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Shift work at Night, Artificial Light at Night, and Circadian Disruption Workshop

March 10-11, 2016

Office of the Report on Carcinogens (ORoC)
Office of Health Assessment and Translation (OHAT)
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

Introduction

Many people experience interruptions in light-dark cycles due to their lifestyle choices (e.g., use of electronic devices at night), location of their residences (e.g., urban light pollution), or working at night (e.g., shift work). Exposures to electrical light at night from artificial sources (referred to in this document as artificial light at night, ALAN) or changes in the timing of exposures to natural light (such as with 'jet lag') may disrupt biological processes controlled by endogenous circadian rhythms, potentially resulting in adverse health outcomes. NTP is interested in understanding the health effects of circadian disruption related to ALAN and shift work. Office of the Report on Carcinogens (ORoC) plans to conduct a health hazard assessment focusing on cancer and Office of Health Assessment and Translation (OHAT) will focus on non-cancer health outcomes. After considering the extent and nature of the existing literature, OHAT is strongly considering analyses of cardiovascular, metabolic, reproductive, gastrointestinal, immunological, and neurological outcomes. Although systematic reviews have been conducted for some of these outcomes, to our knowledge no previous reviews have included consideration of animal and mechanistic studies, which may help address some of the limitations of the human evidence. Given the amount of previous work that has been done, OHAT is inclined not to conduct analyses of worker safety or performance but would welcome discussion on this point at the workshop.

NTP is convening a workshop on March 10-11, 2016, to obtain external scientific input on topics important for informing the literature-based health hazard assessments, including strategies for integrating data across evidence streams and exposure scenarios, and on data gaps and research needs. The workshop has been organized into six sessions, which are scheduled to reflect a progression of the discussion beginning with circadian disruption, then moving to the exposure scenarios – ALAN, shift work, additional overlapping exposures in ALAN/shift work studies – and wrapping up with strategies to synthesize across different types of exposure scenario studies and research needs. Each session will start with a brief presentation followed by a short question-and-answer period and/or moderator-led discussion, consisting of focused questions and key discussants.

The purpose of the session abstracts is to provide a brief introduction of the topic and facilitate the workshop discussions. The reference list provided with each session abstract is not comprehensive but should assist in becoming familiar with the topic. An appendix containing supplementary materials (text, tables, and additional references) for the sessions on ALAN and shift work, organized by health outcome, is also provided. Appendices (listed below) are organized by health outcome and integrate across the various exposures (ALAN and shift work).

- Appendix A: Overview of human studies: Cancer, biomarkers, and interventions
- Appendix B: Overview of experimental animal studies: Carcinogenicity
- Appendix C: Overview of human studies: Non-cancer health outcomes
- Appendix D: Overview of experimental animal studies: Non-cancer health outcomes
- Appendix E: Meeting participants

1. Circadian disruption

1.1. Session goals and discussion topics

The goal of this session is to provide an overview of circadian disruption including biomarkers and experimental models to inform the workshop discussions. The key discussion question is how to define circadian disruption for the purpose of informing NTP literature-based health hazard assessments.

1.2. Background and key references

Circadian rhythms are daily and predictable variations in biological, physiological, and behavioral processes – such as sleep-wake cycles, body temperature, blood pressure, hormone secretion, metabolism, digestion, glucose homeostasis, and cell-cycle regulation – that are regulated by endogenous clocks. The rhythms are entrained to the external environment by repetitive signals, of which the light/dark cycle is the most important. Light exposure transmits time information (time of day, duration of the day, and day of the year) from the photoreceptors (primarily the retinal cells in the eye, via the photopigment melanopsin, and also rods and cones) to the master clocks (or central pacemaker) located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN regulates the numerous peripheral clocks (oscillators) via humoral, endocrine, or neural signals. One of the most important circadian humoral factors is the pineal hormone melatonin, which transmits time information (via peak and duration of melatonin production) to many organs and tissues (IARC 2010). The pineal gland secretes melatonin in response to the light-dark cycle, which peaks at the biological night. Light (depending on the intensity and spectrum) will suppress melatonin production at night. Exposures other than light, such as timing of meals can also provide external time cues for coordinating endogenous rhythms via peripheral clocks located within most cells throughout the body.

Circadian disruption occurs when the endogenous circadian rhythms are out of phase with the external environment or with each other (reviewed by Arendt et al. 2010, Stevens et al. 2011b). Circadian disruption has been proposed to include phase-shifts of the circadian system, displacement of sleep relative to the circadian clock, and/or suppression of nocturnal melatonin production. Examples of environmental disruptors of circadian rhythms include light at night, shift work, and transmeridan travel (jet lag) or social jet lag.

References

Arendt J. 2010. Shift work: coping with the biological clock. *Occupational Medicine* 60(1): 10-20.

Bonde J. P., J. Hansen, *et al.* 2012. Work at night and breast cancer--report on evidence-based options for preventive actions. *Scand J Work Environ Health* 38(4): 380-390.

Haus EL, Smolensky MH. 2013. Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. *Sleep Med Rev* 17(4): 273-284.

International Agency for Research on Cancer (IARC). 2010. Shiftwork in *Painting, Firefighting, and Shiftwork. IARC monographs on the evaluation of carcinogenic risks to humans. World Health Organization, International Agency for Research on Cancer* 98: 9-764

Rea MS and Figueiro MG. 2014. Quantifying light-dependent circadian disruption in humans and animal models. *Chronobiol Int* 31(10):1239-1246

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

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

Summa K.C., Turek, F.W. (2014) Biomedical effects of circadian rhythm disturbances, Chapter 4 in *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*. (S. Redline & N.A. Berger, eds.). Springer Science+Business Media, New York, pp. 77-99.

2. Artificial Light at Night (ALAN)

2.1. Session goals and discussion topics

The goal of this session is to identify the relevant literature (e.g., biomarkers and studies) regarding ALAN that can be used to inform Sessions 5 (strategies for synthesizing across the exposure scenarios) and 6 (data gaps and research needs). The key discussion questions are as follows:

- What characteristics of light are related to circadian disruption? How well do satellite images measure light that causes circadian disruption?
- How can the experimental evidence (e.g., animal models of outcomes and biomarkers and/or *in vitro* studies) and/or biomarker studies in humans inform the interpretation of studies of health effects in humans? How do we translate animal studies to human studies when it comes to the sensitivity to light?
- Which animal exposure models are most representative of potential human exposures and should be considered by NTP? Conversely, which animal exposure models should be excluded?
- What biomarkers could be used to assess interventions to reduce light-induced circadian disruption?

2.2. Background and key references

The invention of electrical light has paved the way for individuals to work, eat, and conduct other activities throughout the 24-hour day and has redefined the sleep/wake cycle and is a hallmark of the industrial world. Studies using satellite data (U.S. Air Force Defense Meteorological Satellite Program) identified nighttime illumination (light pollution) for 99% of the U.S. population that exceeded a threshold of 10% above natural sky brightness at 45° of elevation; 83% were exposed to at least 3 times the natural sky brightness, 62% to 9 times, and 30% to 27 times that light level (Cinzano *et al.* 2001). Electrical light may vary in intensity, timing, or wavelength, all of which can suppress the production and release of nocturnal melatonin, and disrupt endogenous circadian rhythms and sleep (Stevens and Zhu 2015, Stevens et al. 2014). ALAN was hypothesized to play a role in the increasing incidence of breast cancer in the economically developed world based largely on experimental data demonstrating the association of decreased melatonin levels with breast cancer development along with the fact that another product of electric power, electromagnetic fields, may be a risk factor for breast cancer (Stevens et al. 1992). ALAN-induced circadian disruption has also been proposed to be involved with other major health outcomes including several types of cancer and non-cancer outcomes such as metabolic, neurological, reproductive, and cardiovascular disorders.

Although epidemiological studies on shift work were originally conducted to test the ALAN hypothesis, it is a complex exposure scenario, of which ALAN is only one (albeit major) component; thus, shift work is discussed as a separate topic (Session 3). The ALAN section will focus on studies in humans and experimental animals that investigate the impact of altering the type of light and dark periods. Studies on the timing of light are considered with the shift work session.

Human studies

Breast cancer is the most common health outcome in observational epidemiological or ecological studies evaluating ALAN, although some studies report results on other cancers and non-cancer health outcomes as well as biomarkers of circadian rhythm. A key issue in the evaluation of studies of light at night will be the quality of the assessment of exposure to light and its relationship to circadian disruption. Light characteristics assessed in these studies include outdoor light pollution (population-based exposure assessment), lighting habits (individual exposure assessment), and indoor illumination level (actual measurements) (Cho et al. 2015). The association of light pollution and different types of cancer – breast, prostate, colon, and lung – as well as urinary 6-sulfatoxymelatonin (aMT6s) has been evaluated in ecological and cohort/case-referent studies. The studies on lighting habits (primarily in the bedroom) include breast cancer case-control studies, cross-sectional studies of obesity or eye disorders, and longitudinal or cross-sectional studies of serum sex hormone and urinary aMT6s. The studies measuring light intensity are mainly cross-sectional analyses of the relationship of light intensity or duration and biomarkers of circadian disruption, sleep onset, or fatigue; there are some longitudinal studies on obesity and depression (Cho et al. 2015 and see Appendix A)..

In addition to observational studies, there are also experimental studies in humans that have evaluated the effects of light characteristics such as intensity, duration, wavelength, light and dark cycle, and circadian disruption biomarkers or sleep (see Cho et al. 2015 for review) as well as studies evaluating interventions (such as using goggles) to reduce ALAN-induced circadian disruption (see Appendix A).

Experimental animal models

Animal models that may be most similar or informative to human exposure (discussed above) to ALAN or environmental disruption of the light and dark cycle include the following exposure paradigms: (1) constant light or constant darkness versus 12 hour light/dark cycle (12 hours of light and 12 hours of dark) (2) variation in the duration of the light and dark periods (e.g., 16 hours light and 8 hours dark), (3) dim light or light contamination during dark phase (e.g., 12 hours light, 12 hours dark with dim light), and (4) varying light intensity (IARC 2010, Appendix B). (Shift work/jet lag models evaluating the timing of light, are discussed in Session 3.)

For carcinogenicity studies, these models were used to evaluate tumor development (i.e., the incidence or onset of spontaneous tumors), tumor promotion of chemically induced tumors (primarily mammary gland, liver, lung, and colon tumors), or tumor growth of human (MCF breast tumors, epidermoid tumors) or rodent (such as mammary, colon, skin, lung, and bone) implanted tumors or tumor cells. In some studies, melatonin was administered to some groups of animals to evaluate whether it could reverse light effects on tumor development. Many studies measured biomarkers of circadian disruption and/or early markers of carcinogenesis, such as nocturnal melatonin (or its metabolite) production, lipid metabolism – e.g., fatty acid (especially linoleic) uptake, and production of the mitogen 13-hydroxyoctadecadienoic acid (13-HODE), which is a linoleic acid metabolite, markers of aerobic glycolysis, plasma sex hormones, and markers of DNA damage, expression of circadian genes or cancer-related genes, and cellular proliferation.

Studies of circadian disruption in experimental animals including surgical models (such as suprachiasmatic nuclei lesions, or pinealectomy-induced melatonin suppression), genetic models (such as clock gene mutations), direct effects of physiological levels of melatonin on tumorigenesis, circadian timing of carcinogen administration, and non-24 hour photoperiods (IARC 2010, Anisimov et al. 2006) were also identfed. Melatonin is a potential intervention strategy for realigning the circadian clock. While these studies provide supporting information regarding the role of circadian disruption and health effects, they are less relevant to environmental exposures that occur in people. Animal models of blinded animals and studies of blind people may also provide supporting mechanistic information.

Cited or key references

Anisimov VN, Popovich IG, Zabezhinski MA, Anisimov SV, Vesnushkin GM, Vinogradova IA. 2006. Melatonin as antioxidant, geroprotector and anticarcinogen. *Biochim Biophys Acta* 1757(5-6): 573-589.

Bartsch C, Bartsch H, Peschke E. 2009. Light, melatonin and cancer: current results and future perspectives. *Biol Rhythm Res* 40(1): 17-35.

Blask DE, Dauchy RT, Brainard GC, Hanifin JP. 2009. Circadian stage-dependent inhibition of human breast cancer metabolism and growth by the nocturnal melatonin signal: consequences of its disruption by light at night in rats and women. *Integr Cancer Ther* 8(4): 347-353.

Bullough JD, Rea MS, Figueiro MG. 2006. Of mice and women: light as a circadian stimulus in breast cancer research. *Cancer Causes Control* 17(4):375-383.

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.

Cinzano P, Falchi F, and C.D. Elvidge CD. 2001. The first World Atlas of the artificial night sky brightness. *Mon Not R Astron Soc*. 328: 689-707.

Evans JA and Davidson AJ. 2013. Health consequences of circadian disruption in humans and animal models. *Prog Mol Biol Transl Sci*. 119:283-323.

Figueiro MG, Hamner R, Bierman A, Rea MS. Comparisons of three practical field devices used to measure personal light exposures and activity levels. *Lighting Res and Tech* 2013; 45(4): 421-434.

Figueiro MG, Rea MS, Bullough JD. Does architectural lighting contribute to breast cancer? *J Carcinogenesis* 2006; 5(1):20.

International Agency for Research on Cancer (IARC). 2010. Shiftwork in *Painting, Firefighting, and Shiftwork. IARC monographs on the evaluation of carcinogenic risks to humans. World Health Organization, International Agency for Research on Cancer* 98: 9-764

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

Reiter, R. J. (1985) Action spectra, dose-response relationships, and temporal aspects of light's effects on the pineal gland. *Ann NY Acad Sci* 453, 215-230.

Stevens RG, Davis S, Thomas DB, Anderson LE, Wilson BW. 1992. Electric power, pineal function, and the risk of breast cancer. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 6(3): 853-860.

Stevens RG, Brainard GC, Blask DE, Lockley SW, Motta ME. 2014. Breast cancer and circadian disruption from electric lighting in the modern world. *CA Cancer J Clin* 64(3): 207-218.

Stevens RG, Zhu Y. 2015. Electric light, particularly at night, disrupts human circadian rhythmicity: Is that a problem? *Philos Trans R Soc Lond B Biol Sci* 370(1667).

3. Shift Work and Transmeridian Travel

3.1. Session goals and discussion topics

The goal of this session is to identify the relevant literature (e.g., biomarkers and studies) regarding shift work that can be used to inform Sessions 5 (strategies for synthesizing across the exposure scenarios) and 6 (data gaps and research needs). The key discussion questions are as follows:

- What characteristics of shiftwork and transmeridian travel or social jet lag are related to circadian disruption?
- How can the experimental evidence (models and biomarkers) and/or biomarker studies in humans inform the interpretation of studies of health effects in humans?
- Which animal exposure models are most representative of shift work and should be considered by NTP? Conversely, which animal exposure models should be excluded?
- What biomarkers can be used to assess interventions to reduce circadian disruption associated with shiftwork?

3.2. Background information

Economic globilzation and the demand for goods and services at all hours of the day have led to an increase in non-traditional work schedules including night shifts (Evans and Davidson 2013). Occupations and industries with the highest percentages of individuals working night shifts (20% to 50%) include protective services (e.g., police and fire fighters), leisure and hospitality (e.g., food service and hotel workers), healthcare practitioners and healthcare support, transportation and warehousing, manufacturing, and mining (BLS 2005).

Circadian rhythms of individuals who are synchronized to daytime activity and nighttime sleep undergo phase adjustment after a change in work schedule or travel across multiple time zones. Exposure to light in the latter part of the biological night (such as backward [night to day] rotating shift schedule or traveling eastward) can cause phase advances in circadian rhythms whereas exposure to light in the early part of the night (forward rotating work schedule [day to evening to night] or traveling westward) can cause phase delays. Circadian disruption occurs during the period of adaptation to the new work schedule or time change, and people adapt to the new schedule at different rates. The extent of the disruption depends on many factors such as the direction of the phase shift, the type of work schedule, and individual susceptibility (Bonde 2010, Arendt et al. 2010, Stevens et al. 2011b, Haus and Smolensky 2012). In addition, changes in work schedules affect quality and quantity of sleep and are associated with fatigue and timing of meals (see Session 4).

Shift work has been proposed to be associated with a wide variety of adverse health effects including neurological disorders, cardiovascular disease, metabolic syndrome, obesity, immune dysfunction, reproductive complications, and cancer (Evans and Davidson 2013). The major actors thought to produce adverse effects in shift workers include exposure to artificial light at night, circadian misalignment, and sleep deprivation. Shift work may influence behavior or social changes and potentially exposure to sunlight and decreased vitamin D levels, all of which could impact the risk of adverse health effects.

This session focuses on human studies assessing metrics of shift work (such as duration, type of shift work) and health outcomes and animal models of simulated shift work or jet lag. Sleep deprivation, changes in meal timing, and other aspect of shift work are discussed in Section 4.

Human studies

Numerous human epidemiologic studies of shiftwork and health outcomes including cancer (focusing primarily on breast and prostate cancers but also melanoma and cancer of the ovary, colon, and rectum), cardiovascular system, diabetes, endocrine system, metabolic syndrome and obesity, reproductive complications, and mental health have been published. These studies included large population registries, prospective cohorts, occupational cohorts, and nested and population-based case-control studies in various geographical locations and individuals in a wide variety of locations including medical profession (primarily nurses) radio/telegraph operators, teachers, national health insurance enrollees, specific companies, factory or manufacturing workers, truck drivers, firefighters, and off-shore oil rig workers, among others. Ever working as a shift worker, number of years working night or rotating shifts was assessed through self-reported questionnaires or interviews or in a few studies by employment records and a job exposure matrix, e.g., linkages of individual occupational histories with survey data linking occupations to night work. Detailed classifications of shiftwork such as regular/irregular shift schedules, permanent/rotating night shifts, time schedules of each shift, intensity, direction and speed of rotation are available in only a few studies. Some of the studies on cancer also measured urinary aMT6s (24 hours or nocturnal). Many studies were able to evaluate confounders and some studies looked at potential effect modifiers (such as chronotype).

In addition to health outcomes, numerous studies on shift workers have evaluated the relationship between either shiftwork or melatonin and biomarkers of circadian disruption and/or early markers potentially associated with adverse health effects such as melatonin, cortisol, and sex steroid hormones. A growing interest in cancer is looking at expression and methylation of circadian genes. There are several intervention studies evaluating impacts of shift schedules and biomarkers of circadian disruption, the impact of behavioral and pharmacological interventions on various noncancer endpoints, and pharmacological interventions (such as doses of melatonin) on optimization of sleep and increased focus at work after night shifts.

The available studies related to transmeridian travel primarily consist of studies of breast and prostate cancer among flight attendants and pilots, who are also shift workers. In general, these studies have used relatively crude exposure measures (e.g., job title) of circadian disruption or travel, are not usually specific for transmeridian travel (vs. north to south flights), and lack detailed information on potential confounders.

Animal models

The most developed animal models of shift work and jet lag are for evaluating metabolic changes. These models include those evaluating timing of light, food, sleep, and activity. The timing of light models evaluated variations in the light/dark cycle, length, frequency, duration, and direction of the shifts on health outcomes. The meal time models restrict food to the light or dark phase. In the sleep models, sleep is shifted to dark phase for nocturnal animals and may also include interruptions in sleep or complete sleep restriction. Forced activity is assessed by using

rotating wheels and often combined with timing of food and light (Opperhuizen et al. 2015, see Appendix D). Common metabolic effects that were measured included bodyweight, food intake, adiposity, and metabolism of glucose and lipids. Biomarkers of circadian disruption were not as consistently measured across the various exposure scenarios; activity and corticosterone levels were the most commonly measured biomarkers, while melatonin and expression of clock genes were less common. See Appendix D for more information on the measured effects of non-cancer endpoints. Shift work models in design are more limited for cancer and primarily consist of jet lag models although there are some models of changes in shift (periodically switching the light period with the dark period) and a few studies that evaluated changes in meal time in conjunction with changes in light or under standard light/dark cycles. Most of the studies have evaluated timing of light on tumor growth of xenografts; however, there is one study looking at changes in shift and tumor incidence in transgenic mice (Van Dycke et al. 2015). See Appendix B for more details.

Cited or key references

Arendt J. 2010. Shift work: coping with the biological clock. *Occupational medicine* 60(1): 10-20.

Bonde J. P., J. Hansen, *et al.* 2012. Work at night and breast cancer--report on evidence-based options for preventive actions. *Scand J Work Environ Health*, 38: 380-90. 38(4): 380-390

Bureau of Labor Standards. 2005. Workers on flexible and shift schedules in May 2004. *News: United States Department of Labor*. USDL 05-1198. Friday, July 1, 2005. www.bls.gov/news.release/pdf/flex.pdf

Haus EL, Smolensky MH. 2013. Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. *Sleep Med Rev* 17(4): 273-284.

International Agency for Research on Cancer (IARC). 2010. Shiftwork in *Painting, Firefighting, and Shiftwork*. *IARC monographs on the evaluation of carcinogenic risks to humans. World Health Organization, International Agency for Research on Cancer* 98: 9-764

Opperhuizen AL, van Kerkhof LWM, Proper KI, Rodenburg W and Kalsbeek A. 2015. Rodent models to study the metabolic effects of shiftwork in humans. *Front. Pharmacol*. 6:50.

Stevens RG. 2011a. 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. 2011b. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med* 68(2): 154-162

Van Dycke KC, Rodenburg W, van Oostrom CT, van Kerkhof LW, Pennings JL, Roenneberg T, van Steeg H, van der Horst GT. 2015. Chronically alternating light cycles increase breast cancer risk in mice. *Curr Biol* 25(14): 1932-1937

4. Sleep and Other "Exposures" in Studies of ALAN/Shift Work in Humans

4.1. Session goals and discussion topics

The goal of this session is to identify relevant exposures that coincide with night shift work and exposure to ALAN and determine whether these co-exposures should be treated as confounders or effect modifiers in human studies. The key discussion questions are as follows:

- What is the relationship of sleep, meal timing and circadian disruption?
- What health outcomes are potentially related to sleep duration and quality?
- What health outcomes are potentially related to decreased daylight/vitamin D? Are shift workers likely to have vitamin D deficiency?
- Should sleep, meal timing, and daylight (vitamin D), be considered as confounders, or effect modifiers in the human studies of artificial light at night and shift work?

4.2. Background information

A number of co-exposures should be considered when estimating the potential health effects of ALAN, shift work, and circadian disruption. At the same time as exposure to light at night has increased, exposure to natural daylight has fallen, with indoor light levels commonly insufficient to maintain entrainment. In addition, the lack of exposure to daylight may place individuals at greater risk for diseases associated with vitamin D deficiency.

While light is the master regulator of the central circadian clock, other environmental factors termed 'zeitgebers' include timing of sleep, meals, and activity and act to regulate the peripheral circadian clocks. Sleep insufficiency has reached epidemic levels in the United States. Lack of sleep is costly to society leading to decreased job performance and motivation, increased accidents and errors, and strained interpersonal relationships and is also associated with adverse health outcomes including certain cancers, diabetes, hypertension, and depression.

Key references

Asher G and Sassone-Corsi P. 2015. Time for food: the intimate interplay between nutrition, metabolism, and the circadian clock. *Cell* 161: 84-92

Hanlon EC, Van Cauter E. 2011. Quantification of sleep behavior and of its impact on the cross-talk between the brain and peripheral metabolism. *Proc Natl Acad Sci USA* 2011 Sep 13;108 Suppl 3:15609-16. doi: 10.1073/pnas.1101338108. Epub 2011 Aug 18

Leproult R, Holmbäck U, Van Cauter E. 2014. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. Diabetes. 2014 Jun;63(6):1860-9. doi: 10.2337/db13-1546. Epub 2014 Jan 23.

Matheson A, O'Brien L, Reid JA. The impact of shiftwork on health: a literature review. 2014. *J Clin Nurs*. 23(23-24): 3309-3320.

Opperhuizen AL, van Kerkhof LWM, Proper KI, Rodenburg W and Kalsbeek A. 2015. Rodent models to study the metabolic effects of shiftwork in humans. *Front. Pharmacol*. 6:50.

Stevens RG and Rea MS. 2001. Light in the Built Environment: Potential Role of Circadian Disruption in Endocrine Disruption and Breast Cancer. *Cancer Causes & Control,* 12(3): 279-287.

http://www.cdc.gov/features/dssleep/

5. Artificial Light at Night, Shift Work at Night, and Circadian Disruption

The goal of this session is to identify strategies to synthesize across studies of different types of "exposure scenarios" (e.g., shift work, artificial light at night) in order to reach conclusions for NTP's literature-based assessments. A secondary goal is to identify biomarkers that may be useful for evaluating strategies that decrease exposures related to circadian disruption. Discussion questions are as follows:

- What biomarkers or experimental models of circadian disruption are common to both artificial light and shiftwork?
- What are intermediate biological responses or biomarkers of circadian disruption such as changes in hormonal levels (reproductive hormones, melatonin) that may play a role in pathogenesis?
- Can the mechanistic data help integrate across epidemiological studies of shift workers or people exposed to artificial light at night and make conclusions related to circadian disruption and/or artificial light at night?
- Are biomarkers of circadian disruption a good surrogate for predicting whether interventions to prevent disease associated with circadian disruption are working? Are biomarkers specific for health outcomes needed or are there common biomarkers across outcomes?

6. Research Opportunities

6.1. Session goals and discussion

The goal of the session is to identify data needs and research needs that may inform the evaluation and provide information on interventions to reduce exposures that may cause circadian disruption. The former should focus on information that is needed to provide a link between (1) shift work and artificial light at night, (2) shift work and circadian disruption, and (3) artificial light at night and circadian disruption. Specific discussion questions are as follows:

- What short-term clinical (e.g., NIEHS clinical center, scientific community) or experimental studies in animals or cells (e.g., NTP laboratories, scientific community) on biomarkers of circadian disruption or intermediate endpoints can be done to help inform NTP's literature-based assessments?
- What studies on biomarkers are needed to evaluate strategies to minimize circadian disruption from exposure to artificial light or in shift workers?

6.2. Background information

The National Toxicology Program Laboratory (NTPL) provides state-of-the-art laboratory research support that complements and extends the NTP's scientific capabilities and contributes to the identification and understanding of potential health-related issues related to environmental/chemical exposures. NTPL scientists possess expertise in various *in vitro* assays, including stem cell and high throughput toxicological testing and *in vitro* toxicokinetic screens. *In vitro* endpoints include high content imaging and transcriptomic profiling. The NTPL also has *in vivo* capabilities including toxicokinetic studies, short-term transcriptomic profiling, and guideline-like developmental toxicity studies

The NIEHS Clinical Research Unit (CRU) is a 14,000 square foot facility on the NIEHS campus where scientists conduct studies that involve on-site human sample collection, analysis and functional assessment. The CRU staff provides support in the development of a diverse array of translational research protocols, which involve pulmonary diseases, medical genetics, cardiovascular diseases, and reproductive health. The CRU accommodates outpatient research and offers routine patient evaluation, as well as specialized diagnostic and analytical capabilities, such as pulmonary function testing and various imaging procedures.