NTP
National Toxicology Program

Cancer Studies in Experimental Animals

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

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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

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.

Overview of Animal Studies

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.

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Findings from animal models of LAN

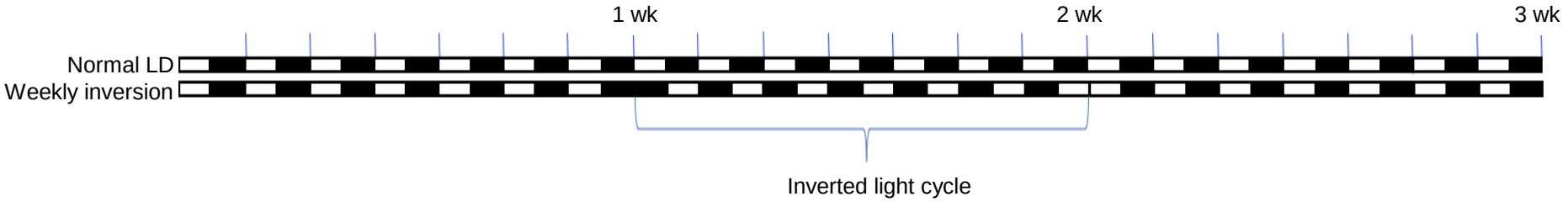
Summary

Simulated Shift Work or Chronic Jet Lag Models

Light schedules

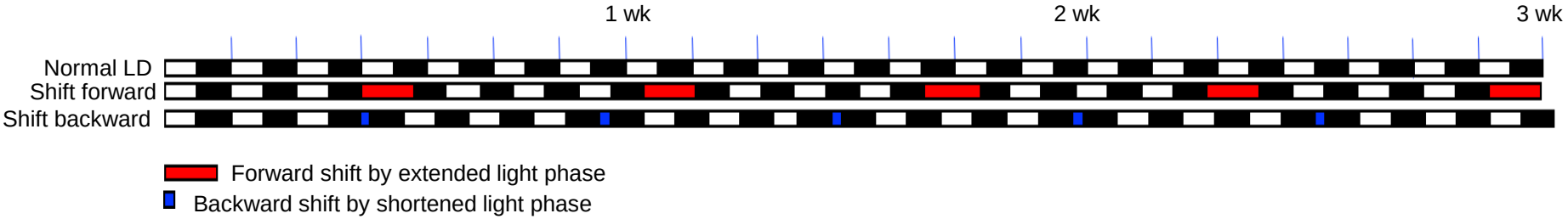
- Shift work model

  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



Simulated shift work or chronic jet lag increases tumor growth

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

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

NMU = N-nitroso-N-methylurea; DEN = diethylnitrosamine

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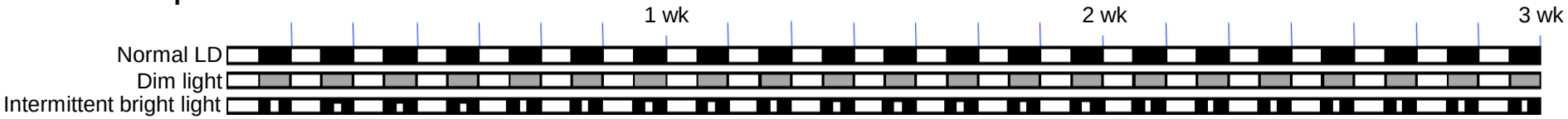
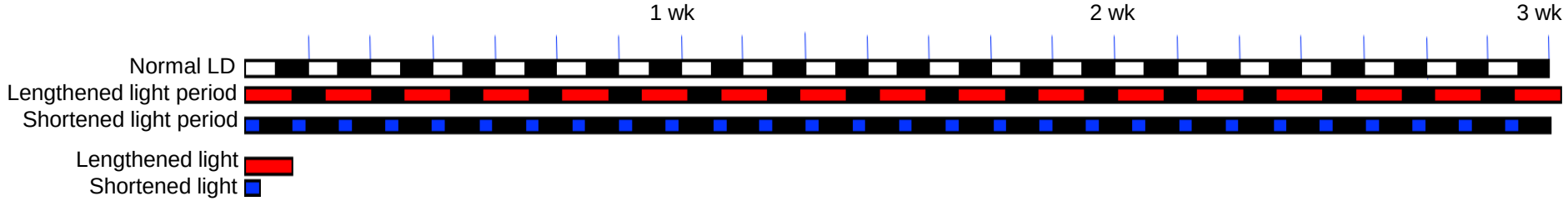
Light schedules (control groups for all models 12:12 h L:D cycle)

- 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



LAN increases growth of breast and mammary tumors

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

Animal models	Constant light (positive/total studies)	Dim or intermittent LAN (positive/total studies)
Co-exposure	DMBA: Mammary gland (3/4) NMU: Mammary gland	DMBA: Mammary gland
Xenografts, injected cells	Breast xenograft (4/4)	Breast xenograft (4/4) Mammary gland
Spontaneous	Mammary gland (transgenic model)	

DMBA = dimethylbenz[a]anthracene;
NMU = N-nitroso-N-methylurea

LAN increases growth of other tumors

Over 25 studies found increased growth with LAN

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

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

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There is compelling evidence that LAN or shift work enhanced tumor growth and decreased tumor latency.

Clarification questions?

Reviewer Comments

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.