Objective and Approach

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

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

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LAN
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Objective and Approach

Environmental disruptors ➔ Circadian disruption ➔ Biological effects ➔ Cancer

- Night shift work
- LAN

- 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>
<td></td>
</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

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Night shift work increases female breast cancer risk

**Exposure**

- Strong but not sufficient

**Breast Cancer**

<table>
<thead>
<tr>
<th>Database</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 studies</td>
<td>Adequate database</td>
<td>Unable to evaluate circadian disruption per se or specific exposure</td>
</tr>
<tr>
<td>1 pooled analysis</td>
<td>Consistency across studies</td>
<td>Evidence: case-control studies and 2 informative cohort studies</td>
</tr>
<tr>
<td></td>
<td>Persistent night shift work: frequent and long-term, especially starting in young adulthood</td>
<td>Most potential biases towards null</td>
</tr>
<tr>
<td></td>
<td>Risk unlikely explained by lifestyle confounders</td>
<td></td>
</tr>
</tbody>
</table>
**Shift work promotes mammary tumor growth in rodents**

**Exposure**

Simulated SW or CJL

↓ mammary gland tumor latency & ↑ multiplicity

**Breast Cancer**

**Database**  | **Strengths**                                                                 | **Limitations**                                                                 |
-------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
2 studies    | Shift work or CJL promotes tumor growth                                     | Cancer susceptible models or co-exposure models                                  |
             | Measured circadian clock genes                                               | Melatonin deficient mice                                                        |

CJL = chronic jet lag
SW = 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
Night Shift Work

Induces melatonin suppression which promotes cancer growth

Exposure
Circadian Disruption
Biological Effects
Breast Cancer

Simulated SW or CJL

Low NMT

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

Humans: Low NMT levels

↑ cancer risk
↓ tumor growth

CJL = chronic jet lag; MT = melatonin; NMT = nocturnal melatonin; SW = shift work
**Night Shift Work**

**Induces CD which plays a role in carcinogenicity**

**Exposure**

Simulated SW or CJL

**Circadian Disruption (CD)**

Clock Genes*

**Biological Effects**

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

**Breast**

Clock gene genetic models

Epidemiology studies

CJL = chronic jet lag; SW = shift work

* Altered clock gene expression

** Cancer not specific for breast cancer
Human studies on breast cancer exposure suggest circadian disruption can lead to biological effects typical of recognized carcinogens. Exposure to simulated shift work (SW) or chronic jet lag (CJL) induces biological effects observed in cancer animal studies of shift work (*) or LAN (**).

- **Biological Effects:**
  - ↓DNA repair/↑damage
  - ↑Oxidative stress*
  - ↑Inflammation or altered immune*
  - Epigenetic changes
  - ↑Estrogen levels**

CJL = chronic jet lag
SW = shift work
Key characteristics of carcinogens

Circadian Disruption

Tumor suppressors and other anti-cancer effects

Biological Effects

Exposure

Simulated SW or CJL

Clock genes*

Breast Cancer

Humans: Low NMT levels

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

↓ tumor growth

MT studies

LAN

Disrupted sleep

Altered meal timing

MT:

* Altered clock gene expression

CJL = chronic jet lag; NMT = nocturnal melatonin; MT = melatonin; SW = shift work;
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></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Few studies or few informative studies</td>
<td></td>
</tr>
<tr>
<td>Animal</td>
<td>Multiple</td>
<td>Growth or promotion of implanted tumors or tumors induced by co-exposures</td>
<td>Convincing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to chemical carcinogens</td>
<td></td>
</tr>
</tbody>
</table>
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.
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
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- Preliminary listing recommendation

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

**Exposure**
- Human studies
- Blood from exposed humans

**Circadian Disruption**
- LAN studies
- Low Melatonin

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

**Breast Cancer**
- 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
Human studies

Exposure

Limited evidence
Outdoor

Breast Cancer

May increase risk of female breast cancer

Exposure

Human studies

Limitations

Exposure metrics varied
Self-reported for subjective metrics

Strengths

Consistent evidence
Exposure response
1 case-control study and 1 ecological study specific for blue light

Database

Outdoor LAN
4 studies measured light using satellite
1 study living near strong artificial LAN

Limitations

Unclear if satellite is measuring circadian light or is a proxy for other activities

LAN in sleeping area
10 studies

Inconsistent findings
Exposure metrics varied
Self-reported for subjective metrics

Human studies

Exposure

Limited evidence
Outdoor

Breast Cancer

May increase risk of female breast cancer

Exposure

Human studies

Limitations

Exposure metrics varied
Self-reported for subjective metrics

Strengths

Consistent evidence
Exposure response
1 case-control study and 1 ecological study specific for blue light

Database

Outdoor LAN
4 studies measured light using satellite
1 study living near strong artificial LAN

Limitations

Unclear if satellite is measuring circadian light or is a proxy for other activities
Causes CD and effects typical of carcinogens

Exposure - Clock genes

Circadian Disruption (CD)

Biological Effects - Tumor suppressors, DNA repair, metabolism, cell cycle, cell proliferation, apoptosis

Breast Cancer

- Human studies
- LAN studies

- Altered estrogen
- Altered metabolism
- ↑ Oxidative stress
- ↓ DNA repair/↑ damage
- ↑ Inflammation or altered immune

* Altered clock gene expression
**Strong mechanistic evidence**

**Exposure**

**Circadian Disruption**

**Biological Effects**

**Breast Cancer**

- **Clock genes**: Tumor suppressors an other anti-cancer activities
- **In vitro and in vivo studies**: Inhibition of oncostatic pathways
- **Key characteristics of carcinogens**

**Human studies**

Blood from exposed humans

**LAN studies**

Low Melatonin

Tumor growth
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?