Studies in Experimental Animals

Outline

Overview of studies in experimental animals

Findings from animal models of simulated shift work and chronic jet lag

Findings from animal models of LAN

Summary
Outline

Overview of studies in experimental animals

Findings from animal models of simulated shift work and chronic jet lag

Findings from animal models of LAN and other relevant exposures

Summary
Overview of Animal Studies

Studies supportive of mechanistic findings

LAN and shiftwork were modeled by different lighting patterns.

Light models used in animal studies are surrogates for LAN and shiftwork human exposures.
Animal models for human exposures

- **Mice and Rats**
  - Nocturnal animals, most active at night
  - Most produce melatonin during the nighttime but some inbred mouse strains have been found to have undetectable blood levels
  - Have a higher absolute sensitivity to LAN-induced circadian disruption than humans; however, humans and nocturnal rodents show similar levels of activity and rest patterns with circadian disruption
  - Several LAN cancer studies measured additional biological effects and/or had co-exposures to melatonin

- **Issues**
  - Multiple study designs used
  - Study details not reported, *e.g.*, necropsy process or type and intensity of light
Overview of Animal Studies

- No level of evidence conclusions given as these are not chronic cancer studies and may not evaluate incidence of specific tumors;

- However, the database was adequate for evaluating tumor growth.

- Tumors with a significant increase in growth, incidence, multiplicity, and/or decrease in latency are listed according to animal model and light schedule.
Studies in Experimental Animals

Outline

Overview of studies in experimental animals

Findings from animal models of simulated shift work and chronic jet lag

Findings from animal models of LAN

Summary
Simulated Shift Work or Chronic Jet Lag Models

**Light schedules**

- **Shift work model**
  Weekly inversion of light-dark cycle compared to 12:12 h L:D cycle

- **Chronic jet lag model**
  Shifting times of lights on/off over a 2-3 day period either forward or backward compared to 12:12 h L:D cycle

**Diagram:**
- Normal LD
- Weekly inversion
- Inverted light cycle

**Legend:**
- Red: Forward shift by extended light phase
- Blue: Backward shift by shortened light phase
Simulated shift work or chronic jet lag increases tumor growth

Tumor growth includes significant increase in incidence, multiplicity, and/or decrease in tumor latency

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Shift work tumors</th>
<th>Chronic jet lag tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation promotion</td>
<td></td>
<td>DEN: liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NMU: mammary gland</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genetic model: lung</td>
</tr>
<tr>
<td>Implants, injected cells</td>
<td>Ehrlich sarcoma or carcinoma</td>
<td>Pancreas, bone, lung, plasmacytoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mammary tumors in lung</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>Mammary gland (genetic model)</td>
<td>Liver</td>
</tr>
</tbody>
</table>

NMU = N-nitroso-N-methylurea; DEN = diethylNitrosamine
Outline

Overview of studies in experimental animals

Findings from animal models of simulated shift work and chronic jet lag

Findings from animal models of LAN

Summary
**LAN Models**

**Light schedules** *(control groups for all models 12:12 h L:D cycle)*

- **Constant light model**
  - Continual bright (> 300 lux) light

- **Dim or intermittent LAN**
  - Dim: Exposure to ~0.21 lux throughout 12 h dark period
  - Intermittent: Applying light (30 min, 300 lux) half-way through the dark period

- **Altered light/dark model**
  - Lengthening or shortening light period of 24 hr cycle, *e.g.*, 8:16 h L:D
Tumor growth includes significant increase in incidence, multiplicity, and/or decrease in tumor latency

<table>
<thead>
<tr>
<th>Animal models</th>
<th>Constant light (positive/total studies)</th>
<th>Dim or intermittent LAN (positive/total studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenografts, injected</td>
<td>Breast xenograft (4/4)</td>
<td>Breast xenograft (4/4) Mammary gland</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>Mammary gland (transgenic model)</td>
<td></td>
</tr>
</tbody>
</table>

DMBA = dimethylbenz[a]anthracene; NMU = N-nitroso-N-methylurea
Over 25 studies found increased growth with LAN

<table>
<thead>
<tr>
<th>Animal models</th>
<th>Constant light (positive/total studies)</th>
<th>Dim or intermittent LAN (positive/total studies)</th>
<th>Altered light dark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-exposure</td>
<td>DEN: Liver (1/2)</td>
<td></td>
<td>DMBA: Skin</td>
</tr>
<tr>
<td></td>
<td>NEU: Kidney, peripheral nervous system</td>
<td></td>
<td>Urethane: Lung*</td>
</tr>
<tr>
<td>Implants, injected</td>
<td>Liver implant (4/4), glioma, skin, cervix</td>
<td>Liver implant (4/4)</td>
<td>Skin, prostate gland</td>
</tr>
<tr>
<td>cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>Leukemia, lung</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increase in tumor growth includes increase in incidence, multiplicity, and/or decrease in tumor latency

* 6:6h LD (short day) vs. 12:12 h LD
DEN = diethylnitrosamine; NEU = N-nitroso-N-ethylurea
Outline

Overview of studies in experimental animals

Findings from animal models of simulated shift work and chronic jet lag

Findings from animal models of LAN

Summary
There is compelling evidence that LAN or shift work enhanced tumor growth and decreased tumor latency.
Clarification questions?
1. Comment on whether the scientific information from cancer studies in experimental animals for light at night, chronic jet lag, or simulated shiftwork is clear, technically correct, and objectively presented.
   
a. Identify any information that should be added or deleted.

2. Comment on whether you agree with the conclusion (Section 5.3) that the animal studies provide strong evidence that light at night, chronic jet lag, or simulated shiftwork can, through circadian disruption, promote tumor growth and decrease tumor latency.