures:* May depend on comparison group (e.g., day workers or non-workers) and study population **Transmeridian travel** *Diet, lifestyle:* Smoking *Occupational co-exposures:* Cosmic/ionizing radiation
Lung	*Diet, lifestyle, and pharmacologic factors:* Low consumption of fruits and vegetables, tobacco smoking, passive smoking, air pollution, radon *Occupational agents***:** asbestos, radon, arsenic, chromium, silica, beryllium, nickel, cadmium, and diesel exhaust	**Shift workers** *Diet, lifestyle, factors:* tobacco smoking, others may depend on comparison group and study population *Occupational co-exposures:* May depend on comparison group (e.g., day workers or non-workers) and study population **Transmeridian travel** *Diet, lifestyle:* Smoking

Sources: WCRF 2018, IARC 2018.
[a]Exposure may also be from medical use.

2.3.5 Potential bias from selective reporting and analysis

Core questions and domain level ratings are provided below. No issues/guideline or ratings were identified that were specific for LAN or shift work. For more information including signaling and follow-up questions, see the RoC Handbook, Part D, Sections 4.2.5 and 4.2.6 and Tables D-6 and D-7.

Selective reporting

Core question

Is there a concern that the study does not provide results for all relevant measures and participants, which would bias its interpretation?

Domain level ratings

Low/minimal concerns: (***) rating

No evidence that reporting of the data or analyses were limited to only a subset of the data that was collected.

Critical concerns: Inadequate rating:

Strong evidence that selective reporting of data or analyses compromised the interpretation of the study.

Analyses bias

Core question

Is there a concern that the data assumptions and analysis are not adequate or the study does not conduct relevant analysis on available data?

Low/minimal concerns: (***) rating:

Study used relevant data, appropriate assumptions and methods of analysis.

Critical concerns (0 rating):

Strong evidence that the study's analytical methods were so limited that the findings were uninterpretable or distorted.

2.3.6 Evaluation of study sensitivity

Core question, domain level ratings and guidelines for the domain level ratings are provided below. For more information on study sensitivity including signaling and follow-up questions, see the RoC Handbook, Part D, Section 4.2.7 and Table D-8.

Core question and ratings

Core question

Does the study have adequate sensitivity to detect an effect from exposure to LAN or shift work (if present)?

Domain level ratings

High utility (***) rating

Study has adequate exposed subjects, with substantial (level, duration, or range) exposure with adequate duration of follow-up for latency.

Inadequate utility

Moderate or small study with few exposed subjects and/or exposure is unlikely to be substantial (based on other knowledge) to detect an effect

Guidelines for domain level ratings

Detection of cancer endpoints requires a relatively large cohort and/or higher exposure prevalence for an adequate ability to detect an effect although statistical power is greater for more common cancers, such as breast cancer, compared to ovarian cancer, for example. Thus, studies with larger numbers of exposed cases in cohort studies and/or controls in case-control studies are considered to be more informative.

Studies of workers in industries or occupations with higher levels of exposure, or workers with longer duration of exposure and sufficient variability in exposure are generally the most informative for evaluating cancer risk. Shift work studies may be less sensitive due to the exposure to LAN in the control population, as virtually all individuals in developed countries are exposed to LAN regardless of their shift work history. If the comparison population has unmeasured high exposure to LAN, this will dilute the ability of the study to detect an effect.

Studies evaluating exposure groups in which the majority of participants classified as "exposed" have very low exposure, very short duration of employment, or limited evidence of actual exposure may be inadequate to detect an effect due to a dilution effect. Studies of light in the sleeping habitat of day workers, for example, may not be adequate to detect an effect. Further, the ability to evaluate exposure-response relationships depends on an adequate range of exposure (in intensity or duration) among the study participants, and adequate numbers of subjects in each exposure category.

Studies reporting minimum latency estimates for cancer from LAN or shift work based on direct observation of latencies would be ideal. Estimates of the lower bound of the distribution of cancer latencies, or minimum latency are required (Howard 2013). Nadler and Zurbenko (2014) estimated the latency for various types of cancer with high mortality rates and limited effective treatment options: estimates were 16.3 years for breast cancer and 44.1 years for ovarian cancer.

However, these estimates are based on multi-stage models of cancer, that is, time from first event. Under this assumption, latency periods of at least 15 to 20 years are required to detect breast and other solid tumors. However, cancer is a stepwise process (Vogelstein and Kinzler 2015) requiring a sequence of acquired genetic events over many years, progressing through initiation (breakthrough), promotion (expansion), and progression (invasion) (Matthews and Thompson 2016). If exposures to LAN in early life are important, among women surviving to participate in studies in their 40s or 50s, exposures in the last 5 to 10 years may be most important (Blask *et al.* 2005). Hormonal factors such as hormone replacement therapy (HRT) is believed to affect growth kinetics of small clones of cancer cells (Vogelstein *et al.* 2013) that might never progress except for their presence and ability to act in the latter stages of carcinogenesis to promote growth. That the risk in users disappears within 5 years of stopping HRT use supports the idea that a long latency period may not be necessary. Similarly, if shiftwork is mediated through changes in the hormone melatonin, it could conceivably have an effect within a short latency period, with different molecular subtypes of breast cancer and other effect modifiers influencing the course of the disease. For this reason, among individuals not

currently working night shifts, the year or age when they last worked night shifts would be important to collect to assess whether the effect disappears after a given interval of time.

Inadequate duration of follow-up may bias findings toward the null for cancer endpoints with longer latencies. Ideally, in addition, if cohort studies are sufficiently large to permit lagged analyses to be conducted to allow for a latency period, such analyses would contribute additional strength to the study and increase the study's sensitivity (Richardson *et al.* 2011).

2.3.7 Judgment for overall informativeness for health hazard evaluation

Study level judgment for overall informativeness for human hazard evaluation for epidemiologic studies is conducted separately for LAN, shift work, and transmeridian travel. How well a study can inform the cancer hazard assessment is based on consideration of both the potential (or risk) for biases (i.e., study quality) and consideration of study sensitivity for each database. Serious concerns about risk of biases would result in lower utility ranking; however, a well-designed study with low study sensitivity (such as few exposed/expected cases for a specific endpoint) could be given a lower ranking. When adequate information is available, a judgment is made for the direction and distortion from the overall biases for a study or whether it has low sensitivity to detect an effect. Studies with critical concern for bias in a domain are usually considered to be uninformative and are not brought forward to the cancer evaluation. This evaluation occurs prior to the cancer assessment (e.g., interpreting the finding of the study).

- High (low/minimal concerns for bias and high sensitivity rating)
- Moderate (low/minimal or some concerns for bias, high or moderate sensitivity rating)
- Low (major concerns, sensitivity rating varies)
- Inadequate (critical concerns for bias, sensitivity rating varies)

2.4 Cancer hazard evaluation

This section outlines the specific approaches for reaching a level of evidence conclusion (e.g., sufficient, limited, or inadequate) for the carcinogenicity of LAN, shift work, and transmeridian travel from studies in humans, and describes the integrated methods for evaluating confounding in each set of studies. Detailed information regarding these methods is described in the RoC Handbook, Part D, Section 5.1.

The application of the RoC listing criteria to the body of studies on each exposure scenario includes evaluating (1) whether there is credible evidence for an association between exposure to LAN, shift work, or transmeridian travel and cancer, and (2) whether such an observed association can be explained by chance, bias, or confounding.

The first step in the cancer hazard assessment is to determine the level of evidence from each study, followed by a synthesis of the level of evidence across studies, considering the key issues and the RoC listing criteria to reach a preliminary level-of-evidence conclusion. The cancer hazard assessment will consider the following factors:

- How consistent is the evidence across studies and what sources of heterogeneity might explain differences in results?

- Key issues: What exposure metrics predict breast cancer risk and/or breast cancer subtype? How does any consideration of latency or recency of exposure in these analyses affect the results? Does chronotype modify the association between night work and breast cancer?
- Can the findings be explained by chance, bias, or confounding?

The most informative studies (i.e., lowest risk of bias and greatest sensitivity to detect an effect) are given the most weight in the evaluation. The identification of the potential for specific types of uncontrolled bias or confounding, the assessment of study sensitivity, and the presence of effect modification are also used to interpret the findings from studies and to help explain heterogeneity across studies.

The level of confidence in the evidence from the individual studies of breast cancer and other cancers will be rated as "evidence," "some evidence," "null," or "inconclusive." Levels are reached by considering the strength of the association, the potential for specific biases or confounding, the expected directions and distortions of those potential biases or confounding, and the sensitivity of the study to detect an effect.

Evidence: High or moderate utility studies reporting statistically significant elevated risk estimates of "extreme exposures"; or studies with multiple elevated non-significant estimates from different type of analyses, exposure-response patterns, or effect modification. Low utility studies can provide evidence of an association if the potential for bias is towards the null.

Some evidence: Lower utility studies reporting an excess risk estimate for ever exposure or one analysis; or studies reporting imprecise elevated risks from multiple analyses. Non-significant risk estimates provide "some evidence" depending on the precision and/or number of analyses. While evidence should come from high or moderate utility studies, studies with low utility can provide some evidence of an association if the potential for bias is towards the null, OR if the study has low sensitivity.

Null: Studies which are considered "null" show effect estimates ≤ 1.0.

Inconclusive: Findings vary; the overall direction of potential biases is unknown; potential confounding may explain the findings; or studies have very low precision and the findings may be due to chance.

The evidence from the studies is then synthesized across studies and systematically evaluated for each of the issues identified above – metrics of exposure, timing of exposure (e.g., first exposure, recency of exposure), type of breast cancer and effect modifiers. In addition, the assessment will evaluate whether confounding can be ruled out across studies. Finally, the evidence from the human epidemiological studies will be integrated with mechanistic data in humans (Section 7) to reach a preliminary level of evidence conclusions from studies in humans. (Note that the RoC listing criteria allows all evidence in humans to be considered.)

3 Scope and Methods to Review Supporting Information

3.1 Circadian regulation and modern electric lighting practices

The purpose of this section is to provide background information related to the exposure scenarios for review. It provides an overview of circadian rhythms, including details on the role of melatonin, clock genes, and circadian rhythms, as well as a description of modern lighting practices, properties of light, and shift work. The congressional mandate for the RoC requires that a significant number of U.S. residents are exposed to the substances. The section also reviews the available information on shift work prevalence, LAN, and transmeridian travel in the U.S. Sources for this information come from reviews or relevant government websites.

3.2 Light at night and night shift work-induced circadian disruption

This section includes an overview of the biomarkers and characteristics of circadian disruption. It also reviews field and experimental studies in humans and animals of LAN and shift work and biomarkers of circadian disruption, focusing on studies of melatonin and suppression. Studies of LAN are usually experimental studies in humans whereas studies of night shift workers are cross-sectional field studies. Primary studies and reviews comprise the source of the information. The literature is considered representative, but not necessarily comprehensive (e.g., due to the large database, it is not certain that every biomonitoring study was identified). This section provides a review of the evidence across studies and does not conduct a formal assessment of study quality.

3.2.1 Evaluation of cancer studies in experimental animals

This section reviews the results of studies on the effects of light-dark cycles and simulated shift work or jet lag on formation and growth of tumors in mice and rats. The effects of light exposure in models of spontaneous tumor formation, cancer xenografts and injection of cancer cells, and chemical initiation and promotion of cancer will be included. Most of the studies in experimental animals are mechanistic studies that examine the growth of tumors after chemical or genetic initiation or after injection of tumor cells or implantation of tissue and were not designed to evaluate incidences of specific tumors as would be reported in chronic cancer studies. Thus, a systematic review of the studies was not conducted. The section provides an overview of the relevant findings from the primary literature and conclusions of the evidence across studies for LAN and night shift work.

3.2.2 Evaluation of mechanistic and other relevant data

This section assesses the strength of mechanistic and relevant information related to the potential carcinogenicity of night shift work and LAN and integrates the relevant information to reach conclusions that inform the hazard evaluation. Included in this section are (1) an overview of the development and susceptibility of breast cancer carcinogenicity, (2) an assessment of the major mechanisms of carcinogenicity related to circadian disruption (e.g., melatonin suppression and altered clock gene expression), (3) human and experimental studies of LAN and shift work and biological effects related to carcinogenicity; and (4) other mechanisms associated with lighting and night shift work including sunlight and sleep. Due to the extensive literature and general acceptance of the oncostatic effects of melatonin and clock genes, this information primarily comes from reviews. Information on studies of exposure to LAN and biological effects, as well

as studies of circadian disurption and cancer (e.g., melatonin and breast cancer risk) is mainly from the primary literature.

3.2.3 Overall evaluation and preliminary listing recommendation

The cancer hazard assessment involves the integration of the relevant evidence from studies evaluating the pathway from exposure to circadian disruption to cancer. The level of evidence conclusions from studies in humans and preliminary listing recommendations are reached by applying the RoC listing criteria to these assessments. The section uses a series of evidence-based tables and figures that summarize the assessments from the entire monograph to provide transparency for the decision-making process for reaching a listing recommendation for LAN and night shift.

4 References

1. Applebaum KM, Malloy EJ, Eisen EA. 2011. Left truncation, susceptibility, and bias in occupational cohort studies. *Epidemiology* 22(4): 599-606.

2. Bajaj A, Rosner B, Lockley SW, Schernhammer ES. 2011. Validation of a light questionnaire with real-life photopic illuminance measurements: the Harvard Light Exposure Assessment questionnaire. *Cancer Epidemiol Biomarkers Prev* 20(7): 1341-1349.

3. Blask DE, Dauchy RT, Sauer LA. 2005. Putting cancer to sleep at night: the neuroendocrine/circadian melatonin signal. *Endocrine* 27(2): 179-188.

4. Bøggild H, Knutsson A. 1999. Shift work, risk factors and cardiovascular disease. *Scand J Work Environ Health* 25(2): 85-99.

5. Bushnell PT, Colombi A, Caruso CC, Tak S. 2010. Work schedules and health behavior outcomes at a large manufacturer. *Ind Health* 48(4): 395-405.

6. Chavance M, Dellatolas G, Lellouch J. 1992. Correlated nondifferential misclassifications of disease and exposure: application to a cross-sectional study of the relation between handedness and immune disorders. *Int J Epidemiol* 21(3): 537-546.

7. Federal Register. 2012. Request for public comment on nominations and call for additional nominations to the Report on Carcinogens. *Fed Reg* 77(12): 2728-2729.

8. Fekedulegn D, Burchfiel CM, Hartley TA, Andrew ME, Charles LE, Tinney-Zara CA, Violanti JM. 2013. Shiftwork and sickness absence among police officers: the BCOPS study. *Chronobiol Int* 30(7): 930-941.

9. Garde AH, Hansen J, Kolstad HA, Larsen AD, Hansen AM. 2016. How do different definitions of night shift affect the exposure assessment of night work? *Chronobiol Int* 33(6): 595-598.

10. Grajewski B, Waters MA, Yong LC, Tseng CY, Zivkovich Z, Cassinelli RT, 2nd. 2011. Airline pilot cosmic radiation and circadian disruption exposure assessment from logbooks and company records. *Ann Occup Hyg* 55(5): 465-475.

11. Härmä M, Laitinen J, Partinen M, Suvanto S. 1994. The effect of four-day round trip flights over 10 time zones on the circadian variation of salivary melatonin and cortisol in airline flight attendants. *Ergonomics* 37(9): 1479-1489.

12. Hebert M, Martin SK, Lee C, Eastman CI. 2002. The effects of prior light history on the suppression of melatonin by light in humans. *J Pineal Res* 33(4): 198-203.

13. Hemiö K, Puttonen S, Viitasalo K, Härmä M, Peltonen M, Lindström J. 2015. Food and nutrient intake among workers with different shift systems. *Occup Environ Med* 72(7): 513-520.

14. Howard J. 2013. *Minimum Latency & Types or Categories of Cancer* World Trade Center Health Program, Centers for Disease Control and Prevention. 9 pp. http://www.cdc.gov/wtc/pdfs/wtchpminlatcancer2013-05-01.pdf.

15. Hulsegge G, Boer JM, van der Beek AJ, Verschuren WM, Sluijs I, Vermeulen R, Proper KI. 2016. Shift workers have a similar diet quality but higher energy intake than day workers. *Scand J Work Environ Health* 42(6): 459-468.

16. Hurley S, Goldberg D, Nelson D, Hertz A, Horn-Ross PL, Bernstein L, Reynolds P. 2014. Light at night and breast cancer risk among California teachers. *Epidemiology* 25(5): 697-706.

17. IARC. 1990. *Some Flame Retardants and Textile Chemicals, and Exposures in the Textile Manufacturing Industry*, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. vol. 48, Lyon, France: International Agency for Research on Cancer. p. 45-181.

18. IARC. 2010. Shift work. In *Painting, Firefighting, and Shiftwork*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, vol. 98. Lyon, France: International Agency for Research on Cancer. p. 563-764.

19. IARC. 2018. *List of Classifications by cancer sites with sufficient or limited evidence in humans, Volumes 1 to 121*. International Agency for Research on Cancer. Updated on 4/18/18. https://monographs.iarc.fr/ENG/Classification/Table4.pdf. Accessed on 5/4/18.

20. Kristensen P. 1992. Bias from nondifferential but dependent misclassification of exposure and outcome. *Epidemiology* 3(3): 210-215.

21. Lennernas MA, Hambraeus L, Akerstedt T. 1993. Nutrition and shiftwork: the use of meal classification as a new tool for qualitative/quantitative evaluation of dietary intake in shiftworkers. *Ergonomics* 36(1-3): 247-254.

22. Licaj I, Jacobsen BK, Selmer RM, Maskarinec G, Weiderpass E, Gram IT. 2017. Smoking and risk of ovarian cancer by histological subtypes: an analysis among 300 000 Norwegian women. *Br J Cancer* 116(2): 270-276.

23. Matthews SB, Thompson HJ. 2016. The Obesity-Breast Cancer Conundrum: An Analysis of the Issues. *Int J Mol Sci* 17(6).

24. Nadler DL, Zurbenko IG. 2014. Estimating cancer latency times using a Weibull model. *Adv Epidemiol* 2014: 8.

25. NTP. 2015. *Handbook for Preparing Report on Carcinogens Monographs*. Research Triangle Park, NC: National Toxicology Program. 89 pp.

26. NTP. 2016. *Workshop: Shift Work at Night, Artificial Light at Night, and Circadian Disruption*. National Toxicology Program. Updated on 7/27/16. http://ntp.niehs.nih.gov/pubhealth/roc/candidates/meetings/workshop_alan.html.

27. Pearce N, Checkoway H, Kriebel D. 2007. Bias in occupational epidemiology studies. *Occup Environ Med* 64(8): 562-568.

28. Picciotto S, Brown DM, Chevrier J, Eisen EA. 2013. Healthy worker survivor bias: implications of truncating follow-up at employment termination. *Occup Environ Med* 70(10): 736-742.

29. Pijpe A, Slottje P, van Pelt C, Stehmann F, Kromhout H, van Leeuwen FE, Vermeulen RC, Rookus MA. 2014. The Nightingale study: rationale, study design and baseline characteristics of a prospective cohort study on shift work and breast cancer risk among nurses. *BMC Cancer* 14: 47.

30. Praestegaard C, Jensen A, Jensen SM, Nielsen TS, Webb PM, Nagle CM, DeFazio A, Hogdall E, Rossing MA, Doherty JA, Wicklund KG, Goodman MT, Modugno F, Moysich K, Ness RB, Edwards R, Matsuo K, Hosono S, Goode EL, Winham SJ, Fridley BL, Cramer DW, Terry KL, Schildkraut JM, Berchuck A, Bandera EV, Paddock LE, Massuger LF, Wentzensen N, Pharoah P, Song H, Whittemore A, McGuire V, Sieh W, Rothstein J, Anton-Culver H, Ziogas A, Menon U, Gayther SA, Ramus SJ, Gentry-Maharaj A, Wu AH, Pearce CL, Pike M, Lee AW, Sutphen R, Chang-Claude J, Risch HA, Kjaer SK. 2017. Cigarette smoking is associated with adverse survival among women with ovarian cancer: Results from a pooled analysis of 19 studies. *Int J Cancer* 140(11): 2422-2435.

31. Pukkala E, Auvinen A, Wahlberg G. 1995. Incidence of cancer among Finnish airline cabin attendants, 1967-92. *BMJ* 311(7006): 649-652.

32. Rea MS, Bierman A, Figueiro MG, Bullough JD. 2008. A new approach to understanding the impact of circadian disruption on human health. *J Circadian Rhythms* 6: 7.

33. Rea MS, Figueiro MG, Bierman A, Bullough JD. 2010. Circadian light. *J Circadian Rhythms* 8(1): 2.

34. Rea MS, Brons JA, Figueiro MG. 2011. Measurements of light at night (LAN) for a sample of female school teachers. *Chronobiol Int* 28(8): 673-680.

35. Reinberg A, Migraine C, Apfelbaum M, Brigant L, Ghata J, Vieux N, Laporte A, Nicolai. 1979. Circadian and ultradian rhythms in the feeding behaviour and nutrient intakes of oil refinery operators with shift-work every 3--4 days. *Diabete Metab* 5(1): 33-41.

36. Reinberg A, Motohashi Y, Bourdeleau P, Touitou Y, Nougier J, Nougier J, Lévi F, Nicolaï A. 1989. Internal desynchronization of circadian rhythms and tolerance of shiftwork. *Chronobiologia* 16(1): 21-34.

37. Richardson DB, Cole SR, Chu H, Langholz B. 2011. Lagging exposure information in cumulative exposure-response analyses. *Am J Epidemiol* 174(12): 1416-1422.

38. Roenneberg T, Allebrandt KV, Merrow M, Vetter C. 2012. Social jetlag and obesity. *Curr Biol* 22(10): 939-943.

39. Romon M, Beuscart R, Frimat P, Debry G, Furon D. 1986. [Caloric intake and weight gain according to the shift schedule of shift workers]. *Rev Epidemiol Sante Publique* 34(4-5): 324-331.

40. Rothman K, Greenland S, Lash T. 2008. *Modern Epidemiology*, vol. 2: Lippincott, Williams & Wilkins. 758 pp.

41. SEER. 2018. *Surveillance, Epidemiology, and End Results Program*. National Cancer Institute. http://seer.cancer.gov/.

42. Snedeker SM. 2006. Chemical exposures in the workplace: effect on breast cancer risk among women. *AAOHN J* 54(6): 270-279; quiz 280-271.

43. Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ, Castaño-Vinyals G, Davis S, Frings-Dresen MH, Fritschi L, Kogevinas M, Kogi K, Lie JA, Lowden A, Peplonska B, Pesch B, Pukkala E, Schernhammer E, Travis RC, Vermeulen R, Zheng T, Cogliano V, Straif K. 2011. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med* 68(2): 154-162.

44. Tajima N, Uematsu M, Asukata I, Yamamoto K, Sasaki M, Hokari M. 1991. Recovery of circadian rhythm of plasma cortisol levels after a 3-day trip between Tokyo and San Francisco. *Aviat Space Environ Med* 62(4): 325-327.

45. Tsai RJ, Luckhaupt SE, Sweeney MH, Calvert GM. 2014. Shift work and cancer screening: do females who work alternative shifts undergo recommended cancer screening? *Am J Ind Med* 57(3): 265-275.

46. Tynes T, Hannevik M, Andersen A, Vistnes AI, Haldorsen T. 1996. Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control* 7(2): 197-204.

47. van Amelsvoort LG, Jansen NW, Kant I. 2006. Smoking among shift workers: More than a confounding factor. *Chronobiol Int* 23(6): 1105-1113.

48. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Jr., Kinzler KW. 2013. Cancer genome landscapes. *Science* 339(6127): 1546-1558.

49. Vogelstein B, Kinzler KW. 2015. The Path to Cancer --Three Strikes and You're Out. *N Engl J Med* 373(20): 1895-1898.

50. Wang XS, Travis RC, Reeves G, Green J, Allen NE, Key TJ, Roddam AW, Beral V. 2012. Characteristics of the Million Women Study participants who have and have not worked at night. *Scand J Work Environ Health* 38(6): 590-599.

51. Wartenberg D, Stapleton CP. 1998. Risk of breast cancer is also increased among retired US female airline cabin attendants. *BMJ* 316(7148): 1902.

52. Waters M, Bloom TF, Grajewski B. 2000. The NIOSH/FAA Working Women's Health Study: evaluation of the cosmic-radiation exposures of flight attendants. Federal Aviation Administration. *Health Phys* 79(5): 553-559.

53. Waters MA, Grajewski B, Pinkerton LE, Hein MJ, Zivkovich Z. 2009. Development of historical exposure estimates of cosmic radiation and circadian rhythm disruption for cohort studies of Pan Am flight attendants. *Am J Ind Med* 52(10): 751-761.

54. WCRF. 2018. *Continuous Update Project: findings & reports*. World Cancer Research Fund. https://www.wcrf.org/int/continuous-update-project/continuous-update-project-findings-reports and select cancer type. Accessed on 5/4/18.

55. Winter M, Blettner M, Zeeb H. 2014. Prevalence of risk factors for breast cancer in German airline cabin crew: a cross-sectional study. *J Occup Med Toxicol* 9: 27.

This Page Intentionally Left Blank

Appendix A: Literature Search Strategy

Introduction

The objective of the literature search is to identify published literature that is relevant for evaluating the potential carcinogenicity of circadian disruption and/or light at night. As discussed in the Concept Document for shift work, light at night, and circadian disruption (https://ntp.niehs.nih.gov/ntp/roc/concept_docs/2014/shiftworkconcept_508.pdf), 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)

- Human Cancer Studies
- Studies of Cancer in Experimental Animals
- Mechanisms and Other Relevant Effects

A.1 General approach

Database searching encompasses selecting databases and search terms and conducting the searches. Searches of several citation databases are generally conducted using search terms for the individual environmental exposures, combined with search terms for cancer and/or specific topics, including epidemiological and mechanistic studies. A critical step in the process involves consultation with an information specialist to develop relevant search terms. These terms are used to search bibliographic databases.

Citation databases, including PubMed, Scopus, and Web of Science, will be searched for epidemiological studies evaluating cancer and shift work, light at night, or transmeridian travel using the strategy outlined in the table below. In addition, searches will be conducted to identify other types of unnatural light exposures, such as the use of consumer electronics or exposure scenarios associated with social jet lag. Because this exposure scenario is less defined than the other exposure scenarios, these search terms are limited (e.g., combined using the word “and”) by terms focused for circadian disruption before being combined with epidemiological and cancer search strings. Cancer studies measuring biomarker-related circadian disruption or among shift workers or people exposed to LAN are expected to be retrieved by these searches.

The results for the searches will be processed in EndNote to remove duplicates before being transferred to Health Assessment Workplace Collaborative (HAWC) for screening.

Table A-1. Major topics for searches

Topic	Search Method	Databases searched
Human Cancer Studies	(shift work OR shiftwork OR night work OR "light at night" OR jet lag) AND (cancer OR tumor)	PubMed
Experimental Animal Studies	(Shift Work String OR Light String) AND Experimental Animals Studies Search AND ORoC Cancer Search	PubMed, Scopus, Web of Science
Biomarkers Studies	ORoC Cancer Search AND (Shift Work String OR Light String) AND Specific Circadian Disruption Biomarkers String AND (Humans & Epidemiology Combined String OR Experimental Animals Studies Search)	PubMed
Mechanism	(Shift Work String OR Light String) AND ORoC Characteristics of Carcinogens Search AND ORoC Cancer Search	PubMed, Scopus, Web of Science

A.2 Standard and Supplementary Searches

A.2.1 Shift Work

PubMed:

(work-schedule*[tiab] OR Alternative-shift*[tiab] OR duty-shift*[tiab] OR Midnight-shift*[tiab] OR night-call[tiab] OR night-shift*[tiab] OR nightshift*[tiab] OR night-work*[tiab] OR nightwork*[tiab] OR rotating-schedule*[tiab] OR rotating-shift*[tiab] OR shift-work*[tiab] OR shiftwork*[tiab] OR split-shift*[tiab] OR swing-shift*[tiab] OR third-shift*[tiab]) OR ((“personnel staffing and scheduling”[mh] OR “work schedule tolerance”[mh]) AND (shift* OR schedul*[tiab] OR hours[tiab] OR night[tiab] OR evening[tiab] OR duty-hour*[tiab] OR duty-period*[tiab] OR night-float*[tiab] OR overtime[tiab] OR on-call[tiab] OR 12-hour[tiab] OR twelve-hour[tiab] OR "long working hours"[tiab] OR "working long hours"[tiab] OR sleep[tiab] OR fatigue[tiab]))

Web of Science:

(TS=("work schedule*" OR "Alternative shift*" OR "duty shift*" OR "Midnight shift*" OR "night call" OR "night shift*" OR "nightshift*" OR "night work*" OR "nightwork*" OR "rotating schedule*" OR "rotating shift*" OR "shift work*" OR "shiftwork*" OR "split shift*" OR "swing shift*" OR "third shift*")) OR ((TS=("personnel OR "staffing" OR "work schedule tolerance")) AND (TS=("shift*" OR "schedul*" OR "hours" OR "night" OR "evening" OR "duty hour*" OR "duty period*" OR "night float*" OR "overtime" OR "on-call" OR "12-hour" OR "twelve-hour" OR "long working hours" OR "working long hours" OR "sleep" OR "fatigue")))

Scopus:

(TITLE-ABS-KEY ("work schedule*" OR "Alternative shift*" OR "duty shift*" OR "Midnight shift*" OR "night call" OR "night shift*" OR "nightshift*" OR "night work*"

OR "nightwork*" OR "rotating schedule*" OR "rotating shift*" OR "shift work*" OR "shiftwork*" OR "split shift*" OR "swing shift*" OR "third shift*")) OR ((KEY ("personnel staffing and scheduling" OR "work schedule tolerance")) AND (TITLE-ABS-KEY ("shift*" OR "schedul*" OR "hours" OR "night" OR "evening" OR "duty hour*" OR "duty period*" OR "night float*" OR "overtime" OR "on-call" OR "12-hour" OR "twelve-hour" OR "long working hours" OR "working long hours" OR "sleep" OR "fatigue")))

A.2.2 Light at Night

PubMed:

(light-dark-cycle*[tiab] OR light-cycle[tiab] OR light-cycles[tiab] OR dark-light-cycle*[tiab] OR Evening-light* OR Light-at-night OR Light-pollut* OR Night-light* OR Night-time-ligt* OR Nocturnal-light* OR bedroom-light* OR Sleeping-habitat*)

Web of Science:

TS=("light-dark cycle*" OR "light cycle" OR "light cycles" OR "dark-light cycle*" OR "Evening light*" OR "Light at night" OR "Light pollut*" OR "Night light*" OR "Night time light*" OR "Nocturnal light*" OR (bedroom NEAR/3 light*) OR “Sleeping habitat*”)

Scopus:

(TITLE-ABS-KEY(“light-dark cycle*" OR "light cycle" OR "light cycles" OR "dark-light cycle*" OR "Evening light*" OR "Light at night" OR "Light pollut*" OR "Night light*" OR "Night time light*" OR "Nocturnal light*” OR (bedroom w/3 light*) OR “Sleeping habitat*”))

A.2.3 Animal Studies

The PubMed, Web of Science, and Scopus Strings are the same as described in the Handbook Appendix (https://ntp.niehs.nih.gov/ntp/roc/handbook/rochandbookappendix_508.pdf).

A.2.4 Humans & Epidemiology Combined

PubMed:

((humans[mh] OR human development[mh] OR household*[tiab] OR public[tiab] OR neighborhood*[tiab] OR human*[tiab] OR person*[tiab] OR people[tiab] OR age groups[mh] OR pediatric*[tiab] OR paediatric*[tiab] OR baby[tiab] OR babies[tiab] OR newborn*[tiab] OR infant*[tiab] OR toddler*[tiab] OR child*[tiab] OR youth*[tiab] OR youngster*[tiab] OR tween*[tiab] OR teen[tiab] OR teens[tiab] OR teenager*[tiab]) OR (("in utero"[tiab] OR prenat*[tiab] OR perinat*[tiab] OR neonat*[tiab] OR postnat*[tiab] OR adult*[tiab] OR juvenile*[tiab]) NOT (mice[tiab] OR mouse[tiab] OR rat[tiab] OR rats[tiab])) OR preschool*[tiab] OR pre-school*[tiab] OR kindergarten*[tiab] OR schoolchild*[tiab] OR student*[tiab] OR middle-age*[tiab] OR aged[tiab] OR elder*[tiab] OR senior-citizen*[tiab] OR seniors[tiab] OR retiree*[tiab] OR septuagenarian*[tiab] OR octagenarian*[tiab] OR sexagenarian*[tiab] OR nonagenarian*[tiab] OR centenarian*[tiab] OR nuclear family[mh] OR parent[tiab] OR parents[tiab] OR father*[tiab] OR mother*[tiab]

OR sibling*[tiab] OR brother*[tiab] OR sister*[tiab] OR twin[tiab] OR twins[tiab] OR step-father*[tiab] OR step-mother*[tiab] OR step-daughter*[tiab] OR step-son*[tiab] OR aunt*[tiab] OR uncle*[tiab] OR niece*[tiab] OR nephew*[tiab] OR grandparent*[tiab] OR grandfather*[tiab] OR grand-father*[tiab] OR grandmother*[tiab] OR grand-mother*[tiab] OR grandchild*[tiab] OR granddaughter*[tiab] OR grandson*[tiab] OR spouse*[tiab] OR partner*[tiab] OR husband*[tiab] OR wife[tiab] OR wives[tiab] OR guardian*[tiab] OR caregiver*[tiab] OR care-giver*[tiab] OR men[mh] OR women[mh] OR men[tiab] OR man[tiab] OR boy[tiab] OR boys[tiab] OR boyhood[tiab] OR women[tiab] OR woman[tiab] OR girl[tiab] OR girls[tiab] OR girlhood[tiab] OR population groups[mh] OR vulnerable populations[mh] OR African-American*[tiab] OR Asian-American*[tiab] OR hispanic*[tiab] OR latina*[tiab] OR latino*[tiab] OR Mexican-American*[tiab] OR underserved[tiab] OR disadvantaged[tiab] OR underprivileged[tiab]) OR (epidemiolog*[tiab] OR epidemiology[sh] OR "epidemiologic studies"[mh] OR "double-blind method"[mh] OR "single-blind method"[mh] OR epidemiology[sh] OR case-control*[tiab] OR cohort[tiab] OR "cross sectional"[tiab] OR "follow-up study"[tiab] OR longitudinal[tiab] OR prospective[tiab] OR retrospective[tiab] OR case-reports[pt] OR "clinical trial"[pt] OR "observational study"[pt] OR "randomized controlled trial"[pt] OR "twin study"[pt] OR case-report*[tiab] OR clinical-trial*[tiab] OR observational[tiab] OR randomized-control-trial*[tiab]) OR ("research subjects"[mh] OR "human experimentation"[mh] OR patients[mh] OR "patient participation"[mh] OR human-subject*[tiab] OR research-subject*[tiab] OR client*[tiab] OR patient*[tiab] OR inpatient*[tiab] OR outpatient*[tiab] OR participant*[tiab] OR volunteer*[tiab] OR "occupational groups"[mh] OR "occupational exposure"[mh] OR occupation*[tiab] OR workplace[tiab] OR "work place"[tiab] OR work-related[tiab] OR administrator*[tiab] OR aides[tiab] OR assistant*[tiab] OR crew[tiab] OR crews[tiab] OR employee*[tiab] OR personnel[tiab] OR professional*[tiab] OR staff[tiab] OR technician*[tiab] OR worker*[tiab] OR educator*[tiab] OR instructor*[tiab] OR teacher*[tiab] OR clinician*[tiab] OR doctor*[tiab] OR physician*[tiab] OR pharmacist*[tiab] OR nurse*[tiab] OR residents[tiab] OR veterinarian*[tiab] OR adolescent[tiab]) OR "meta-analysis"[pt] OR workmen*[tiab] OR seroepidemiologic-stud*[tiab] OR ecological-study[tiab] OR ecological-studies[tiab] OR correlation-stud*[tiab] OR case-series[tiab] OR case-referent[tiab] OR record-link*[tiab])

A.2.5 Specific Circadian Disruption Biomarkers

PubMed:

(corticosterone[tiab] OR cortisol[mh] OR cortisol[tiab] OR melatonin[mh] OR melatonin[tiab] OR "body temperature"[mh] OR body-temperature*[tiab])

A.2.6 Characteristics of Carcinogens

The PubMed, Web of Science, and Scopus Strings are the same as described in the Handbook Appendix (https://ntp.niehs.nih.gov/ntp/roc/handbook/rochandbookappendix_508.pdf).

A.2.7 RoC Cancer String

The PubMed, Web of Science, and Scopus Strings are the same as described in the Handbook Appendix (https://ntp.niehs.nih.gov/ntp/roc/handbook/rochandbookappendix_508.pdf).

A.2.8 Transmeridian Travel

PubMed:

“jet lag syndrome”[mh] OR jetlag[tiab] OR jet-lag[tiab] OR ((timezone[tiab] OR time-zone*[tiab] OR transmeridian[tiab] OR long-haul[tiab]) AND (travel*[tiab] OR shift*[tiab] OR change*[tiab]))

Web of Science:

(TS=("jet lag syndrome” OR jetlag OR jet-lag)) OR ((TS=(timezone* OR time-zone* OR transmeridian OR long-haul)) AND (TS=(travel* OR shift* OR change*)))

Scopus:

(KEY("jet lag syndrome")) OR (TITLE-ABS-KEY(jetlag OR jet-lag)) OR ((TITLE-ABS-KEY(timezone* OR time-zone* OR transmeridian OR long-haul)) AND (TITLE-ABS-KEY(travel* OR shift* OR change*)))

A.2.9 Unnatural light exposure

PubMed:

(artificial-light*[tiab] OR electric-light*[tiab] OR electrical-light*[tiab] OR environmental-light*[tiab] OR environmental-illumination[tiab] OR dim-light*[tiab] OR DMLO[tiab]) OR (Computers[mh:noexp] OR “computers, handheld”[mh] OR computer[ti] OR computers[ti] OR consumer-electronic*[ti] OR ereader*[ti] OR e-reader*[ti] OR electronic-device*[ti] OR electronic-screen*[ti] OR light-emitting-device*[ti] OR mobile-device*[ti] OR screenlight*[ti] OR screen-light*[ti] OR screen-time[ti] OR television[ti] OR cellphone*[ti] OR cell-phone*[ti] OR smartphone*[ti] OR smart-phone*[ti] OR media-use[ti]) AND (light[mh] OR lighting[mh] OR light*[tiab]) OR ((Light[mh] OR Lighting[mh]) AND light*[ti])

Web of Science:

(TS=(artificial-light* OR Electric-light* OR electrical-light* OR environmental-light* OR environmental-illumination OR dim-light* OR DMLO)) OR ((TS=(computer OR computers OR consumer-electronic* OR ereader* OR e-reader* OR electronic-device* OR electronic-screen* OR light-emitting-device* OR mobile-device* OR screenlight* OR screen-light* OR screen-time OR television OR cellphone* OR cell-phone* OR smartphone* OR smart-phone* OR media-use)) AND (TS=light*))

Scopus:

((TITLE-ABS("computers, handheld" OR computer OR computers OR consumer-electronic* OR ereader* OR e-reader* OR electronic-device* OR electronic-screen* OR light-emitting-device* OR mobile-device* OR screenlight* OR screen-light* OR screen-time OR television OR cellphone* OR cell-phone* OR smartphone* OR smart-phone* OR media-use)) AND (TITLE-ABS-KEY(light*))) OR (TITLE-ABS-KEY(artificial-light* OR electric-light* OR electrical-light* OR environmental-light* OR "environmental illumination" OR dim-light* OR DMLO))

A.2.10 Focused circadian disruption string

PubMed:

(biologic-clock*[tiab] OR biologic-oscillator*[tiab] OR biologic-pacemaker*[tiab] OR “biological clocks”[mh] OR biological-clock*[tiab] OR biological-rhythm*[tiab] OR biorhythm*[tiab] OR “circadian rhythm”[mh] OR circadian[tiab] OR diurnal[tiab] OR master-clock*[tiab] OR peripheral-clock*[tiab] OR tissue-clock*[tiab] OR “suprachiasmatic nucleus”[mh] OR suprachiasmatic-nucl*[tiab] OR chronobiolog*[tiab] OR chronodisrupt*[tiab] OR entrain*[tiab] OR re-entrain*[tiab] OR zeitgeber[tiab] OR light-entrainment[tiab] OR photoentrainment[tiab] OR nonphotic-entrainment[tiab] OR light-induced-phase-delay[tiab] OR phase-advance*[tiab] OR “ARNTL transcription factors”[mh] OR circadian-gene*[tiab] OR clock-gene*[tiab] OR “clock proteins”[mh] OR “period circadian proteins”[mh] OR “circadian rhythm signaling peptides and proteins”[mh])

4.1.1 A.2.11 Non-specific circadian disruption biomarkers

PubMed:

(("c-reactive Protein"[Mh] OR c-reactive-Protein*[tiab]) OR (steroid-hormon*[tiab] OR "gonadal Steroid Hormones"[Mh] OR sex-hormon*[tiab] OR testosterone[tiab] OR estrogen[tiab] OR progesterone[tiab] OR prolactin[tiab]))

4.1.2 A.2.12 Light string

PubMed:

(light-dark-cycle*[tiab] OR light-cycle[tiab] OR light-cycles[tiab] OR dark-light-cycle*[tiab]) OR (evening-light* OR light-at-night OR light-pollut* OR Night-light* OR night-time-light* OR nocturnal-light* OR bedroom-light* OR Sleeping-habitat*) OR (periodicity[mh] OR photoperiod[mh] OR photoperiod*[tiab]) OR (ambient-light*[tiab] OR Artificial-light*[tiab] OR electric-light*[tiab] OR electrical-light*[tiab] OR environmental-light*[tiab] OR environmental-illumination[tiab] OR dim-light*[tiab] OR DMLO[tiab]) OR ((short-wavelength*[tiab] OR short-wave-length*[tiab] OR red-light*[tiab] OR blue-light*[tiab] OR enhanced-light*[tiab] OR direct-light*[tiab] OR indirect-light*[tiab]) NOT (phototherap*[tiab] OR therapy[tiab] OR treatment[tiab] OR imaging[tiab] OR tomography[tiab] OR hydrogel*[tiab] OR dyes[tiab] OR laser*[tiab] OR diode*[tiab])) OR (Computers[mh:noexp] OR “computers, handheld”[mh] OR computer[ti] OR computers[ti] OR consumer-electronic*[ti] OR eReader*[ti] OR e-Reader*[ti] OR electronic-device*[ti] OR electronic-screen*[ti] OR light-emitting-device*[ti] OR mobile-device*[ti] OR screenlight*[ti] OR screen-light*[ti] OR screen-time[ti] OR television[ti] OR cellphone*[ti] OR cell-phone*[ti] OR smartphone*[ti] OR smart-phone*[ti] OR media-use[ti]) AND (light[mh] OR lighting[mh] OR light*[tiab]) OR ((Light[mh] OR Lighting[mh]) AND light*[ti])