Objectives and Methods

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
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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
Four-Part Process

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
- 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

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Opportunity for Public Comment

Process for the Preparation of the RoC

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Peer Review: Current Step

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Select Substances for Evaluation

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
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Next steps
Prepare Draft RoC Monograph

Process for preparing draft monograph on LAN and night shift work

- Develop protocol and post on RoC website
  - Workshop
  - Technical advisors
- Develop draft RoC monograph
  - Technical advisors
- Interagency review of NTP listing recommendation

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

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

- **Circadian disruption**

- **Biological effects**
  - Key characteristics of carcinogens

**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.
<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>
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<td>Experimental animals studies</td>
<td>LAN proxies, Simulated shift work</td>
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blue: main effects; light blue: supporting, grey: intermediate effects
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**Environmental disruptors**
- Night shift work
- LAN

**Cancer**

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”

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**Environmental disruptors**

**Circadian disruption**

Section 1: Background on circadian regulation and disruption

Section 2: Studies of exposure and circadian disruption

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**Framework: “PECO-like”**

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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.
Literature tagging and data extraction

Methods

https://hawcproject.org/assessment/393/
Methods

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

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

Team of 3 epidemiologists
Technical advisor input
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Evidence integration
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- Mechanistic and other relevant data
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.*
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.
• Collective evidence of both human cancer epidemiologic studies and mechanistic studies.
  – Aristolochic acids
  – 1,3-Butadiene
  – Ethylene oxide
  – 2,3,7,8,-Tetrachlordibenzo-p-dioxin

• Human mechanistic data only
  – Dyes metabolized to benzidine
  – Neutrons
### 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

### Section 1

### Reviewer instructions

- Use their judgment as to whether the exposure information in the draft monograph supports the NTP conclusions on significant exposure

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Evaluate whether a significant number of U.S. residents work night shifts or exposed to LAN
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Contributors

- Whitney Arroyave
- Andrew Ewens
- Alton Peters

**Technical Advisors**
- David Blask
- Mariana Figueiro
- Johnni Hansen

**Collaborators**
- Stanley Atwood
- Sanford Garner
- Gloria Jahnke
- Ruth Lunn (Co-lead)
- Suril Mehta

**Pam Schwingl (Co-lead)**

**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
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Clarification questions?