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

Background
- Report on Carcinogens (RoC)
- RoC process
- Selection of LAN and night shift work for review

Preparation of RoC Monograph
- Scientific input
- Objective and framework
- Systematic review methods

Reach Cancer Hazard Conclusions
- RoC listing criteria

Next steps
Outline

Background

- Report on Carcinogens (RoC)
- RoC process
- Selection of LAN and night shift work for review

Preparation of RoC Monograph

- Scientific input
- Objective and framework
- Systematic review methods

Reach Cancer Hazard Conclusions

- RoC listing criteria

Next steps
The Report on Carcinogens (RoC) is congressionally mandated

- Identifies substances that pose a cancer hazard to people residing in the United States
  - Two listing categories: known and reasonably anticipated to be a human carcinogen

- Substance profile is written for each listing
  - Listing status, scientific information key to listing and data on properties, uses, production, exposure, and regulations to limit exposure

- Each edition of the report is cumulative

- NTP prepares the RoC for the Secretary of the Department of Health and Human Services using a four-part formal process and established listing criteria

http://ntp.niehs.nih.gov/go/roc
Process for the Preparation of the RoC

Select substances for evaluation

- Invite nominations
- Conduct scoping and problem formulation activities
- Develop draft concepts
- Finalize concepts and select substances for review

Prepare draft RoC monographs

- Develop protocol as needed
- Develop draft RoC monograph
- Interagency review of NTP listing recommendation

Peer review and finalize RoC monographs

- Release draft RoC monograph
- Present summary of peer review; prepare revised draft RoC monograph
- Finalize RoC monograph

Publish and release RoC

- Submit recommended listing status of new substances
- Interagency review of NTP listing recommendation
- Secretary, HSS reviews and approves
- Publish and release RoC

Key
- BSC = Board of Scientific Counselors
- HHS = Health and Human Services
- NTP = National Toxicology Program
- RoC = Report on Carcinogens
- * Federally chartered advisory groups

https://ntp.niehs.nih.gov/go/rocprocess
Opportunity for Public Comment

Process for the Preparation of the RoC

Select substances for evaluation

- Invite nominations
  - Conduct scoping and problem formulation activities
  - Scientific and/or public input as needed
  - Public comment
  - NTP BSC review (public meeting & comment)
  - NTP Director
- Develop draft concepts
- Interagency review of NTP listing recommendation
- Finalize concepts and select substances for review

Prepare draft RoC monographs

- Develop protocol as needed
- Scientific and/or public input as needed
- Develop draft RoC monograph
- Interagency review of NTP listing recommendation

Peer review and finalize RoC monographs

- Release draft RoC monograph
- Public comment
- Expert peer review draft RoC monograph
- NTP Peer review panel* or letter review
- Present summary of peer review; prepare revised draft RoC monograph
- NTP BSC (public meeting)
- NTP Director
- Finalize RoC monograph

Publish and release RoC

- Submit recommended listing status of new substances
- NTP Executive Committee
- Secretary, HSS reviews and approves
- Publish and release RoC

Key
BSC = Board of Scientific Counselors
HHS = Health and Human Services
NTP = National Toxicology Program
RoC = Report on Carcinogens
* Federally chartered advisory groups

https://ntp.niehs.nih.gov/go/rocprocess
Process for the Preparation of the RoC

Select substances for evaluation
- Invite nominations
  - Conduct scoping and problem formulation activities
    - Scientific and/or public input as needed
  - Develop draft concepts
    - Public comment
      - NTP BSC review (public meeting & comment)
    - NTP Director
  - Finalize concepts and select substances for review

Prepare draft RoC monographs
- Develop protocol as needed
- Develop draft RoC monograph
  - Scientific and/or public input as needed
  - Interagency review of NTP listing recommendation

Peer review and finalize RoC monographs
- Release draft RoC monograph
  - Public comment
  - Expert peer review draft RoC monograph
    - NTP Peer review panel* or letter review
  - Present summary of peer review; prepare revised draft RoC monograph
    - NTP BSC (public meeting)
    - NTP Director
  - Finalize RoC monograph

Publish and release RoC
- Submit recommended listing status of new substances
  - NTP Executive Committee
  - Secretary, HSS reviews and approves
  - Publish and release RoC

Key
BSC = Board of Scientific Counselors
HHS = Health and Human Services
NTP = National Toxicology Program
RoC = Report on Carcinogens
* Federally chartered advisory groups

https://ntp.niehs.nih.gov/go/rocprocess
Peer Review: Current Step

Process for the Preparation of the RoC

Select substances for evaluation
- Invite nominations
- Conduct scoping and problem formulation activities
  - Scientific and/or public input as needed
- Develop draft concepts
  - Public comment
  - NTP BSC review (public meeting & comment)
- NTP Director
  - Finalize concepts and select substances for review

Prepare draft RoC monographs
- Develop protocol as needed
  - Scientific and/or public input as needed
- Develop draft RoC monograph
- Interagency review of NTP listing recommendation

Peer review and finalize RoC monographs
- Public comment
  - Scientific and/or public input as needed
- Present summary of peer review; prepare revised draft RoC monograph
- NTP BSC (public meeting)
- NTP Director
  - Finalize RoC monograph

Publish and release RoC
- Submit recommended listing status of new substances
  - NTP Executive Committee
  - Secretary, HSS reviews and approves
  - Publish and release RoC

Key
- BSC = Board of Scientific Counselors
- HHS = Health and Human Services
- NTP = National Toxicology Program
- RoC = Report on Carcinogens
- * Federally chartered advisory groups

https://ntp.niehs.nih.gov/go/rocprocess
Select Substances for Evaluation

Invite nominations

- Conduct scoping and problem formulation activities
  - Request for Information

Develop draft concepts

- Public comment
  - NTP BSC review
  - June 2013
- NTP Director

Finalize concepts and select substances for review

Light at night (LAN) - nominated by several individuals

- Public commentators expressed interest in light exposure
- IARC concluded “shiftwork that involves circadian disruption” is probably carcinogenic to humans (Group 2A)
Select Substances for Evaluation

Invite nominations

Conduct scoping and problem formulation activities

Request for Information

Develop draft concepts

Public comment
NTP BSC review
June 2013

NTP Director

Finalize concepts and select substances for review

Shift Work at Night, Light at Night, and Circadian Disruption”

- Proposed workshop
Outline

Background
- Report on Carcinogens (RoC)
- RoC Process
- Selection of LAN and night shift work for review

Preparation of RoC Monograph
- Scientific input
- Objective and framework
- Systematic review methods

Reach Cancer Hazard Conclusions
- RoC listing criteria

Next steps
Prepare Draft RoC Monograph

Process for preparing draft monograph on LAN and night shift work

1. Develop protocol and post on RoC website
2. Workshop
   - Technical advisors
3. Develop draft RoC monograph
4. Technical advisors
5. Interagency review of NTP listing recommendation

March 2016 workshop
- Purpose: obtain scientific input on topics important for informing the literature based hazard assessments
- Recommendation: Frame as modern lighting practices
Objective and scope

Objectives

- Reach a preliminary listing recommendation for night shift work and exposure to LAN for the RoC
- Adequately define these two exposure scenarios as they relate to cancer.
### Framework: “PECO-like”

<table>
<thead>
<tr>
<th>Evidence stream</th>
<th>Exposure</th>
<th>Comparator</th>
<th>Effect or outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human epidemiology studies</td>
<td>Night shift workers</td>
<td>Day shift workers</td>
<td>Breast, prostate, CRC, lung, female hormonal cancer</td>
</tr>
<tr>
<td>Human epidemiology studies</td>
<td>LAN</td>
<td>Low exposure to LAN</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Experimental animals studies</td>
<td>LAN proxies</td>
<td>Standard lighting conditions (usually 12 hr light/12 hr dark)</td>
<td>Mainly tumor proliferation &amp; growth, or latency. Tumor type: Dependent on initiator or xenograft</td>
</tr>
<tr>
<td>Human molecular epidemiology studies or reviews</td>
<td>Night shift workers or night shift</td>
<td>Day shift workers or day shift</td>
<td>CD: melatonin, clock genes expression. Biological effects</td>
</tr>
<tr>
<td>Human experimental studies or reviews</td>
<td>LAN</td>
<td>Standard lighting conditions</td>
<td>CD: melatonin: clock genes</td>
</tr>
<tr>
<td>Experimental animals studies or reviews</td>
<td>Shift work and LAN models</td>
<td>Standard lighting conditions</td>
<td>CD: clock genes expression, melatonin (only shift work). Biological effects</td>
</tr>
<tr>
<td>Human studies</td>
<td>Melatonin proxies</td>
<td>Low melatonin, or sighted people</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Experimental studies (in vitro and in vivo) Reviews</td>
<td>CD: Melatonin &amp; clock genes</td>
<td>Varies</td>
<td>Biological effects and cancer</td>
</tr>
</tbody>
</table>

blue: main effects; light blue: supporting, grey: intermediate effects

**Objective and Methods**
## Framework: “PECO-like”

<table>
<thead>
<tr>
<th>Evidence steam</th>
<th>Exposure</th>
<th>Comparator</th>
<th>Effect or outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human epidemiology studies</td>
<td>Night shift workers</td>
<td>Day shift workers</td>
<td>Breast, prostate, CRC, lung, female hormonal cancer</td>
</tr>
<tr>
<td>Human epidemiology studies</td>
<td>LAN</td>
<td>Low exposure to LAN</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Experimental animals studies</td>
<td>LAN proxies Simulated shift work</td>
<td>Standard lighting conditions (usually 12 hr light/12 hr dark)</td>
<td>Mainly tumor proliferation &amp; growth, or latency Tumor type: Dependent on initiator or xenograft</td>
</tr>
</tbody>
</table>

### Environmental disruptors
- Night shift work
- LAN

### Section 3: Human Breast Cancer
### Section 4: Other Cancers
### Section 5: Experimental Animal Studies
### Appendices B to G

blue: main effects; light blue: supporting
### Framework: “PECO-like”

<table>
<thead>
<tr>
<th>Evidence stream</th>
<th>Exposure</th>
<th>Comparator</th>
<th>Effect or outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human molecular epidemiology studies</td>
<td>Night shift workers or night shift</td>
<td>Day shift workers or day shift</td>
<td>CD: melatonin, clock genes expression</td>
</tr>
<tr>
<td>Human experimental studies</td>
<td>LAN</td>
<td>Standard lighting conditions</td>
<td>CD: melatonin: clock genes</td>
</tr>
<tr>
<td>Experimental animals studies</td>
<td>Shift work</td>
<td>Standard lighting conditions</td>
<td>CD: clock genes expression, melatonin</td>
</tr>
<tr>
<td>Experimental animals studies</td>
<td>LAN</td>
<td>Standard lighting conditions</td>
<td>CD: clock genes expression,</td>
</tr>
</tbody>
</table>

**Section 1: Background on circadian regulation and disruption**

**Section 2: Studies of exposure and circadian disruption**

Environmental disruptors → Circadian disruption

blue: main effects; light blue: supporting, grey: intermediate effects
### Framework: “PECO-like”

<table>
<thead>
<tr>
<th>Evidence stream</th>
<th>Exposure</th>
<th>Comparator</th>
<th>Effect or outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human molecular epidemiology studies</td>
<td>Night shift workers or night shift</td>
<td>Day shift workers or day shift</td>
<td>Biological effects: Characteristics of cancer</td>
</tr>
<tr>
<td>Experimental animals studies</td>
<td>Shift work models</td>
<td>Standard lighting conditions</td>
<td>Biological effects</td>
</tr>
<tr>
<td>Experimental animals studies</td>
<td>LAN models</td>
<td>Standard lighting conditions</td>
<td>Biological effects</td>
</tr>
<tr>
<td>Human studies</td>
<td>CD: Melatonin proxies</td>
<td>Low melatonin, or sighted people</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Experimental studies (in vitro and in vivo)</td>
<td>CD: Melatonin &amp; clock genes</td>
<td>Varies</td>
<td>Biological effects and cancer</td>
</tr>
</tbody>
</table>

**Environmental disruptors**
- Night shift work
- LAN

**Biological effects**
- Key characteristics of carcinogens

**Circadian Disruption**
- Melatonin
- Clock genes
- Other shift work exposures

**Biological effects**
- Key characteristics of carcinogens

Grey: intermediate effects; CD = circadian disruption

Section 6
Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria.
Methods

Literature tagging and data extraction

https://hawcproject.org/assessment/393/
Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria.
Outline

Background
- Report on Carcinogens (RoC)
- RoC Process
- Selection of LAN and night shift work for review

Preparation of RoC Monograph
- Scientific input
- Objective and framework
- Systematic review methods

Reach Cancer Hazard Conclusions
- RoC listing criteria

Next steps
Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria

**Methods**

**Selection of studies**
- Systematic literature search
- Inclusion/Exclusion Criteria
- Literature tagging using HAWC

**Data extraction**
- Table Builder
- Result and appendix tables

**Evaluation of study quality**
- Formal framework for human studies
- RoC Handbook
- Protocol

**Level of evidence conclusions**
- Human cancer studies
- RoC handbook
- RoC listing criteria

**Evidence integration**
- Human cancer studies
- Animal cancer studies
- Mechanistic and other relevant data
Reach level of evidence conclusion for carcinogenicity from studies in humans*

<table>
<thead>
<tr>
<th>Sufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Causal relationship between exposure to the agent, substance, or mixture, and human cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Limited evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded</td>
</tr>
</tbody>
</table>

*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.
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 known human carcinogens

• Collective evidence of both human cancer epidemiologic studies and mechanistic studies.
  – Aristolochic acids
  – 1,3-Butadiene
  – Ethylene oxide
  – 2,3,7,8,-Tetrachlordibenzop-dioxin

• Human mechanistic data only
  – Dyes metabolized to benzidine
  – Neutrons
Evaluate whether a significant number of U.S. residents work night shifts or exposed to LAN

**Congressional mandate**
- Publish a report that lists substances which are *known* or *reasonably anticipated to be human carcinogens* and to which a *significant number of persons residing in the United States are exposed*.

**Evaluate data**
- Past and present exposure inferred using data on environmental and occupational exposure
- Not a formal exposure assessment

**Reviewer instructions**
- Use their judgment as to whether the exposure information in the draft monograph supports the NTP conclusions on significant exposure
Process for the Preparation of the RoC

Select substances for evaluation
- Invite nominations
- Conduct scoping and problem formulation activities
  - Scientific and/or public input as needed
- Develop draft concepts
  - Public comment
  - NTP BSC review (public meeting & comment)
  - NTP Director
- Finalize concepts and select substances for review

Prepare draft RoC monographs
- Develop protocol as needed
  - Scientific and/or public input as needed
- Develop draft RoC monograph
  - Interagency review of NTP listing recommendation

Peer review and finalize RoC monographs
- Release draft RoC monograph
  - Public comment
  - Expert peer review draft RoC monograph
    - NTP Peer review panel* or letter review
    - Present summary of peer review; prepare revised draft RoC monograph
      - NTP BSC (public meeting)
      - NTP Director
- Finalize RoC monograph

Publish and release RoC
- Submit recommended listing status of new substances
  - NTP Executive Committee
  - Secretary, HSS reviews and approves
- Publish and release RoC

Key
- BSC = Board of Scientific Counselors
- HHS = Health and Human Services
- NTP = National Toxicology Program
- RoC = Report on Carcinogens
* Federally chartered advisory groups

https://ntp.niehs.nih.gov/go/rocprocess
Contributors
Stanley Atwood
Sanford Garner
Gloria Jahnke
Ruth Lunn (Co-lead)
Suril Mehta
Pam Schwingl (Co-lead)

Contributors
Whitney Arroyave
Andrew Ewens
Alton Peters

Technical Advisors
David Blask
Mariana Figueiro
Johnni Hansen

NIEHS/NTP Review Committee
John Bucher (Chair)
Windy Boyd
Tania Carreon-Valencia (NIOSH)
Claire Caruso (NIOSH)
Suzanne Fenton
Gopi Gadupudi
Stephanie Holmgren
Christina Lawson (NIOSH)
Scott Masten
Arun Pandiri
Leslie Reinlib
Amy Wang

Acknowledgments
Susan Dakin
Ella Darden
Jessica Geter
Lara Handler
Tracy Saunders

Peer Review
Mary Wolfe
ICF Staff
Clarification questions?