Evidence Integration

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National Institute of Environmental Health Sciences

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

Night Shift Work
- Evidence integration
- Definition
- Preliminary listing recommendation

LAN
- Evidence integration
- Definition
- Preliminary listing recommendation
Objective and Approach

Night Shift Work
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LAN
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Objective and Approach

Environmental disruptors

- Night shift work
- LAN

Circadian disruption

Biological effects

Cancer

- Integrate the evidence from Sections 1 to 6 and reach a preliminary listing recommendation for night shift work and for exposure to LAN for the RoC
- Adequately define these two exposure scenarios as they relate to cancer.
## Detailed analysis of data for specific evidence stream: examples

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Type of studies</th>
<th>Strengths &amp; Limitations</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSW</td>
<td>Breast cancer</td>
<td>Human epidemiological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSW</td>
<td>Melatonin</td>
<td>Human cross-sectional</td>
<td></td>
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</tr>
</tbody>
</table>

## Mechanistic related data

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Evidence stream</th>
<th>Confidence</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin</td>
<td>Breast cancer</td>
<td>Human &amp; animal Epidemiology &amp; experimental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clock gene desynchrony</td>
<td>Cancer</td>
<td>Same as above</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Overall evaluation

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Evidence stream</th>
<th>Confidence of the evidence</th>
<th>Overall evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSW</td>
<td>Breast cancer</td>
<td>Human &amp; animal Mechanistic &amp; cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAN</td>
<td>Breast cancer</td>
<td>Same as above</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LAN = light at night, NSW = night shift work
Objective and Approach

Night Shift Work
- Evidence integration
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LAN
- Evidence integration
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Night shift work increases female breast cancer risk

**Exposure**

- 21 studies
- 1 pooled analysis
- Adequate database
- Consistency across studies
- Persistent night shift work: frequent and long-term, especially starting in young adulthood
- Risk unlikely explained by lifestyle confounders

**Breast Cancer**

- Strong but not sufficient

**Database**

- 21 studies
- 1 pooled analysis

**Strengths**

- Adequate database
- Consistency across studies
- Persistent night shift work: frequent and long-term, especially starting in young adulthood
- Risk unlikely explained by lifestyle confounders

**Limitations**

- Unable to evaluate circadian disruption per se or specific exposure
- Evidence: case-control studies and 2 informative cohort studies
- Most potential biases towards null
Shift work promotes mammary tumor growth in rodents

**Exposure**

- Simulated SW or CJL

**Breast Cancer**

↓ mammary gland tumor latency & ↑ multiplicity

<table>
<thead>
<tr>
<th>Database</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 studies</td>
<td>Shift work or CJL promotes tumor growth&lt;br&gt;Measured circadian clock genes</td>
<td>Cancer susceptible models or co-exposure models&lt;br&gt;Melatonin deficient mice</td>
</tr>
</tbody>
</table>

CJL = chronic jet lag<br>SW = shift work
Night Shift Work

Risk patterns in humans consistent with mechanistic or animal data

Greater risk in humans with recency of exposure and receptor positive cancers

- Simulated SW or CJL

↓ mammary gland tumor latency & ↑ multiplicity

Strong but not sufficient

Breast cancer

CJL = chronic jet lag
SW = shift work
CJL = chronic jet lag; MT = melatonin; NMT = nocturnal melatonin; SW = shift work
Induces CD which plays a role in carcinogenicity

Exposure

Circadian Disruption (CD)

Biological Effects

Breast

Simulated SW or CJL

Clock Genes*

Tumor suppressors, DNA repair, metabolism, cell cycle, cell proliferation, apoptosis

Clock gene genetic models

Epidemiology studies

CJL = chronic jet lag; SW = shift work

* Altered clock gene expression

** Cancer not specific for breast cancer
Night Shift Work

Induces biological effects typical of recognized carcinogens

Exposure

Simulated SW or CJL

Circadian Disruption

Biological Effects

Breast Cancer

↓DNA repair/↑damage
↑Oxidative stress*
↑Inflammation or altered immune*

Epigenetic changes
↑Estrogen levels**

Epidemiology studies

Biological effects observed in cancer animal studies of shift work (*) or LAN (**)  

CJL = chronic jet lag
SW = shift work
Night Shift Work

Strong human and mechanistic evidence

Exposure

Circadian Disruption

Biological Effects

Breast Cancer

Simulated SW or CJL

Clock genes*

Tumor suppressors and other anti-cancer effects

Clock gene models

Low NMT

MT: In vivo and in vitro studies: Inhibition of oncostatic pathways

MT studies

LAN

Disrupted sleep

Altered meal timing

Key characteristics of carcinogens

↓ tumor growth

↑ cancer risk

Humans: Low NMT levels

CJL = chronic jet lag; NMT = nocturnal melatonin; MT = melatonin; SW = shift work;
* Altered clock gene expression
Night shift work is associated with increased risk of prostate cancer

<table>
<thead>
<tr>
<th>Evidence stream</th>
<th>Cancer</th>
<th>Findings</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Prostate</td>
<td>Consistent findings</td>
<td>Limited</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less robust than breast cancer</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>Colorectal</td>
<td>Inconsistent</td>
<td>Inadequate</td>
</tr>
<tr>
<td></td>
<td>Female hormonal</td>
<td>Few studies or few informative studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal</td>
<td>Multiple</td>
<td>Growth or promotion of implanted tumors or tumors induced by co-exposures to chemical carcinogens</td>
<td>Convincing</td>
</tr>
</tbody>
</table>
Persistent Night Shift Work

Definition of exposure

- *Persistent* defined as frequent and long-term night shift work, especially beginning at an early age

- In general female night shift workers at elevated risk for breast cancer
  - Started working before age 30
  - Worked at least 3 times/week for at least 10 years
  - However, the exact conditions may vary

- Night shift work
  - At least 3 hours between midnight and 5 AM
  - Includes exposure to LAN, disrupted sleep, altered meal timing and other behavioral changes
RoC Listing Criteria: Two Categories

**Known to be a human carcinogen**

- Sufficient evidence of carcinogenicity from studies in humans

**Reasonably anticipated to be a human carcinogen**

- Limited evidence from studies in humans
  OR
- Sufficient evidence from studies in experimental animals
  OR
- Belongs to well-defined structurally related class of substances listed in the RoC or demonstrates convincing mechanistic evidence

Conclusions based on scientific judgment considering all relevant information such as chemical structure, metabolism, pharmacokinetics, genetic effects, and mechanisms of action.
RoC Listing Criteria

Reach level of evidence conclusion for carcinogenicity from studies in humans*

**Sufficient evidence**

- Causal relationship between exposure to the agent, substance, or mixture, and human cancer

**Limited evidence**

- Causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded

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

- Collective body of evidence from cancer epidemiological studies and mechanistic studies in humans and in experimental animals
- Human epidemiological studies provide evidence that persistent night shift is associated with an increase in female breast cancer risk
- Animal and in vitro mechanistic studies provide evidence that circadian disruption plays a role in the cancer pathway
- Human mechanistic studies provide evidence that night shift work is associated with circadian disruption and similar biological effects as that observed in animal cancer models

Limited evidence that night shift work is associated with an increased risk of prostate cancer
Clarification questions?
Objective and Approach

Night Shift Work
- Evidence integration
- Definition
- Preliminary listing recommendation

LAN
- Evidence integration
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Strong evidence melatonin plays a role in LAN carcinogenicity

Exposure

Circadian Disruption

Biological Effects

Breast Cancer

- MT *In vivo* and *in vitro* studies: Inhibition of oncostatic pathways

- Tumor growth

Database

- Light proxies
- Spontaneous tumors,
  co-exposures,
  implants

Strengths

- Consistent evidence
- Human implants

Limitations

- Animals more sensitive than humans
- Evidence limited to promotion or growth
**May increase risk of female breast cancer**

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<tr>
<td>Outdoor LAN</td>
<td>4 studies measured light using satellite 1 study living near strong artificial LAN</td>
<td>Consistent evidence Exposure response 1 case-control study and 1 ecological study specific for blue light</td>
<td>Unclear if satellite is measuring circadian light or is a proxy for other activities</td>
</tr>
<tr>
<td>LAN in sleeping area</td>
<td>10 studies</td>
<td>-</td>
<td>Inconsistent findings Exposure metrics varied Self-reported for subjective metrics</td>
</tr>
</tbody>
</table>
Causes CD and effects typical of carcinogens

**Exposure**
- Human studies

**Circadian Disruption (CD)**
- Clock genes*

**Biological Effects**
- Tumor suppressors, DNA repair, metabolism, cell cycle, cell proliferation, apoptosis
- Altered estrogen
- Altered metabolism
  - ↑ Oxidative stress
  - ↓ DNA repair/↑ damage
- ↑ Inflammation or altered immune

**Breast Cancer**

* *Altered clock gene expression*
Human studies

Exposure

Circadian Disruption

Biological Effects

Breast Cancer

Human studies

Blood from exposed humans

LAN studies

Clock genes

Tumor suppressors and other anti-cancer activities

In vivo and in vitro studies: Inhibition of oncostatic pathways

Tumor growth

Key characteristics of carcinogens
Definition of exposure

• Excessive LAN: Characteristics most likely to cause circadian disruption
  – Shorter wavelength (e.g., blue light)
  – Longer duration
  – Timing: exposure to electric light during the biological night,
  – Higher light intensity or levels

• Insufficient daylight exposure
  – Experimental animal studies
    • Blue light exposure during the day positively affected the circadian regulation and decreased the growth of implanted prostate and liver tumors
  – Humans
    • Night time sensitivity to LAN influence by exposure to light during the day
Reasonably anticipated to be a human carcinogen

- Strong evidence that LAN acts through mechanisms that are likely to cause cancer in humans
  - Toxicological and mechanistic data indicate that exposure to LAN causes melatonin suppression and other types of circadian disruption, which lead to the proliferation and growth of breast or mammary-gland cancer in experimental animals
  - LAN causes biological effects that are characteristics of recognized carcinogens
- LAN causes melatonin suppression and may increase breast cancer risk in humans (i.e., limited evidence of carcinogenicity from epidemiological studies)
Clarification questions?