Report on Carcinogens Protocol:

Health consequences of electric lighting practices in the modern world: Human cancer and biomarker studies

Running title- Electric Light: RoC Protocol

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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*:

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Introduction

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 *Health consequences of electric lighting practices in the modern world.* This monograph will evaluate whether scenarios associated with exposure to electrical light that lead to circadian disruption, including light at night, 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) to issues specific for these exposure scenarios. This version of the protocol provides the methods for evaluating cancer and biomarkers studies in humans. An addendum, with methods for the approach for preparing the sections describing the data on human exposure and mechanistic and other relevant data will be published at a later time.

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.

Light at night (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 light at night) 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 light at night" and solicited public comments in January 2012 (77FR2728). Three public comments voiced concern about environmental exposure to light at night ("light pollution") to the general public. Based on this input, NTP then developed a concept on shift work at night, light at night, 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.

Based on this recommendation 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. However, assessments will be conducted separately for human studies evaluating each exposure scenario, i.e., light exposure, shift work, and transmeridian travel. As sleep can be considered to be an outcome of unnatural light exposure, sleep itself will not be directly considered as an exposure scenario. Also, any studies on social jet lag and the use of consumer electronics in relation to cancer that become available during the evaluation will be included in the evaluation. Assessments will be determined by the nature and scope of existing data on various cancers.

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. However, relevant studies will be summarized as a group, and included in discussions of mechanisms and interventions as appropriate. The methods to be used to summarize these studies will be included in the final protocol.

Cancer hazard evaluation

The purpose of the cancer evaluation component is to assess the available scientific evidence, apply the RoC listing criteria[1] to this evidence, and reach a preliminary level of evidence conclusion from studies in humans and recommendation for a listing status in the RoC. Briefly, the RoC listing criteria for the two listing categories are as follows:

Known to be a human carcinogen

- Sufficient evidence of carcinogenicity from studies in humans

Reasonably anticipated to be a human carcinogen

- Limited evidence of carcinogenicity from studies in humans
- 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.

The goal of the cancer hazard evaluation component of the draft RoC monograph is to conduct an assessment of the scientific literature, utilizing information from the primary literature as well as from supporting studies of secondary endpoints, and authoritative and other reviews. The monograph will evaluate the level of evidence from individual studies of cancer in humans, as well as from the body of literature on secondary endpoints including biomarkers studies of exposure to light and shift work.

[1] For the formal Report on Carcinogens listing criteria, see http://ntp.niehs.gov/go/15209.

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.

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: Methods for Evaluating Properties and Human Exposure Information– To be included in the final protocol
- Part 3: Methods for Evaluating Human Cancer
- Part 4: Methods for Evaluating Human Biomarker Studies of Circadian Disruption in Humans
- Part 5: Methods for Evaluating Mechanistic and Other Relevant Data – To be included in final protocol

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

This version of the RoC protocol includes Part 1 (Outline of the Draft RoC Monograph), Part 3 (Methods for Evaluating Human Cancer Studies) Part 4 (Methods for Evaluating Biomarkers Studies of Circadian Disruption, and relevant parts of Appendix A (Search strings related to Parts 3 and 4). Part 2 (Methods for Evaluation Properties and Human Exposure) and Part 5 (Methods for Mechanisms and Other Relevant Data) are not included in this version of the protocol and will be added at a later date as an addendum to the protocol.

1 Outline of the Draft RoC Monograph

The draft RoC monograph on *Electric lighting practices in the modern world* focuses on the relationship between cancer and exposure to unnatural light in a variety of exposure scenarios. The cancer evaluation component of the monograph is organized by topic and includes several sub-sections, as described below. Appendices to the monograph contain additional information, including descriptions of the quality evaluation of the human cancer studies and supporting studies.
The major sections in the cancer evaluation are as follows:

1.1 Properties and human exposure

This section includes details on the properties of light and defines shift work. It also provides an overview of the available information on human exposure to light at night, shift work, and transmeridian travel in the United States.

1.2 Human cancer studies

This section separately reviews and assesses the quality and utility of the available studies of cancer in humans in the context of exposure scenarios related to electric lighting practices, primarily – (1) light at night *per se* (e.g., light in the sleep area due to use of electric lighting at night); (2) work during the night and mistiming of light (e.g., shift work); and (3) transmeridian travel. In addition, studies of social jet lag (i.e., parents with infants, weekend/weekday differences in sleep schedules, adolescent sleep schedules, use of electronics at night, etc.) will be evaluated should such studies become available during the evaluation. In Section 5, evidence from the human studies of each scenario will be synthesized with evidence of mechanistic studies on light, shift work, and circadian disruption.

1.3 Human biomarker studies of light or shift work and circadian disruption

This section summarizes as a group the quality and utility of human studies investigating the relationship between light or shift work with biomarkers of circadian disruption.

1.4 Mechanisms and other relevant data

This section assesses the strength of mechanistic and related evidence for effects resulting from exposure scenarios related to electric lighting practices and circadian disruption. Included in this section are (1) studies in humans and animals that evaluate the association between biomarkers of circadian disruption and cancer or biomarkers of carcinogenicity, (2) studies using animal models of LAN, shiftwork, and circadian disruption, and (3) a discussion of studies in humans, animal models and *in vitro* models on potential mechanisms of LAN-related carcinogenicity, focusing on the relationship between circadian disruption and cancer.

1.5 Overall cancer evaluation

The final section of the draft RoC monograph describes the methods used to integrate the evidence from the cancer studies in humans with mechanistic and other relevant data and applies the RoC listing criteria to reach the NTP preliminary listing recommendation for exposure scenarios associated with electric lighting in the RoC.

1.6 References

1.7 Appendices

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

2 Methods for Evaluating Human Cancer

2.1 Introduction and objectives

The human cancer evaluation component of the draft monograph separately evaluates the relationship of cancer and three exposure scenarios related to exposure to electric lighting practices: primarily (1) light at night *per se*, (2) shift work, 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.

Level of evidence conclusions can only be made about the three exposure scenarios based on available human cancer studies. However, supporting information from studies of circadian disruption in relation to light and shift work from mechanistic and exposure studies, when considered together, may help redefine the topic.

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

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.

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 transmeridan 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?

2.1.1 Approach: Steps in the cancer hazard evaluation process

The five steps for conducting the human cancer hazard evaluation are outlined below. The procedures and guidelines for conducting each step are described in Sections 2.2 through 2.5 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 2.2)
2. Systematic extraction of data from the epidemiologic studies of cancer (Section 2.3)
3. Assessment of the utility of individual epidemiologic studies for each exposure scenario (Section 2.4)

4. Cancer hazard assessment of the level of evidence of carcinogenicity (sufficient, limited, or inadequate) from studies in humans (Section 2.5)

2.2 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, 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 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. Cancer studies measuring biomarker-related circadian disruption or among shift workers or people exposed to LAN should be retrieved by these searches.

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 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/) 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, light at night, 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 epidemiology 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 light at night, 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.
- 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 GLOBOCAN) database will not be included in the evaluation. Such ecological studies provide exposure measurements from geographically defined areas that are correlated with group level disease data from cancer registries, neither of which provide individual level data on exposure to light nor cancer. In addition, similar to all ecological studies, confounding is often a serious source of bias, as confounders are also not measured at the individual level. However, if these studies contain relevant background information they will be considered as supporting information and will be included in the integration of the scientific evidence in the hazard evaluation.
- Only those peer-reviewed, primary research studies of transmeridian travel that assess exposure based on the number of time zones or a proxy for the number of time zones crossed will be included in the quality evaluation.

2.3 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 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 is 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.

2.4 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 light at night, 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:* 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 the three exposure scenarios (light at night, 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.

2.4.1 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., light at night, shift work, or transmeridian travel) and to cancer?

Domain level ratings

Low/minimal concerns: (***) rating

Case 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., light at night, shift work, or transmeridian travel) and cancer.

Cohort is clearly defined (e.g., includes groups of those exposed [e.g., to light at night, 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 light at night, 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 – may be relevant in this literature (Applebaum et al. 2011, Picciotto et al. 2013).

Nested case-control studies conducted either within retrospective manufacturing cohorts or 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.

No cohort studies are available on light exposure, but several types of cohort studies of shift work have been conducted. These include (a) registry studies that calculate incidence of disease in a complete census of geographically defined workers with particular job titles (e.g., nurses, pilots) during a particular timeframe and compare this to the incidence of disease in the overall population; (b) retrospective cohorts of workers in manufacturing or industrial settings assembled to study chemical exposures, in which shift work is one of multiple exposures examined; and (c) prospective longitudinal cohorts in which multiple exposures and endpoints are examined among volunteer individuals from professions in which shift work is common (e.g., nurses, health workers). Completion of follow-up is a key factor to consider in all of these studies.

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., 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. When both were followed over time, those with low amplitude rhythms (those who did not complain and shifted easily), eventually became intolerant to shift work, and then became free running with 21-hour rhythms for temperature, and complained of gastrointestinal disorders, chronic fatigue, mood disorder, and other chronic symptoms ["free running" refers to the absence of zeitgebers or external cues like light that influence the body's rhythms Kyriacou and Hastings 2010]). Also, the overlapping concept of left truncation can occur when workers hired prior to the start of the study and are 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 compare results with those from the full cohort.

Registry studies and retrospective cohort studies of workers with a particular job title (e.g., nurses, pilots) and studies of shift work in manufacturing settings are susceptible to HWE, as risks of disease are typically compared to the entire population. Internal analyses (e.g., nested case-control studies) or comparisons with low exposure/non- exposed workers examining risk associated with duration of work, membership status, or years since leaving the profession, can avoid this bias. 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 change over time, and individuals susceptible to disruption from such schedules may remove themselves from the cohort. Analyses excluding short-term workers would be helpful to expose such bias.

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 (Pearce et al. 2007, Piciotto et al. 2013, Applebaum et al. 2011).

Finally, selection bias in the prospective or longitudinal 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. Similarly, follow-up time of disease

outcomes may be differential 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 light at night or shift work would be known and shown not to differ between cases and controls. Also, participation rates should be high and should 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 healthy worker effect (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. These data suggest that there are differences in health seeking behaviors that may extend to participation in health studies; also, that cancers of daytime workers may be more likely to be detected or detected sooner, with the implication that night-time workers considered to be disease free may be more likely than day workers to have undetected cancers due to lower screening rates.

2.4.2 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 light at night, 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 light at night, 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 light at night, 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.

Guidelines for reaching domain level rating

Detailed exposure assessment is desirable primarily to reduce measurement error. At the most general level to avoid misclassification, in-person interviews are preferred over mailed or phone interviews, and information obtained directly from the subject is preferred over information from proxies. Ideally, exposure assessment investigators and interviewers should be blinded to the status of cases and controls. Of these, the blinding of the investigators conducting exposure assessments is considered the most important; blinding in-person interviewers may not be feasible, depending on, e.g., the health of the subject with cancer.

Ideally, a biologically relevant exposure metric should be used to quantify the effect of the exposure on cancer.

Light at night

Metrics chosen to characterize light at night are best linked to their ability to disrupt circadian rhythm; when they are not linked, misclassification bias can result. Light does not affect the body in the form of direct toxicity of chemicals or other toxicants, and the dose-response relationship of light at night and circadian disruption or cancer is not currently well understood (Cho et al. 2015).

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 light at night (Hurley et al. 2014). An ideal study of light at night 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 (Rea et al. 2008, 2010, Hebert et al. 2002), 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). In addition, as age, chronotype (the propensity for the individual to sleep at a particular time during a 24-hour period), and photic history vary between individuals, measurements of these variables would also ideally be included.

Studies including more detailed assessments would be assigned higher quality ratings than those with less detail. 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) would capture some information about dose, timing, and duration of exposure. Questions assessing the intensity of light in the sleeping

habitat, such as type of illumination source for bedroom light and reading light, ability to read at night at work, to see across the room, to see to the end of the bed, etc. would capture information about light intensity. 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.

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. Light at night 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 these studies is differential by case and control status, although this consideration should not be excluded.

Finally, 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.

Shift work

Shift work is a complex multi-dimensional exposure with a range of associated effects or exposures; and, at this time, the most relevant exposure metrics for any particular cancer are unknown (see Figure 2-1 below). Guidance on measurement issues is provided below.

Shift work schedule

Studies of shift work and cancer should ideally attempt to quantify three shift work features of exposure over a lifetime course: (1) shift schedule (evening, night, rotating), (2) years on each type of shift schedule, and (3) shift intensity according to the IARC Working Group Report (Stevens et al. 2011b), which refers 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). In a recent publication based on the Danish Working Hour Database, Garde et al. (2016) found that the proportion of classified night shifts differs little when night shifts are based on definitions including a period during the night. The authors concluded that studies based on other definitions may be less comparable.

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).

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 or job exposure matrices. For

example, registry studies of nurses as a general occupational title, or production workers, transport operators, and laborers may broadly assess exposure as ever having worked in such occupations characterized by frequent shift work. Potential misclassification of exposure can be reduced in these studies using a job-exposure matrix (JEM) or expert assessment of information on tasks and jobs collected via detailed occupational questionnaires and interviews. For example, nested studies in retrospective manufacturing or industrial cohorts would ideally use a job-exposure matrix in which the details of shift work schedules and duration are known to characterize exposure.

Changing shift work patterns over time can occur as cohort effects in cohort studies. Ideally, cohort studies would address potential cohort effects as interactions or as effect modifiers, conducting analyses of shift work and cancer within various periods characterized by different patterns of shift work. 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).

Shift work associated effects or exposures

As shift work is a complex exposure (Figure 2-1), the ideal study of shift work would capture measurements of associated exposures including chronotype, disturbed social, sleep, and dietary patterns, lifestyle/behavioral changes, and changes in light at night and sun exposure in addition to lifetime patterns of shift work. These potentially relevant associated exposures are best measured by self-report in interviews or questionnaires, or by direct measurements using actigraphy, anthropometry, 24-hour recall logs, light sensors, and biomarkers in urine, blood, saliva or feces. Ideally, studies should capture information about sleep, mealtimes, etc. using questionnaires or interviews. These can capture information on disturbed patterns of light, sleep, diet, reproductive events, social activities, symptoms of stress, changes in tobacco and alcohol use, physical activity, and sun exposure. Ideally, data on the timing of changes in these patterns relative to changes in shift work schedules would be aligned. 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 reported that self-report of light at night in the distant past is likely to be subjected to greater error.

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 (Tajima et al. 1991, Härma et al. 1994). Traveling west to east, compared to east to west, for most persons whose inherited circadian period tends to be slightly greater than

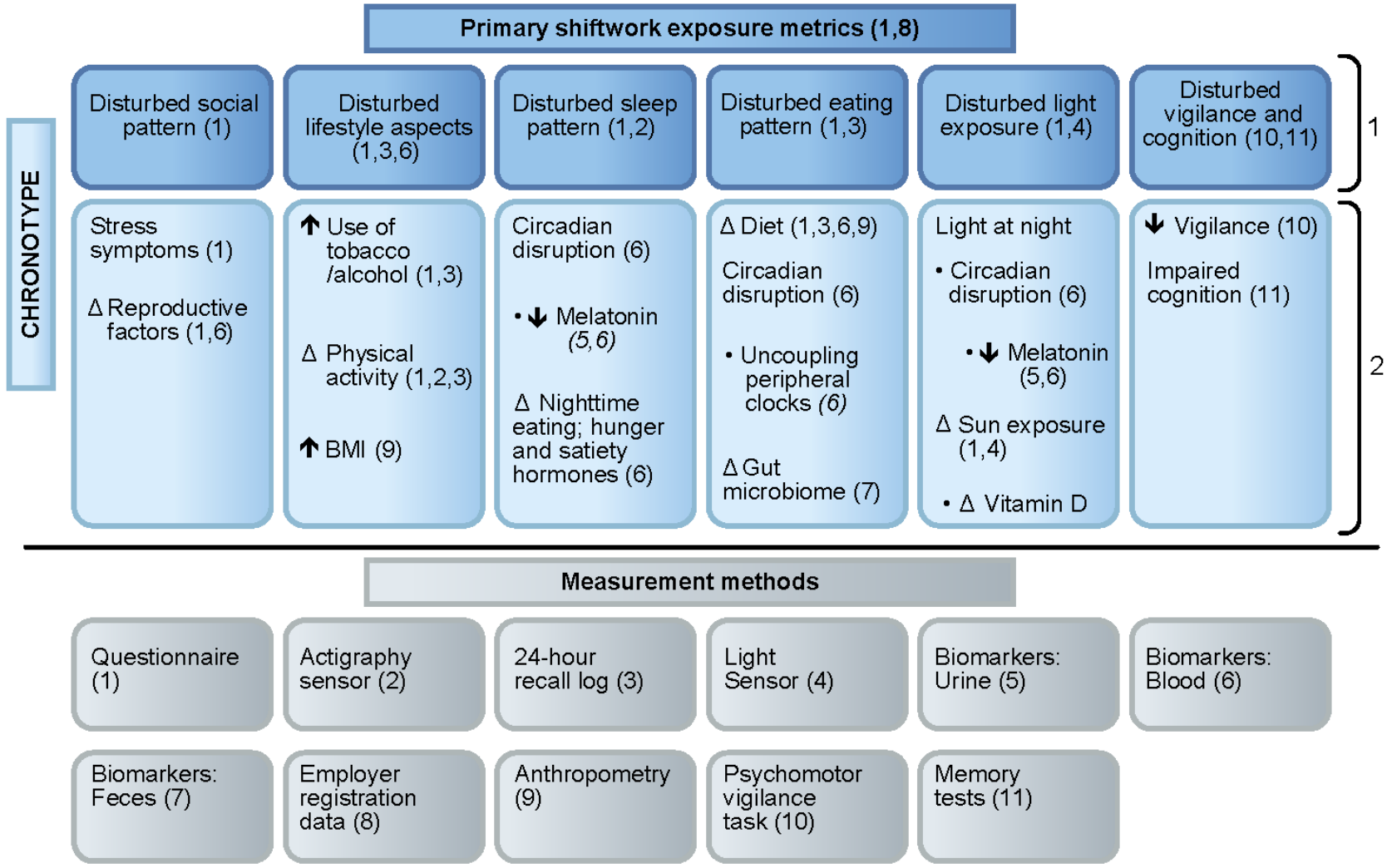

Figure 2-1. Design considerations for epidemiological studies of shift workers. Potentially relevant exposures are measured by self-report (e.g., interviews or questionnaires), employer data, actigraphy, 24-hour recall logs, light sensors, urinary, blood, or fecal biomarkers, anthropometry, psychomotor vigilance tasks, and memory tests. Gray boxes represent methods to measure these complex exposures and intermediate outcomes; numbers in the related exposures or intermediate effects boxes relate to the corresponding type of "measurement methods" to assess the factors; (Δ = change, arrows indicate direction of change). Based on the design for the Nightingale study (Pijpe et al. 2014)**.**

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 metric for assessing exposure to circadian disruption is a count of the number of time zones crossed and flight hours worked during standard sleep hours (Waters 2009, Grajewski et al. 2011). Studies using this metric would be assigned a higher quality rating than those using only a job title to assess exposure to descynchrony.

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 2012). Studies of social jet lag would ideally assess exposure using self-reported lifetime weekly sleep habits.

2.4.3 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 light at night 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 (or 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 and non-Hodgkin lymphoma (NHL) 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, 11.9 for ovarian cancer, and 23.7 (male) and 16.1 (female) for NHL. Five-year survival rates based on SEER age-adjusted data from 2009 to 2013 vary for these cancers: colorectal, 65.1%; lung, 17.7%;ovary, 46.2%, and NHL,70.7%, suggesting that both mortality and incidence data are informative for lung cancer, while incidence data would be more informative for colorectal and ovarian cancer, and NHL (http://seer.cancer.gov/statfacts/html).

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 (positive or negative) would be reported (e.g., Cordina-Duverger et al. 2016).

2.4.4 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 light at night, shift work, and transmeridian travel. Methods for assessing the impact of potential confounders on study findings is discussed in Section 2.5.

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 light at night 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, (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, light at night, 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 light at night 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 (Waters et al. 2000, Pukkala et al.1995). Among those flying in the 1950s and 1960s exposure to organochlorine pesticides was also common (Wartenberg et al. 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 light at night 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 light at night sought to assess exposure by studying populations working outside of a standard daytime shift schedule in order to constitute the most extreme exposure to light at night, shift work is now recognized as a complex exposure scenario (Figure 2-1) and not a simple surrogate for light at night. Thus, in addition to exposure to light at night, 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. 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 light at night, 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 OC use, and lower HRT 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 UK, 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 (Reinberg et al. 1979, Romon et al. 1986, Lennernäs et al. 1993). 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, or non-Hodgkins disease 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 or non-Hodgkins lymphoma, 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. 2016; Praestegaard et al. 2017). Winter (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 (Winter et al. 2014, Hemiö et al 2015). 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 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 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, lung, and non Hodgkins disease

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 *Diet, lifestyle factors:* Alcohol consumption *Demographics:* Lower socioeconomic status/education, population-specific characteristics *Occupational co-exposures:* depends on comparison group (e.g., day workers or non-workers) and study population **Light at night studies** *Reproductive and family history factors:* Age of first full-term pregnancy *Diet, lifestyle factors:* Alcohol consumption *Demographics:* Lower 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 *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, high consumption of processed meat, high alcohol consumption (men), low	**Shift workers** *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

Cancer site	Cancer risk factors	Potential major confounder (i.e., possibly associated with exposure scenario and disease)
	fiber diet; *Schistosoma japonicum* *Occupational agents:* X-radiation, [a] gamma-radiation, [a] asbestos	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
Non-Hodgkin Lymphoma	*Viral agents:* HIV/AIDS, *Helicobacter pylori (H. pylori)* infection, Epstein-Barr virus, human T-cell leukemia/lymphoma virus, human herpes virus 8, hepatitis C virus *Occupational agents:* industrial solvents, vinyl chloride, herbicides. Occupations may include chemists, farmers, grain handlers, petroleum refinery workers, anesthesiologists, pathologists, and wood workers.	**Shift workers** *Occupational co-exposures:* May depend on comparison group (e.g., day workers or non-workers) and study population

http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports (select cancer type), https://monographs.iarc.fr/ENG/Classification/Table4.pdf).

[a]Exposure may also be from medical use.

2.4.5 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 light at night 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 analytical methods were so limited that the findings were uninterruptable or distorted.

2.4.6 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 4.27 and Table D-8.

Core question and ratings

Core question

Does the study have adequate sensitivity to detect an effect from exposure to light at night 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 light at night in the control population, as virtually all individuals in developed countries are exposed to light at night regardless of their shift work history. If the comparison population has unmeasured high exposure to light at night, 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 light at night 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 for ovarian cancer. Prostate cancer and melanoma were not included in this analysis due to low mortality rates and the availability of various treatment options.

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 et al. 2015) requiring a sequence of acquired genomic events over many years, progressing through initiation (breakthrough), promotion (expansion), and progression (invasion). (Matthews et al. 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).

2.4.7 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 light at night, 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 endpoints) 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)
- Moderate/low (major to low concerns for bias, sensitivity rating varies)
- Low (major concerns, sensitivity rating varies)
- Inadequate (critical concerns for bias, sensitivity rating varies)

2.5 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 light at night, 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 lighting includes evaluating (1) whether there is credible evidence for an association between exposure to light at night, shift

work, or transmeridian travel and cancer, and (2) whether such an observed association can 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.

However, the presence of potential bias (e.g., selection bias, information bias) or confounding bias in a study does not necessarily mean that the study should be excluded from the evaluation. Blair et al. (2007) caution that the actual likelihood of occurrence and the direction and magnitude of the effect should be carefully and realistically considered when making judgments about study design or data interpretation, and suggest that examples of substantial confounding are rare in occupational epidemiology. On the other hand, exposure misclassification is common, with relatively small amounts of misclassification biasing relative risks substantially towards the null. In the case of studies of shift work, exposure misclassification is likely to be quite serious. Thus, conclusions about the evidence from each study should consider the strengths and weaknesses of the study, the direction and distortion of the biases, the role of measured and unmeasured effect modifiers, and the strength of the association between exposure and the cancer endpoint.

The evidence from the studies is then synthesized across studies and several considerations – strength of the association, consistency across studies, evidence of an exposure-response gradient, and temporality of exposure – are used to help reach a level of evidence conclusion. Meta-analyses will not be used to synthesize results across studies, as these analyses are of value when exposure metrics are similar across studies, and studies in this body of literature vary widely by type of exposure metric used. However, sources of heterogeneity - for example, effect modifiers – across studies should be examined (see Section 2.5.2)

2.5.1 Evaluation of confounding

There may be evidence from the study to suggest that although the risk estimate may be explained in part by confounding or bias, the bias cannot explain all excess risk. Thus, the evaluation of confounding is considered in several steps in the cancer hazard evaluation and therefore merits a cohesive discussion. In addition to considering the study methods for evaluating confounding discussed in Section 2.4.4, the evaluation of potential confounding may also consider (1) the distribution of the potential confounder in the exposed (e.g., shiftworkers) and non-exposed individuals or the correlation of the potential confounder with the exposure; (2) the strength of the association of the potential confounder with the endpoint of interest; and (3) the magnitude of the risk estimate or strength of exposure-response relationship for light at night and shift work and specific cancer endpoints. Once such considerations are weighed, and the results are examined, bias may be ruled out.

2.5.2 Evaluation of effect modification

Effect modification is likely to be present when the effect of a variable on the outcome differs across subgroups and the difference may feasibly reflect the biology of the disease. In shiftwork

studies, associations between shift work and cancer may vary by chronotype, tumor characteristics, reproductive histories, and genetic polymorphisms. To increase the ability to correctly compare results across studies of different populations, assessing the associations of shift work and cancer within strata of these variables can help explain heterogeneity in overall results across studies.

Ideally, studies will have collected information on potential effect modifiers, and will have powered the study to detect a difference between subgroups. Matching on the potential effect modifier will not have been done to allow examination of the effect of the potential modifier. Group-specific estimates should be provided and appropriate statistical methods used to assess their differences by strata (e.g., depending on the study design, Breslow-Day test for homogeneity of the estimates, extended Mantel-Haenszel method, or -2 log likelihood test from logistic regression, or proportional hazards regression).

Gene-environment interaction studies examining the effect modification of genetic susceptibility provide insight into how shift work together with common genetic variants in genes regulating circadian rhythm may affect cancer risk. In such studies, it is possible to analyze multiple polymorphisms in core circadian genes that influence gene expression, protein function, and protein-protein interactions. An ideal study of this type would have a large case group, a large reference group of non-shift workers, and a large number of exposed individuals with long durations of shift work. As these studies typically involve very large numbers of comparisons in subgroup analyses, it is important that sufficient prior probabilities for multiple testing be incorporated into the analyses to avoid false positive or negative findings.

3 Biomarker Studies of Circadian Disruption in Humans

3.1 Introduction and objective

Biomarkers indicating molecular, cellular, or other biological changes can indicate evidence of exposure, of early effects, cellular, tissue or organism responses, of individual susceptibility or host responses, or can point to causal mechanisms. Biomarker studies of circadian disruption that measure levels of melatonin, sex hormones, cortisol, or body temperature in relation to exposure to shift work or to light conditions in the field can inform how characteristics of light at night alter hormone status and disrupt circadian rhythms and ultimately lead to cancer. While these studies do not provide evidence for adverse or protective health effects, they can offer background information which can provide context or other information (e.g., exposure or metabolism data) potentially useful when evaluating confidence in bodies of evidence, interpreting heterogeneity across studies with different light or shiftwork conditions, or integrating evidence across human, animal, and mechanistic data from the included studies.

In this section, studies of biomarkers in relation to the light and shift work exposure scenarios will be summarized according to their utility for the cancer hazard evaluation.

3.2 Selection of the literature of human biomarker studies

Because this literature is supporting, the literature search is a more focused search using the strategy outlined in Table 3-1, and will be conducted in PubMed. Many studies have evaluated light characteristics, so a broader set of terms for light will be used rather than the more focused light at night terms. In order to increase the specificity of the search strategy (because of the broader category of light), the search strategy will be limited to specific biomarkers of circadian disruption, including melatonin, core body temperature, cortisol, and two important but less specific biomarkers, c-reactive protein, and sex steroid hormones. C-reactive proteins and sex steroid hormone terms will be combined with circadian disruption terms to retrieve literature relevant for the evaluation. Since the studies may be experimental or epidemiological, search strings will be for human and not restricted to epidemiological terms.

Table 3-1 Literature search strategy for biomarker studies in humans

Type of "exposure"	Search strategy[a]
Night shift work	(Shift work string[a]) and (specific circadian disruption biomarkers string[b]) and (human and epidemiological combined string[c])
	(Shift work string[a]) and (non-specific circadian disruption biomarkers string and focused circadian disruption string[b]) and (human and epidemiological combined string[c])
Light (characteristics of light)	(Light string[b]) and (specific circadian disruption biomarkers string[b]) and (human and epidemiological combined string[c])
	(Light string[b]) and (non-specific circadian disruption biomarkers string and focused circadian disruption string[b]) and (human and epidemiological combined string[c])

[a]See Appendix A, Exposure scenarios for search string terms.
[b]See Appendix A, Intermediate effects for search string terms.
[b]See Appendix A, Evidence stream for search string terms.

Search results are processed in Endnote and imported into Health Assessment Workplace Collaborative (HAWC) (https://hawcproject.org) and screened at two levels (title and abstract and full text) as described in Section 2.
Human biomarker studies will be considered if they provide relevant background information or context useful to evaluating the confidence in the bodies of evidence or integrating evidence across human, animal, and mechanistic data from included studies. Specifically, primary, peer-reviewed studies of biomarkers of circadian disruption in subjects exposed and unexposed to light or to shift work, including analytical, experimental, and descriptive studies will be included.

3.3 Evaluation of biomarker studies of circadian disruption

Biomarker studies will be evaluated as a group for quality; the overall findings from the studies will be summarized and considered in the integration of the scientific evidence for shift work and light at night and cancer.

The evaluation of these studies occurs prior to the cancer assessment (e.g., used to interpret the findings of the study). Both the characterization of exposure assessment methods (e.g., the measurement of shift work or light at night) as well as the overall sensitivity and specificity of methods used to measure biomarkers will be taken into consideration in rating the body of literature.

The body of biomarker studies of circadian disruption as a whole will be evaluated for the following:

- Strength of the **study designs** (e.g., experimental studies will receive a higher rating than cross-sectional studies)
- Quality of the **exposure assessments** for light at night and shift work (e.g., see Section D). Studies with more specificity about characteristics of exposures (rotations vs. “night work”; type of light [e.g., spectrum], etc.) will receive a higher rating than those with less specificity.
- Appropriateness of the biomarker for the analysis (e.g., melatonin, the source of the biomarker sample [i.e., urine, blood, saliva], core body temperature, cortisol). Studies most appropriate for the analysis will receive a higher rating than those less appropriate.
- Whether a single sample or **multiple samples** taken at various times are analyzed. Studies with multiple samples will receive higher ratings than studies of single samples.
- Whether the sensitivity and specificity of the methods used to measure biomarkers are adequate, and the methods of collection, handling, and processing appear to follow standard accepted approaches. Those studies with **detailed descriptions of methods**, which allow for an assessment of the quality of the standards and meet acceptable standards, will receive a higher rating than studies with less detail or unacceptable methods.

Studies will be grouped as above and rated accordingly:

- High (low/minimal concerns for bias)
- Moderate (low/minimal or some concerns for bias)

- Moderate/low (major to low concerns for bias)
- Low (major concerns)
- Inadequate (critical concerns for bias)

3.4 Specific biomarkers

Melatonin is the most frequently measured biomarker in relation to circadian disruption; however, glucocorticoids, clock genes, epigenetic methylation, immune factors, c-reactive protein (CRP), cytokine panels, core body temperature, cortisol, sex hormones, genetic polymorphisms, and the microbiome have also been explored or suggested. Biomarkers that are independent of time and reflect long term effects of circadian disruption on the biological system are ideal. However, while one such measure, CD36, has been suggested (Van Dycke et al. 2015), research is currently ongoing. Such measures would be ideal for use in large population-based studies using archived samples to investigate health outcomes.

In general, the sensitivity and specificity of the method for measuring biomarkers in different biological media (e.g., urine, serum, plasma) is important to know, together with their limits of detection. Knowledge of the time period over which the biomarker integrates dose is also important for determining the exposure period over which the biomarker is a valid indicator.

Details regarding melatonin, cortisol, core body temperature, and c-reactive protein as biomarkers are discussed below.

3.4.1 Melatonin

Melatonin is most relevant for measuring short-term circadian disruption; however, circadian disruption can occur with or without suppression of melatonin (Van Dycke et al. 2015), so it is not always clear what is being measured by melatonin in studies of LAN and shiftwork.

Melatonin is a monoamine hormone with a strong daily rhythm, normally low in the day and high at night. It is a robust marker of circadian rhythmicity in the presence of various external influences (Pandi-Perumal et al. 2007) such as biochemical and physiologic factors, so it more reliably measures circadian phase position than cortisol or body temperature (Lewy 1999). Pineal function and modulation of circadian rhythms can be measured non-invasively in urine in epidemiologic studies by measuring melatonin or its metabolite, 6-hydroxymelatonin sulfate (aMT6s).

Urinary melatonin

Paakkonen et al. (2006) reported that the mean nocturnal increase of urinary melatonin is about 2-fold in young adult men, and that of urinary aMT6s is about 4-5-fold from low daytime to high nocturnal levels. Both urinary melatonin and aMT6s correlated significantly with area under the curve during the night, during the day and throughout a 24-hr observation period. The ratio between urinary melatonin and aMT6s excretion had significant diurnal variation, being 9-fold higher at 4 p.m. than at 7 or 9 a.m. (Figure 3-1). The authors proposed that the 9-fold decrease in the urinary melatonin/aMT6s excretion ratio between the evening and the morning may reflect increased liver metabolism of melatonin during the night. Both urinary melatonin and aMT6s in this study were good indicators of melatonin secretion, but the variation was significantly smaller for the urinary melatonin.

The measurement of the urinary melatonin metabolite aMT6s reflects the cumulative amount of circulating melatonin corresponding to the time period between the prior urine void and the subsequent urine void; thus, urinary aMT6s can be used to measure excretion, fluctuation, amplitude, and acrophase. aMT6s is assayed by RIA or ELISA using commercial kits; with the concentration of this metabolite often adjusted by urinary creatinine concentrations. Unlike body temperature and cortisol, it is unaffected by excessive carbohydrate intake (Kräuchi et al. 2002), which makes it preferable to these two biomarkers. Its onset of production is unaffected by urine output volume between persons; and for separate urine collections within individuals (Klante et al. 1997). Measurements are highly and significantly correlated on consecutive days, as well as between measurement sessions over a long time period (up to a 5 year time period in several studies (Travis et al 2003). However, the interpretation of a single measurement at a single point in time, even when it is integrated over a 12-hour period (e.g., first morning void) or 24-hour period (24-hour urine collections) is not clear for the measurement of circadian dysfunction. Urinary measures of melatonin can be affected by liver disease; thus in populations where there is likely to be a high proportion of liver disease, kidney and brain function markers are important to assess (Chojnacki et al. 2012).

Plasma and serum melatonin

Plasma melatonin has a short biological half-life and is rapidly metabolized by the liver; samples reflect the amount of melatonin circulating at the point in time of sample collection. Serum melatonin levels increase nearly 10-fold from low daytime to high nocturnal values (Paakkonen et al 2006). Contrasted to a single blood collection, multiple hourly blood collections enable circadian rhythms to be divided into several categories: 1) onset of melatonin secretion, 2) duration of melatonin secretion, 3) peak levels of circulating melatonin, 4) time when peak secretion occurred; and 5) total amount of melatonin secreted.

There is a high correlation between nocturnal urinary melatonin or urinary aMT6s, and plasma or serum levels. Graham et al. (1998) found that combining two urinary measures of aMT6s and melatonin accounted for 72% of variance in total plasma melatonin; and peak nocturnal levels of plasma melatonin were significantly related to morning levels of urinary melatonin and aMT6s. Cook et al. (2000) found very high correlations between first morning void melatonin and creatinine-corrected aMT6s and both nocturnal plasma melatonin output and peak nocturnal plasma melatonin. High correlations of plasma and serum melatonin with urinary melatonin and/or aMT6s over a 24-hour period have been reported (Markey et al 1985, Baskett et al 1998). Total 24-hr urinary excretion of aMT6s was significantly correlated with the area under the curve of profiles for plasma melatonin ($r = 0.75$) and plasma aMT6s ($r = 0.70$) (Bojkowski et al. 1987). Klerman et al. (2002) reported that among three methods of calculating circadian phase, plasma melatonin data were less variable than those calculated using core body temperature or plasma cortisol data. The standard deviation for the phase estimates went from 0.78 hours for core body temperature to 0.23 to 0.35 hours for plasma melatonin, with plasma cortisol mid-way between these.

In a study of serum melatonin, the circadian profile of melatonin was shown to be highly reproducible over a six-week period, in both individuals and groups (Selmaoui and Touitou, 2003), indicating that serum melatonin can be a stable marker of the circadian time structure and useful for validating rhythms synchronization of individuals.

Salivary melatonin

Salivary melatonin is frequently used in epidemiologic studies due to being non-invasive, acceptable to study participants, and able to be self-collected. Salivary levels of steroid hormones and other analytes that are protein bound in serum reflect the unbound and active concentration of the hormone (Hofman 2001). A high correlation exists between serum and saliva melatonin concentrations; thus, saliva melatonin is a reliable indicator of serum melatonin (Arendt et al. 1985, Laakso et al. 1990, Klante et al. 1997, Davis et al. 2001, Gooneratne et al. 2003).

However, the correlation is weaker in people with low serum melatonin levels with the proportion of melatonin in saliva decreasing with increasing serum melatonin levels (Laakso et al. 1990, Gooneratne et al. 2003), suggesting that saliva doesn't always reflect the absolute concentration in the blood. Like plasma and serum, salivary melatonin reflects the level circulating in the body at time of collection, and repeated samples are needed to describe circadian rhythms. In addition, Jensen et al. (2014) reported large inter-laboratory variation for melatonin measured in saliva and emphasized the importance of external quality control for the analysis of salivary melatonin.

3.4.2 Cortisol

Secretion of cortisol is affected by the diurnal rhythm, sleep–wake cycle, neurological stress signals, and other factors (Refinetti 2006). Cortisol secretion is lowest during light sleep and gradually increases before deep sleep (Kudielka et al. 2007). The highest levels are achieved within 30 min after awakening, and continuously decrease throughout the day. The range of cortisol-level fluctuations remains stable throughout the day and night; however, cortisol secretion increases under physical or mental stress (Kudielka et al. 2007). The cortisol profiles of day shift workers typically increase in secretion at 6 am and decrease at 9 pm, which is consistent with the circadian rhythms of fixed-day workers (Knauth and Rutenfranz, 1976). By contrast, night-shift nurses, who sleep during the day and provide patient care under stressful conditions during the night, have constantly high cortisol profiles. Fluctuations in cortisol profiles are lower during night shifts than during day shifts (Holmbäck et al. 2003, Kudielka et al.,2007, Lac and Chamoux 2004, Mitani et al. 2006). Czeisler et al. (1986) indicated that circadian rhythms require several days to readjust and that new circadian rhythms adjust at a rate of 1 hour/day, suggesting that measurements may vary according to sampling protocols. Selmaoui and Touitou (2003) showed that the circadian profile of serum cortisol was highly reproducible over a six-week period, in both individuals and groups, indicating that it is a stable marker of the circadian time structure. As with salivary melatonin, Jensen et al. (2014) reported large inter-laboratory variation for cortisol measured in saliva, and emphasized the importance of external quality control for the analysis of salivary cortisol.

3.4.3 Core body temperature (CBT)

Core body temperature rhythm is tightly coupled to the endogenous circadian pacemaker in the suprachiasmatic nucleus (SCN). The standard method for measuring CBT is continuous sampling using rectal thermometry, which is not practical for epidemiologic studies. Based on a review of data using peripheral thermometers to measure CBT, they do not have clinically acceptable accuracy (Weed HG 2016). Various alternatives to rectal or wired data loggers to obtain a valid measure of circadian rhythms have been used in smaller exposure studies and

include an ingestible, temperature-sensitive capsule (Darwent et al. 2011). However, measurement bias was noted and attributed to temperature gradations across the alimentary canal.

3.4.4 C-Reactive protein (CRP)

CRP is a metabolic and inflammatory biomarker associated with cancer risk that has been suggested as a potential modulator of circadian disruption. Recent studies indicate that feeding and nighttime fasting are associated with reductions in CRP levels (Marinac 2015); furthermore, CRP concentrations are not subject to time-of-day variation (Meier-Ewert et al. 2001).

4 References

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

Arendt J, Bojkowski C, Folkard S, Franey C, Marks V, Minors D, Waterhouse J, Wever RA, Wildgruber C, Wright J. 1985. Some effects of melatonin and the control of its secretion in humans. *Ciba Found Symp* 117: 266-283.

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.

Baskett JJ, Cockrem JF, Antunovich TA. 1998. Sulphatoxymelatonin excretion in older people: relationship to plasma melatonin and renal function. *J Pineal R*es 24(1): 58-61.

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

Blair A, Stewart P, Lubin J, Forastiere F. 2007. Methodological issues regarding confounding and exposure misclassification in epidemiological studies of occupational exposures. *Amer J Indust Med* 50:199–207.

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

Bojkowski CJ, Arendt J, Shih MC, Markey SP. 1987. Melatonin secretion in humans assessed by measuring its metabolite, 6-sulfatoxymelatonin. *Clin Chem* 33(8): 1343-1348.

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

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.

Cho Y, Ryu SH, Lee BR, Kim KH, Lee E, Choi J. 2015. Effects of artificial light at night on human health: A literature review of observational and experimental studies applied to exposure assessment. *Chronobiol Int* 32(9): 1294-1310.

Chojnacki C, Walecka-Kapica E, Klupinska G, Wachowska-Kelly P, Zylinska K, Winczyk K, Chojnacki J. 2012. Serotonin and melatonin secretion and metabolism in patients with liver cirrhosis. *Pol Arch Med Wewn* 122(9): 392-397.

Cook MR, Graham C, Kavet R, Stevens RG, Davis S, Kheifets L. 2000. Morning urinary assessment of nocturnal melatonin secretion in older women. *J Pineal Res* 28: 41-47.

Cordina-Duverger E, Koudou Y, Truong T, Arveux P, Kerbrat P, Menegaux F, Guenel P. 2016. Night work and breast cancer risk defined by human epidermal growth factor receptor-2 (HER2) and hormone receptor status: A population-based case-control study in France. *Chronobiol Int* 33(6): 783-787.

Czeisler CA, Allan JS, Strogatz SH, Ronda JM, Sanchez R, Rios CD, Freitag WO, Richardson GS, Kronauer RE. 1986. Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. *Science* 233(4764): 667-671.

Darwent D, Zhou X, van den Heuvel C, Sargent C, Roach GD. 2011. The validity of temperature-sensitive ingestible capsules for measuring core body temperature in laboratory protocols. *Chronobiol Int* 28(8): 719-726.

Davis S, Mirick DK, Stevens RG. 2001. Night shift work, light at night, and risk of breast cancer. J Natl *Cancer Inst* 93(20): 1557-1562.

Fekedulegn D, Burchfiel CM, Hartley TA, et al. 2013. Shiftwork and Sickness Absence Among Police Officers: The BCOPS Study. *Chronobiol Int* 30(7): 930-941.

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.

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.

Gooneratne NS, Metlay JP, Guo W, Pack FM, Kapoor S, Pack AI. 2003. The validity and feasibility of saliva melatonin assessment in the elderly. *J Pineal Res* 34(2): 88-94.

Graham C, Cook MR, Kavet R, Sastre A, Smith DK. 1998. Prediction of nocturnal plasma melatonin from morning urinary measures. *J Pineal Res* 24: 230-238.

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.

Härma 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: 1479-1489.

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

Hofman LF. 2001. Human saliva as a diagnostic specimen. *J Nutr* 131(5): 1621S-1625S.

Holmback U, Forslund A, Lowden A, Forslund J, Akerstedt T, Lennernas M, Hambraeus L, Stridsberg M. 2003. Endocrine responses to nocturnal eating--possible implications for night work. *Eur J Nutr* 42(2): 75-83.

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.

Hulsegge G, Boer JM, van der Beek AJ, Verschuren WM, Sluijs I, Vermeulen R, Proper KI. 2014. Shift workers have a similar diet quality but higher energy intake than day workers. *Scand J Work Environ Health* 2016 Sep 15. pii: 3593. doi: 10.5271/sjweh.3593.

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.

IARC. 1990. *Some Flame Retardants and Textile Chemicals, and Exposures in the Textile Manufacturing Industry*, vol. 48. Lyon, France: International Agency for Research on Cancer. pp. 45-181.

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. pp. 563-764.

Jensen MA, Mortier L, Koh E, Keevil B, Hyttinen S, Hansen AM. 2014. An interlaboratory comparison between similar methods for determination of melatonin, cortisol and testosterone in saliva. *Scand J Clin Lab Invest* 74(5): 454-461.

Klante G, Brinschwitz T, Secci K, Wollnik F, Steinlechner S. 1997. Creatinine is an appropriate reference for urinary sulphatoxymelatonin of laboratory animals and humans. *J Pineal R*es 23(4): 191-197.

Klerman EB, Gershengorn HB, Duffy JF, Kronauer RE. 2002. Comparisons of the variability of three markers of the human circadian pacemaker. *J Biol Rhythms* 17(2): 181-193.

Knauth P, Rutenfranz J. 1976. Experimental shift work studies of permanent night, and rapidly rotating, shift systems. I. Circadian rhythm of body temperature and re-entrainment at shift change. *Int Arch Occup Environ Health* 37(2): 125-137.

Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. 2002. Alteration of internal circadian phase relationships after morning versus evening carbohydrate-rich meals in humans. *J Biol Rhythms* 17(4): 364-376.

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

Kudielka BM, Buchtal J, Uhde A, Wust S. 2007. Circadian cortisol profiles and psychological self-reports in shift workers with and without recent change in the shift rotation system. *Biol Psychol* 74(1): 92-103.

Kyriacou CP and Hastings MH. 2010. Circadian clocks: Genes, sleep, and cognition. *Trends in Cognitive Science* 14, 259-267.

Laakso ML, Porkka-Heiskanen T, Alila A, Stenberg D, Johansson G. 1990. Correlation between salivary and serum melatonin: dependence on serum melatonin levels. *J Pineal Res* 9(1): 39-50.

Lac G, Chamoux A. 2004. Biological and psychological responses to two rapid shiftwork schedules. *Ergonomics* 47(12): 1339-1349.

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.

Lewy AJ. 1999. The dim light melatonin onset, melatonin assays and biological rhythm research in humans. *Biol Signals Recept* 8(1-2): 79-83.

Licaj I, Jacobsen BK, Selmer RM, Maskarinec G, Weiderpass E, Gram IT. 2016. Smoking and risk of ovarian cancer by histological subtypes: an analysis among 300 000 Norwegian women. *Br J Cancer*. doi: 10.1038/bjc.2016.418.

Marinac CR, Sears DD, Natarajan L, Gallo LC, Breen CI, Patterson RE. 2015. Frequency and circadian timing of eating may influence biomarkers of inflammation and insulin resistance associated with breast cancer risk. *PLoS One* 10(8): e0136240.

Markey SP, Higa S, Shih M, Danforth DN, Tamarkin L. 1985. The correlation between human plasma melatonin levels and urinary 6-hydroxymelatonin excretion. *Clin Chim Acta* 150(3): 221-225.

Matthews SB, Thompson HJ. 2016. The obesity-breast cancer conundrum: an analysis of the issues. *Int J Mol Sci* 17(6). pii: E989. doi: 10.3390/ijms17060989.

Meier-Ewert HK, Ridker PM, Rifai N, Price N, Dinges DF, Mullington JM. 2001. Absence of diurnal variation of C-reactive protein concentrations in healthy human subjects. *Clin Chem* 47(3): 426-430.

Miller D, Bierman A, Figueiro M, Schernhammer E, Rea M. 2010. Ecological measurements of light exposure, activity, and circadian disruption. *Light Res Technol* 42(3): 271-284.

Mitani S, Fujita M, Shirakawa T. 2006. Circadian variation of cardiac autonomic nervous profile is affected in Japanese ambulance men with a working system of 24-h shifts. *Int Arch Occup E*nviron Health 79(1): 27-32.

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

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

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.

Pääkkönen T, Mäkinen TM, Leppäluoto J, Vakkuri O, Rintamäki H, Palinkas LA, Hassi J. 2006. Urinary melatonin: a noninvasive method to follow human pineal function as studied in three experimental conditions. *J Pineal Res* 40(2): 110-115.

Pandi-Perumal SR, Smits M, Spence W, Srinivasan V, Cardinali DP, Lowe AD, Kayumov L. 2007. Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 31(1): 1-11.

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

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.

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.

Praestegaard C, Jensen A, Jensen SM, Nielsen TS, Webb PM, Nagle CM, DeFazio A; Australian Ovarian Cancer Study Group. 2017. Høgdall 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; Ovarian Cancer Association Consortium. 2017. Cigarette smoking is associated with adverse survival among women with ovarian cancer: Results from a pooled analysis of 19 studies. *Int J Cancer* Jan 7. doi: 10.1002/ijc.30600.

Pukkala E, Auvinen A, Wahlberg G. 1995. Incidence of cancer among Finnish airline cabine attendants, 1967–92. *BMJ* 311: 649–52.

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.

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

Refinetti R. 2005. *Circadian Physiology* 2nd Ed.: CRC Press. 688 pp.

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.

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

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

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

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.

SEER. 2016. Surveillance, Epidemiology, and End Results Program. National Cancer Institute. http://seer.cancer.gov/.

Selmaoui B, Touitou Y. 2003. Reproducibility of the circadian rhythms of serum cortisol and melatonin in healthy subjects: a study of three different 24-h cycles over six weeks. *Life Sci* 73(26): 3339-3349.

Snedeker SM. 2006. Chemical exposures in the workplce: effect on breast cancer risk among women. *AAOHN J* 54(6):270-9; quiz 280-281.

Stevens RG. 2011. Testing the light-at-night (LAN) theory for breast cancer causation. *Chronobiol Int* 28(8): 653-656.

Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ, Castano-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.

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: 325-327.

Textor J, Hardt J, Knuppel S. 2011. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology* 22(5): 745.

Travis RC, Allen NE, Peeters PH, van Noord PA, Key TJ. 2003. Reproducibility over 5 years of measurements of 6-sulphatoxymelatonin in urine samples from postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 12(8): 806-808.

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.

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.

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

Van Dycke KC, Pennings JL, van Oostrom CT, van Kerkhof LW, van Steeg H, van der Horst GT, Rodenburg W. 2015b. Biomarkers for circadian rhythm disruption independent of time of day. *PLoS One* 10(5): e0127075.

Vogelstein, B.; Kinzler, K.W. 2015. The path to cancer—Three strikes and you're out. *N Engl J Med* 373: 1895-1898.

Vogelstein, B.; Papadopoulos, N.; Velculescu, V.E.; Zhou, S.; Diaz, L.A., Jr.; Kinzler, K.W. 2013. Cancer genome landscapes. *Science* 339: 1546-1558.

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.

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

Waters M, Bloom TF, Grajewski B. 2000. The National Institute for Occupational Safety and Health/Federal Aviation Administration (NIOSH/FAA) working women's health study: Evaluation of the cosmic-radiation exposures of flight attendants. *Health Phys* 79(5):553-559.

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.

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. doi: 10.1186/1745-6673-9-27.

WCRF. 2006. Systematic Literature Review Report: The associations between food, nutrition, physical activity and the risk of skin cancer and underlying mechanisms. London, UK: World Cancer Research Fund International. 950 pp.

WCRF. 2016. Breast Cancer. World Cancer Research Fund International. http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports/breast-cancer. Accessed on 8/4/16.

WCRF. 2016. Ovarian Cancer. World Cancer Research Fund International. http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports/ovarian-cancer. Accessed on 8/4/16.

Weed HG. 2016. Review: Peripheral thermometers do not have clinically acceptable accuracy for measuring core body temperature. *Ann Intern Med* 164(6): JC32.

Weng HY, Hsueh YH, Messam LL, Hertz-Picciotto I. 2009. Methods of covariate selection: directed acyclic graphs and the change-inestimate procedure. *Am J Epidemiol* 169(10):1182–90.

Appendix A: Literature Search Strategy

This section provides the search strings (referenced in Tables 2-1 and 3-1) that are specific for the draft RoC monograph on exposure scenarios related to electric light practices. It includes strings for the exposure scenarios (shiftwork, electric light, and transmeridian travel), intermediate effects (circadian disruption and biomarkers of circadian disruption), and evidence stream (human and epidemiological studies combined). General search strings, such as those for cancer, epidemiological studies, animal studies, and mechanistic and other data related to carcinogenicity, are available in the RoC handbook appendix (http://ntp.niehs.nih.gov/ntp/roc/handbook/rochandbookappendix_508.pdf .

Exposures scenarios

Search strings for the different exposures are provided in the tables below. A separate table is created for each exposure scenario (shift work, LAN, transmeridian travel, and other unnatural light exposures) which will be used to search three databases

Table A-1. Shift work string: Three databases

Database	Shift work string[a]
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 (WOS)	(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]See Table 3-1 for strategies using these terms.

Table A-2. Light at Night (LAN) string: Three databases

Database	LAN string[a]
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 (WOS)	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]See Table 3.1 for strategies using these terms.

Table A-3. Transmeridian travel strings: Three databases

Database	Transmeridian travel string[a]
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 (WOS)	(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]See Table 3.1 for strategies using these terms.

Table A-4. Unnatural light exposure: Three databases

Database	Unnatural light exposure string[a, b]
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 (WOS)	(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]See Table 3.1 for strategies using these terms.
[b]As per Table 3.1, this search string is combined with focused circadian search string to focused the literature.

Intermediate effects (e.g., circadian disruption-related search terms): PubMed

These search strings were created to either focus the literature or identify human studies of biomarkers of circadian disruption (see Section 4.4 for a discussion of the biomarkers of interest).

Table A-5. Intermediate effects: PubMed

Type of effect	Search string
Focused circadian disruption string	(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])
Specific circadian disruption biomarkers	(corticosterone[tiab] OR cortisol[mh] OR cortisol[tiab] OR melatonin[mh] OR melatonin[tiab] OR "body temperature"[mh] OR body-temperature*[tiab])
Non-specific circadian disruption biomarkers	(("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]))
Light string[c]	(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])

[a]See Tables 3-1 and 4-1 for strategies using these terms.
[c]As per Table 4-1, this search string is for identifying biomarker studies of light.

Evidence steam

A search string was created that combines human and epidemiological terms to identify both experimental and epidemiological studies in humans (see Table 4-1). Search strings for other evidence streams are available in the RoC Handbook

Table A-6. Human and epidemiological combined string: 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])