



Introduction and Exposure

Studies of Circadian Disruption

Ruth Lunn, DrPH
Office of the Report on Carcinogens (RoC)
National Institute of Environmental Health Sciences

Draft RoC Monograph on Night Shift Work and Light at Night
Peer Review Meeting
5 October 2018



Outline

Modern lighting practices: Characteristics and exposure

- Electric Light at Night (LAN)
- Night Shift Work

Circadian regulation and disruption

Studies of circadian disruption biomarkers

- Electric LAN in humans and animal models
- Night shift work in humans and animal models



Outline

Modern lighting practices: Characteristics and exposure

- Electric Light at Night (LAN)
- Night Shift Work

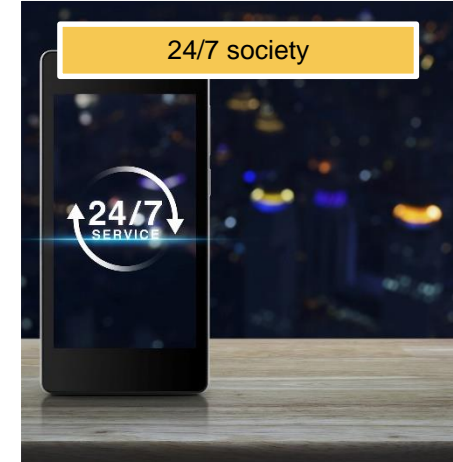
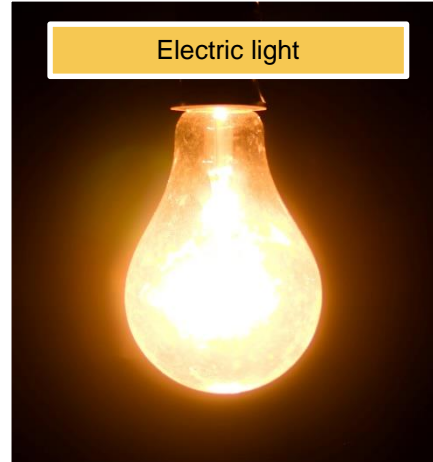
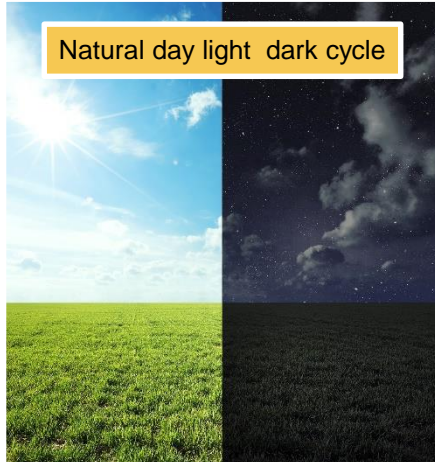
Circadian regulation and disruption

Studies of circadian disruption biomarkers

- Electric LAN in humans and animals
- Night shift work in humans and animal models



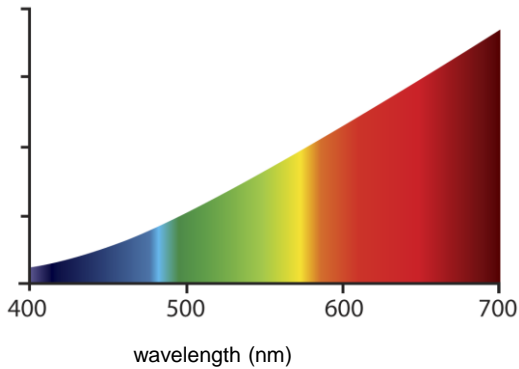
Electric light has transformed society



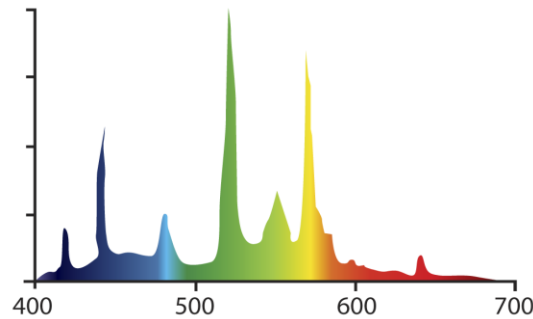
- Enables people to work, sleep, eat, and receive services throughout the 24 hour day
- Two exposure scenarios related to modern lighting practices
 - Electric LAN and Shift Work at Night
- These exposure scenarios can cause circadian disruption and possible health effects



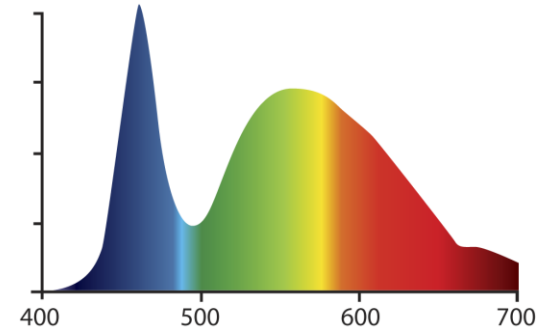
Technology advances has lead to a greater proportion of short wavelengths



Incandescent light bulb
1890s



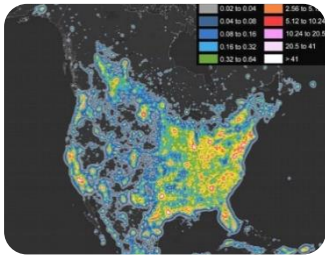
Fluorescent Light
Mid 1900's



Blue and White LED
Late 1900's



Significant number of US residents are exposed to electric light at night



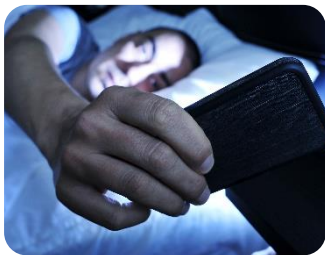
Outdoor light

- > 99% are exposed to sky glow at night



Light before or during sleeping

- Levels vary from 13 to > 400 lux



Self-luminous electronics

- 90% used some form 1 hour before bed time
- Light is closer to the eye



Night shift work is a complex exposure scenario



Extreme LAN



Sleep
disruption



Altered meal
timing



Vitamin D



Stress and
behaviors



Types of night shift work



- Typically working at least 3 hours between midnight and 5 AM
- Types of shifts vary



Types of night shift work



- Typically working at least 3 hours between midnight and 5 AM
- Types of shifts vary

Day	1	2	3	4	5	6	7	8
Permanent	N	N	N	N	N	R	R	N
Forward rotating	D	D	E	E	N	N	R	R
Backward rotating	N	N	E	E	D	D	R	R

D = day, E = evening, N = night, R = rest



Significant number of US residents frequently work night shifts



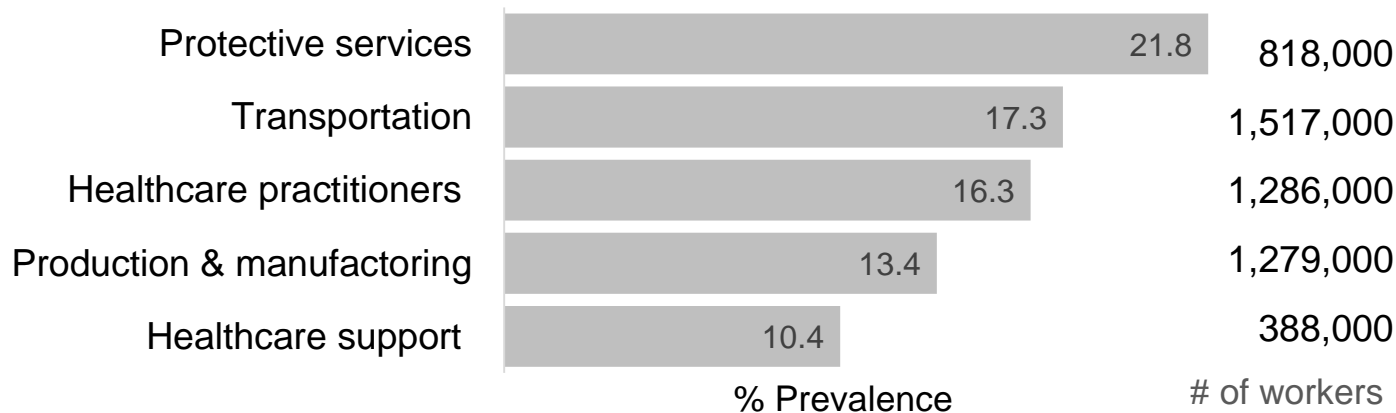
- > 10 million adults frequently work nights
- More common among men, minorities, people in lower socioeconomic groups



Significant number of US residents frequently work night shifts



- > 10 million adults frequently work nights
- More common among men, minorities, people in lower socioeconomic groups





Outline

Modern lighting practices: Characteristics and exposure

- Electric Light at Night (LAN)
- Night Shift Work

Circadian regulation and disruption

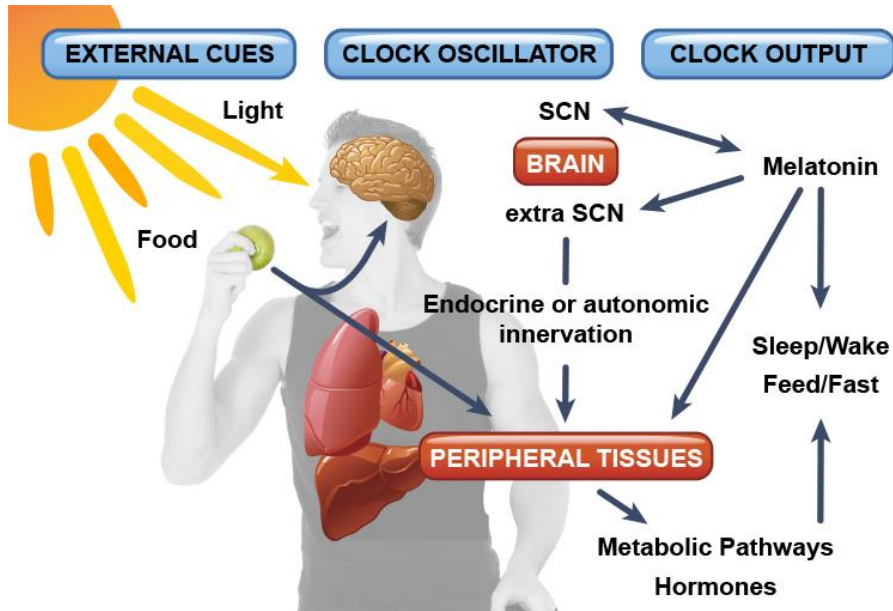
Studies of circadian disruption biomarkers

- Electric LAN in humans and animals
- Night shift work in humans and animal models



Circadian Regulation

Light:dark cycle is a key environmental cue that synchronizes the circadian system to the 24 hour day

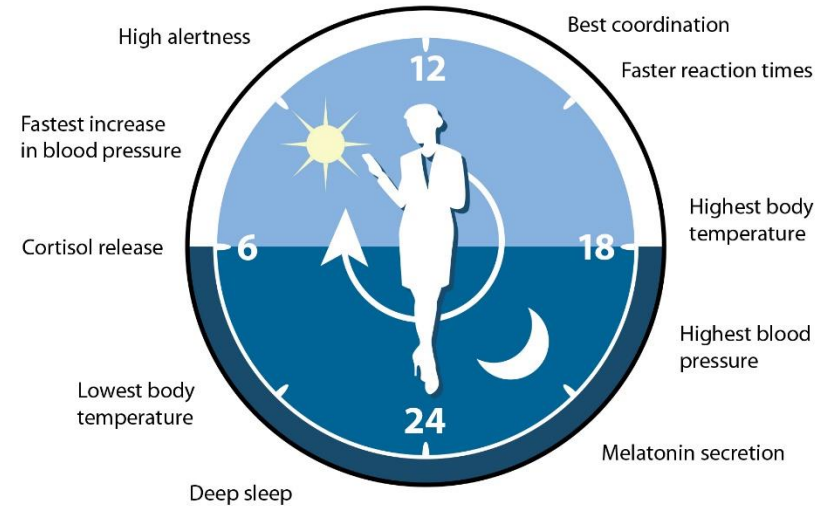
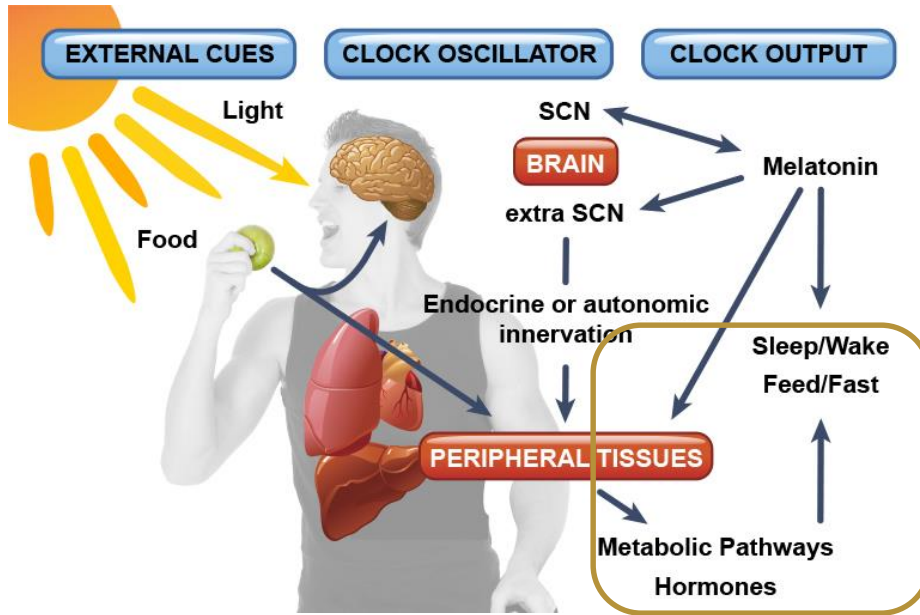


SCN = suprachiasmatic nucleus



Circadian Regulation

Light:dark cycle is a key environmental cue that synchronizes the circadian system to the 24 hour day



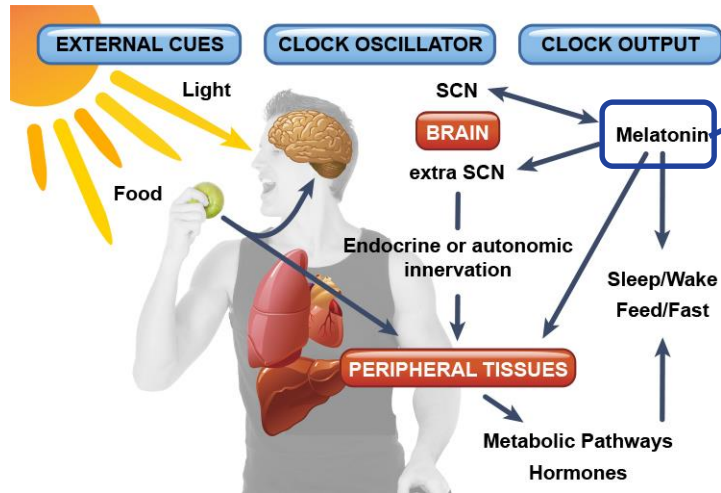
SCN = suprachiasmatic nucleus

Circadian rhythms

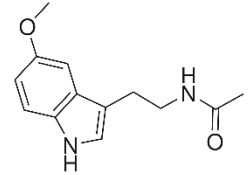


Circadian Regulation

Melatonin and clock genes



Produced by the pineal gland and regulated by SCN



Internal synchronizer of circadian rhythms

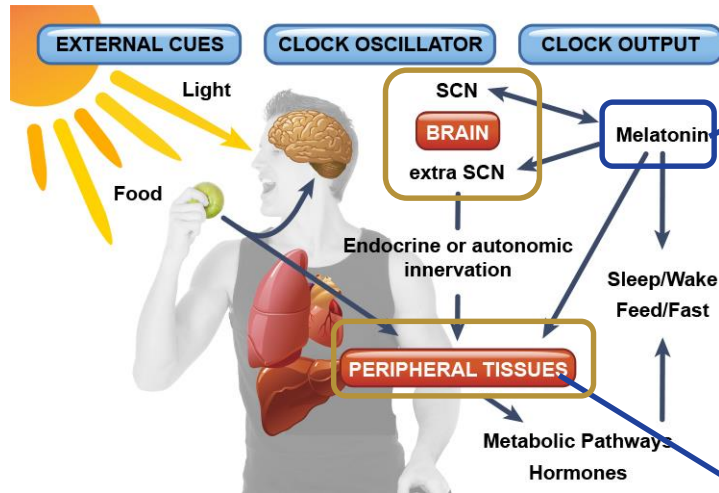
Other clock gene entrainers include cortisol and other glucocorticoids

SCN = suprachiasmatic nucleus



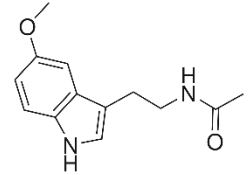
Circadian Regulation

Melatonin and clock genes



SCN = suprachiasmatic nucleus

Produced by the pineal gland and regulated by SCN



Internal synchronizer of circadian rhythms

Other clock gene entrainers include cortisol and glucocorticoids

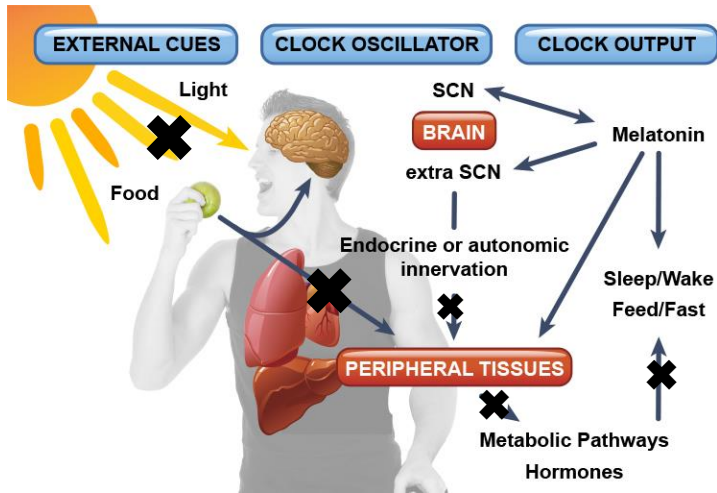
Controls expression of thousands of genes

Generates circadian oscillations in cell-autonomous transcriptional-translational feedback loops

Major genes: *CLOCK*, *BAML1*, *PER1*, *PER2*, *PER3*, *CRY1*, *CRY2*, *REV-ERBA*



Circadian Disruption



Environmental Disruptors



Night Shift Work;
LAN



Sleep disturbances



Transmeridian
travel



Social jet lag

SCN = suprachiasmatic nucleus

“Internally or externally induced, acute or chronic temporal disorganization including, but not limited to, misalignment of the time structure”



Circadian Disruption Biomarkers

Modern lighting practices

- Electric Light at Night (LAN)
- Night Shift Work

Circadian regulation and disruption

Studies of circadian disruption biomarkers

- Electric LAN in humans and animals
- Night shift work in humans and animal models



- LAN
- Night shift work

Circadian disruption

- Melatonin
- Altered clock genes

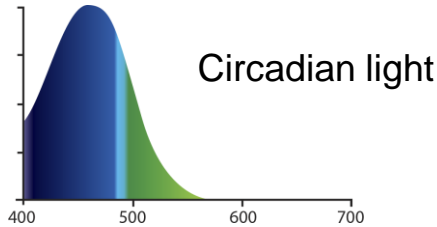


Melatonin Suppression

LAN induces melatonin suppression depending on light characteristics and susceptibility

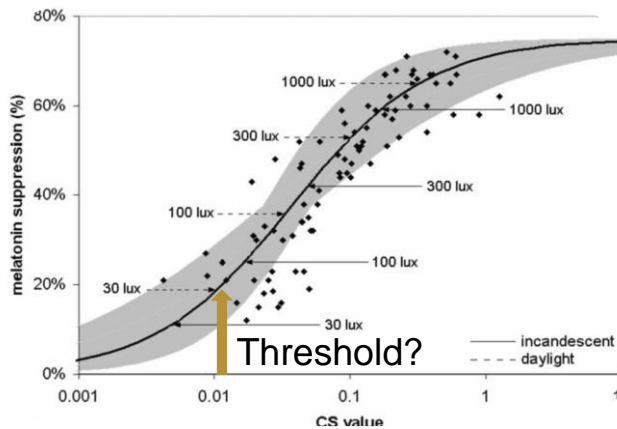
Wavelength

Shorter more effective



Level

Dose response



Duration

- Depends on other light characteristics

Timing of light

- Morning – phase advance
- Early evening – phase delay

Total Light exposure

- Insufficient daytime light exposure is also important

Susceptibility

- Younger age
- Chronotype
- Clock gene polymorphisms

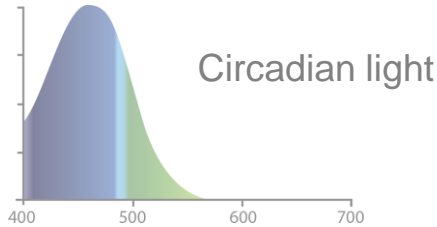


Melatonin Suppression

LAN induces melatonin suppression depending on light characteristics and susceptibility

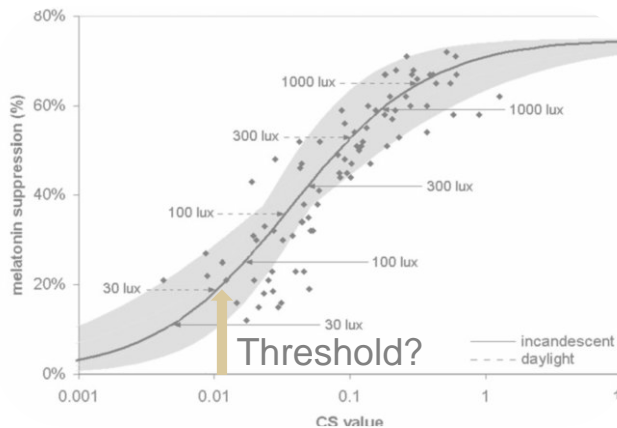
Wavelength

Shorter more effective



Level

Dose response



Duration

- Depends on other light characteristics

Timing of light

- Morning – phase advance
- Early evening – phase delay

Total Light exposure

- Insufficient daytime light exposure is also important

Susceptibility

- Younger age
- Chronotype
- Clock gene polymorphisms



Studies using different sources of electric light



Electronics with self-luminous displays

- Acutely suppress melatonin onset
- Disrupt sleep
- Blue light greater effect



Light in the sleeping area

- Most observational studies were negative
- Limited methodology: May not have had the ability to detect an effect



Outdoor Light: measured by satellite

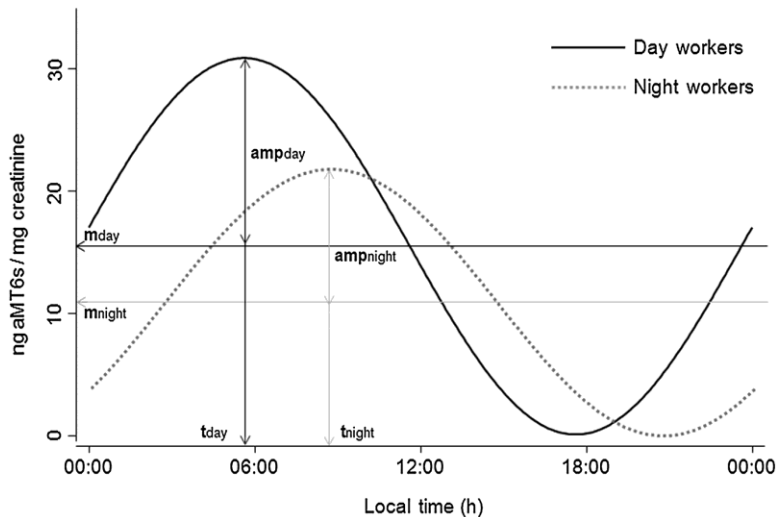
- 1 study found a small non-significant inverse relationship between light and 24-hr urinary melatonin
- Light may be too low to suppress melatonin during sleep (closed eyes) and closed curtains



Melatonin Suppression

Night shift work suppresses or disrupts melatonin levels

- Few shift workers adapt their rhythms to their sleep schedule
- ↓ Night time melatonin levels or average melatonin found in night shift workers compared to day shift workers in almost all studies
- ↓ Night time melatonin or average melatonin levels associated with persistent night shift work
- Exposure to LAN among night shift workers may contribute in part to melatonin suppression; however, limited number of studies



- Cosinor modeling of melatonin metabolite (aMT6s) production over time
- Day and permanent night shift workers from Spain
- Papantoniou *et al.* 2014



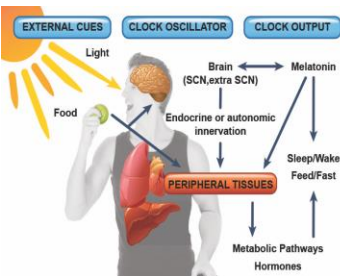
LAN and shift work are associated with altered clock gene expression

- Strongest evidence is from animal studies
 - Gene expression measured in peripheral tissue, brain tissue, as well as in the master clock
 - Almost all studies found that shift work and LAN altered clock gene expression
 - Findings for specific genes varied and may be dependent on tissue and sample findings
- Human studies provide some support
 - Gene expression measured in blood or surrogate tissue
 - 2 experimental studies of LAN; 3 studies of independent populations of night shift work
 - Findings for specific genes may depend on sample timing and relationship to work schedule



Significant number of US residents

- Are exposed to electric LAN
- Frequently work night shifts



Night shift work is a complex exposure scenario, which includes exposures, such as LAN, that regulate the circadian system



Modern lighting practices are associated with circadian disruption biomarkers

- Melatonin suppression
- Altered clock gene expression



Clarification questions?



Introduction and exposure: Section 1

- Comment on whether the description of the topic is clear and technically accurate and identify any information that should be added or deleted
 - Circadian regulation and disruption
 - Light at night
 - Shift work
 - Transmeridian travel and social jet lag
- Comment on whether the information supports the RoC criteria that
 - Significant number of U.S. residents work night shifts
 - Significant number of U.S. residents are exposed to LAN



Circadian disruption studies: Section 2

- Biomarkers and characteristics of circadian disruption
 - Comment on whether the description of the topic (listed below) is clear and technically accurate and identify any information that should be added or deleted
 - Provide critical comments on NTP assessment
- LAN and circadian disruption biomarkers
 - Comment on whether the description of the topic (listed below) is clear and technically accurate and identify any information that should be added or deleted
 - Provide critical comments on NTP assessment
- Shift work and circadian disruption biomarkers
 - Comment on whether the description of the topic (listed below) is clear and technically accurate and identify any information that should be added or deleted
 - Provide critical comments on NTP assessment