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
Outline

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

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**Key**

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

[https://ntp.niehs.nih.gov/go/rocprocess](https://ntp.niehs.nih.gov/go/rocprocess)
Opportunity for Public Comment

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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
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**Next steps**
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

Process for preparing draft monograph on LAN and night shift work
Objective and scope

- Environmental disruptors
  - Night shift work
  - LAN

- Circadian disruption

- Biological effects
  - Key characteristics of carcinogens

- Cancer

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>
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<td>Shift work and LAN models</td>
<td>Standard lighting conditions</td>
<td>CD: clock genes expression, melatonin (only shift work) Biological effects</td>
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<td>Low melatonin, or sighted people</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Experimental studies (\textit{in vitro} and \textit{in vivo}) Reviews</td>
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<td>Varies</td>
<td>Biological effects and cancer</td>
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blue: main effects; light blue: supporting, grey: intermediate effects

**Objective and Methods**
### Evidence streams

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#### Framework: “PECO-like”

- **Blue:** main effects
- **Light blue:** supporting

### Section 3: Human Breast Cancer

### Section 4: Other Cancers

### Section 5: Experimental Animal Studies

### Appendices B to G

- Environmental disruptors
  - Night shift work
  - LAN

- **Cancer**

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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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**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/
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Next steps
Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria.
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 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,-Tetrachlordibeno-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

Reviewer instructions

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

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

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ICF Staff
Clarification questions?