



## Objectives and Methods

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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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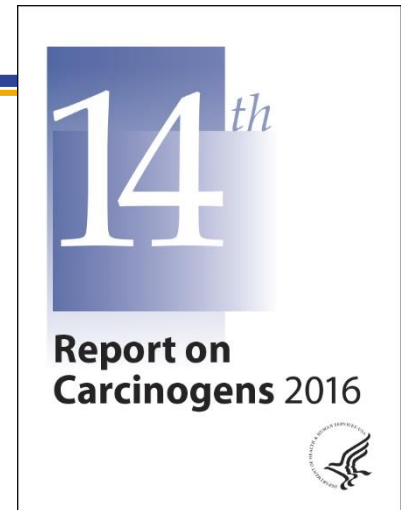
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## Next steps



## 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





# Four-Part Process

## Process for the Preparation of the RoC

### Select substances for evaluation



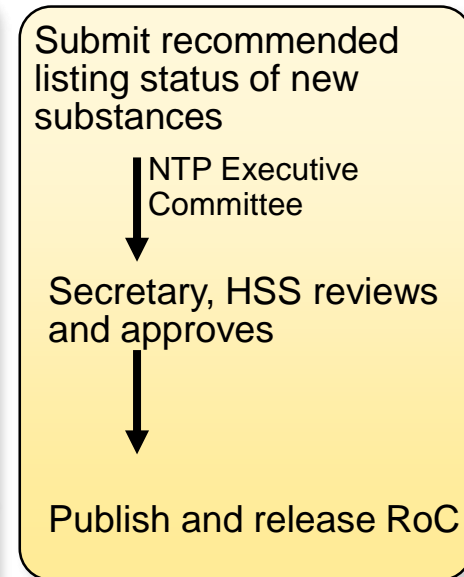
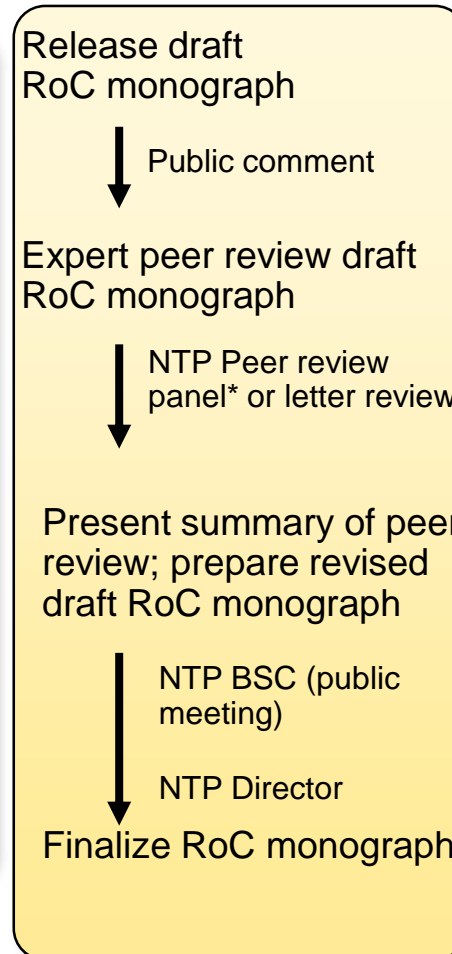
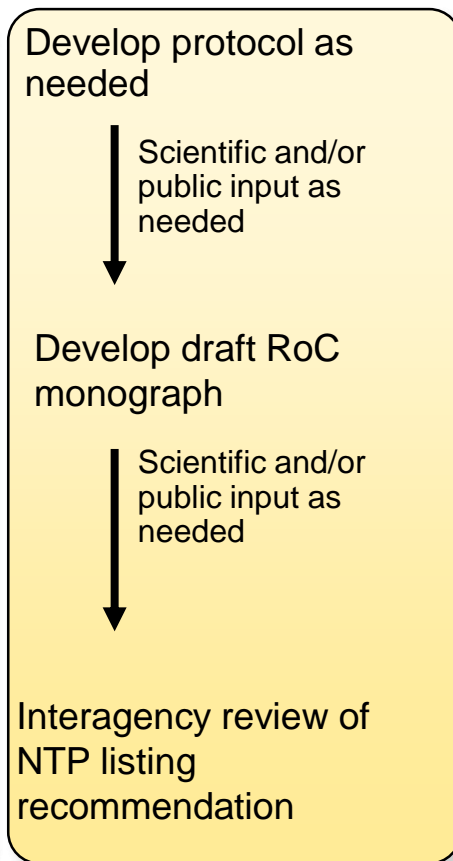
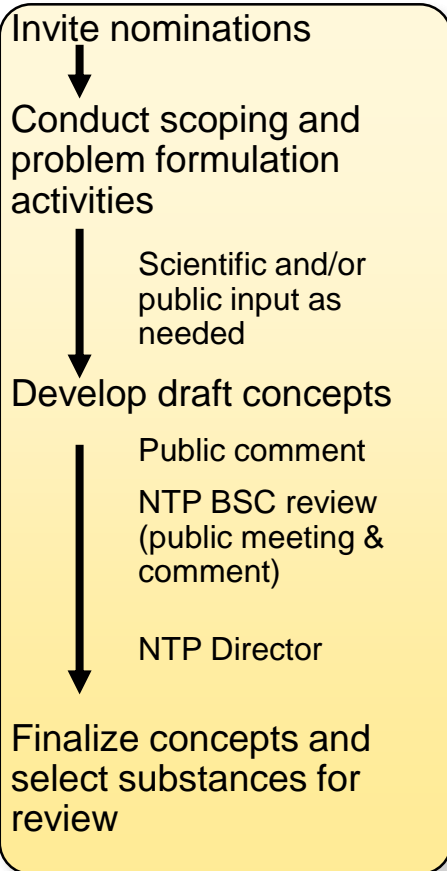
### Prepare draft RoC monographs



### Peer review and finalize RoC monographs



### 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



# Opportunity for Public Comment

## Process for the Preparation of the RoC

Select substances for evaluation



Prepare draft RoC monographs



Peer review and finalize RoC monographs



Publish and release RoC

### 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

Develop protocol as needed

↓ Scientific and/or **public input** as needed

Develop draft RoC monograph

↓ Scientific and/or **public input** as needed

Interagency review of NTP listing recommendation

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

Submit recommended listing status of new substances

↓ NTP Executive Committee

Secretary, HHS reviews and approves

↓  
Publish and release RoC

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## Process for the Preparation of the RoC

### Select substances for evaluation



### Prepare draft RoC monographs



### Peer review and finalize RoC monographs



### Publish and release RoC

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

Develop protocol as needed

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Develop draft RoC monograph

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# Peer Review: Current Step

## Process for the Preparation of the RoC

### Select substances for evaluation



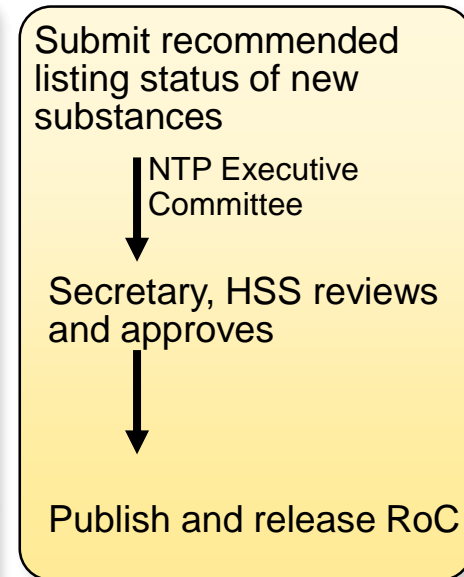
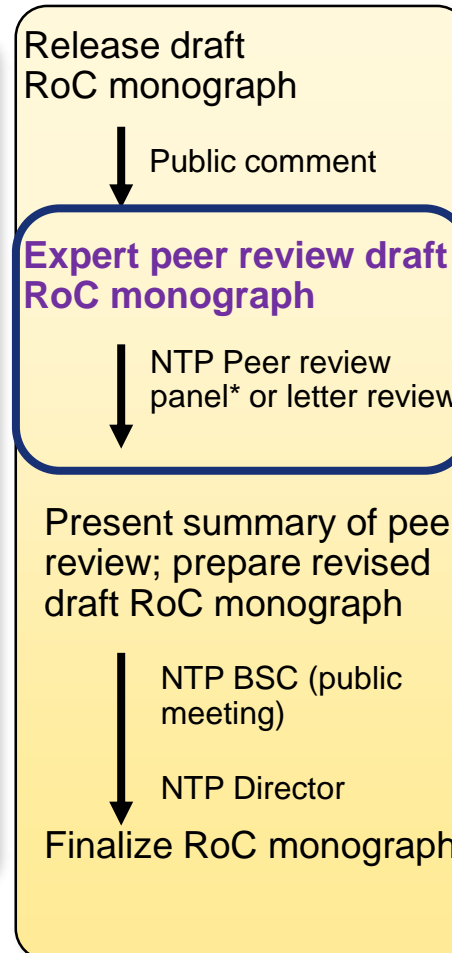
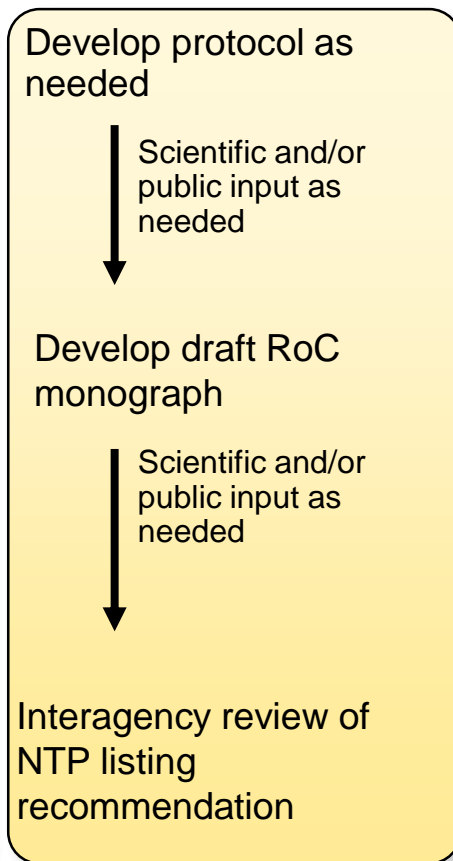
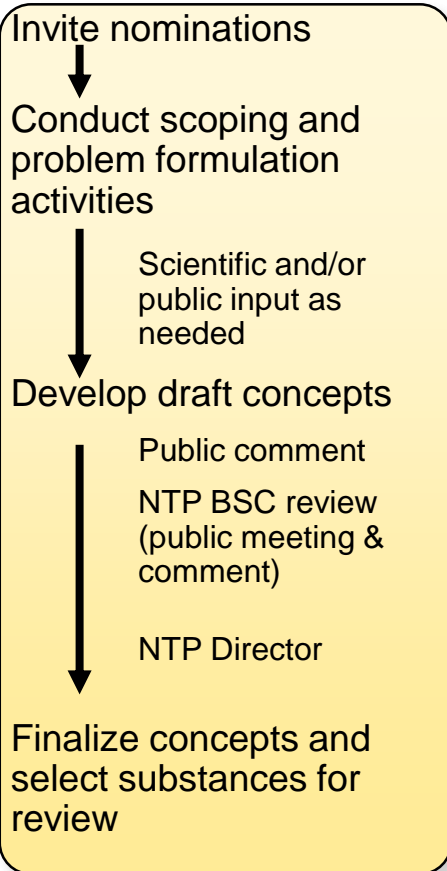
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# Select Substances for Evaluation

## 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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## Reach Cancer Hazard Conclusions

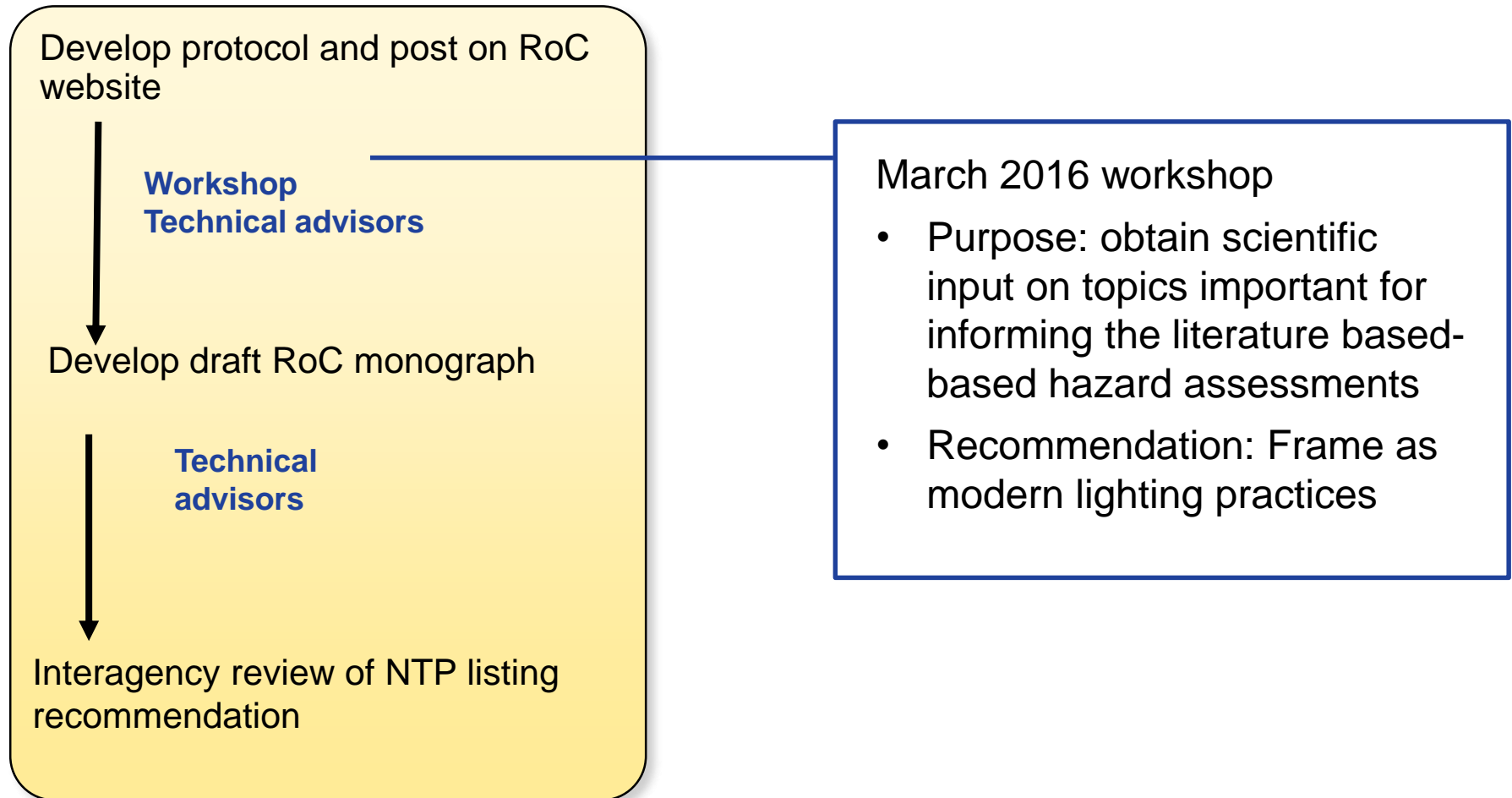
- RoC listing criteria

## Next steps



# Prepare Draft RoC Monograph

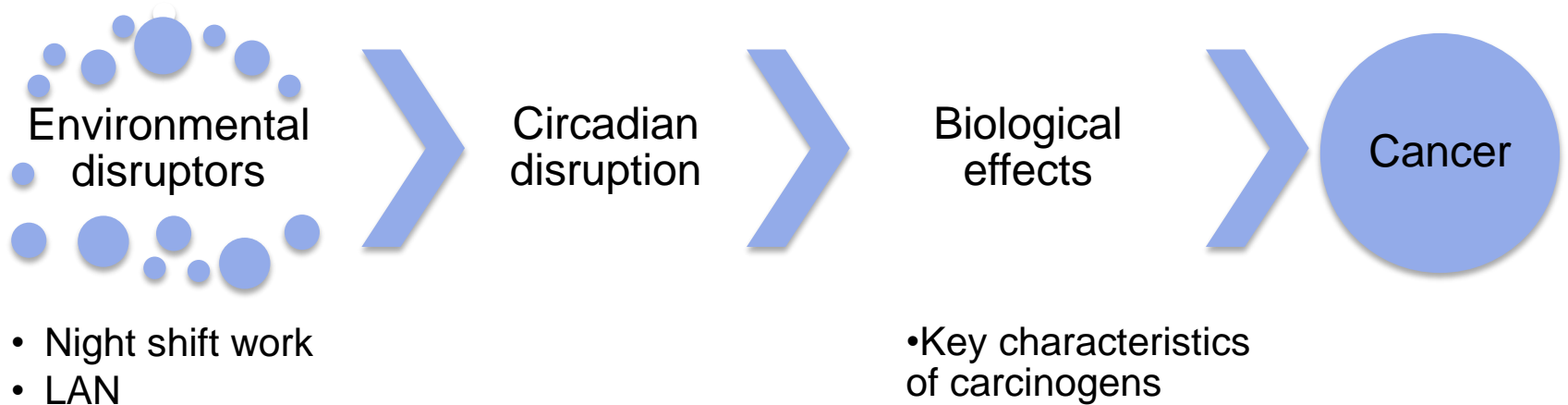
## Process for preparing draft monograph on LAN and night shift work





# Prepare Draft RoC Monograph

## 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”

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

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

Objective and Methods



# Framework: “PECO-like”

Evidence stream	Exposure	Comparator	Effect or outcome
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Section 3: Human Breast Cancer:  
Section 4: Other Cancers  
Section 5: Experimental Animal Studies  
Appendices B to G



# Framework: “PECO-like”

Evidence steam	Exposure	Comparator	Effect or outcome
Human molecular epidemiology studies	Night shift workers or night shift	Day shift workers or day shift	CD: melatonin, clock genes expression
Human experimental studies	LAN	Standard lighting conditions	CD: melatonin: clock genes
Experimental animals studies	Shift work	Standard lighting conditions	CD: clock genes expression, melatonin
Experimental animals studies	LAN	Standard lighting conditions	CD: clock genes expression,



Section 1: Background on circadian regulation and disruption  
Section 2: Studies of exposure and circadian disruption

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





# Framework: “PECO-like”

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



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



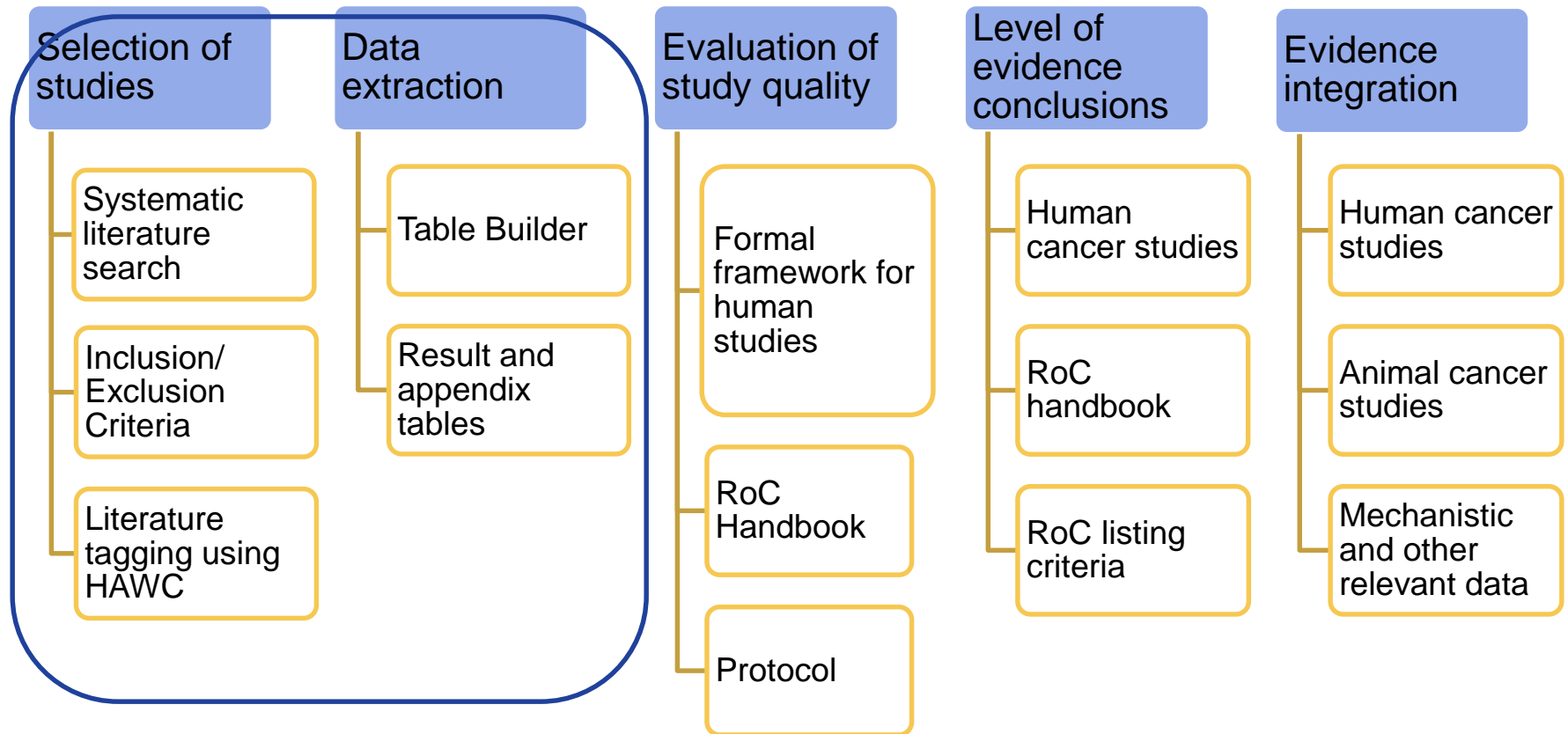
Cancer

Grey: intermediate effects; CD = circadian disruption

Section 6



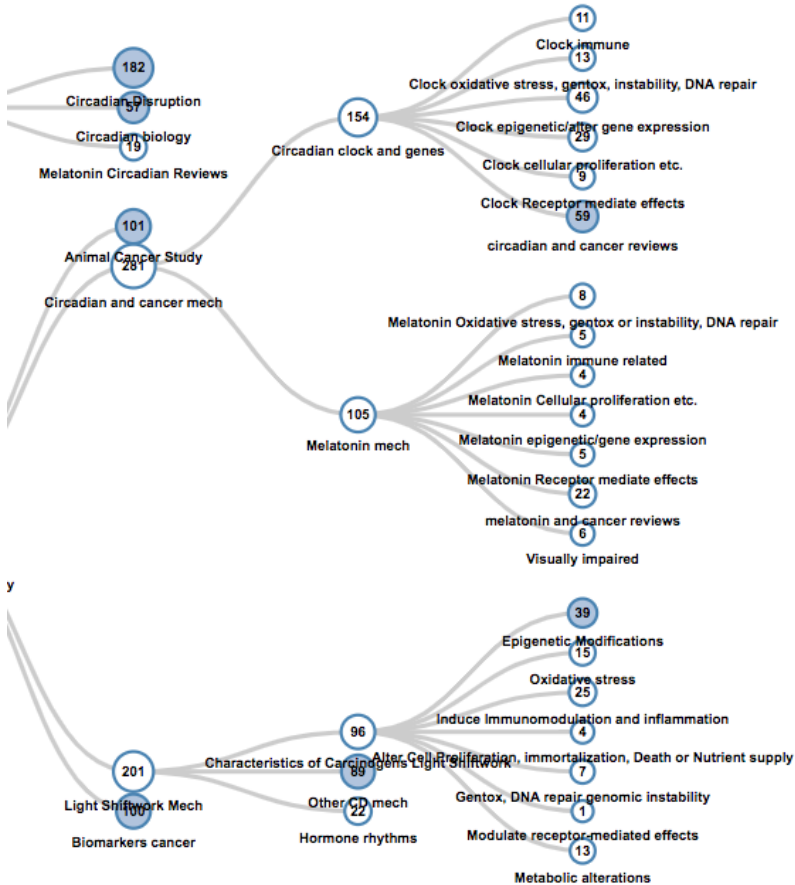
## Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria





## Literature tagging and data extraction

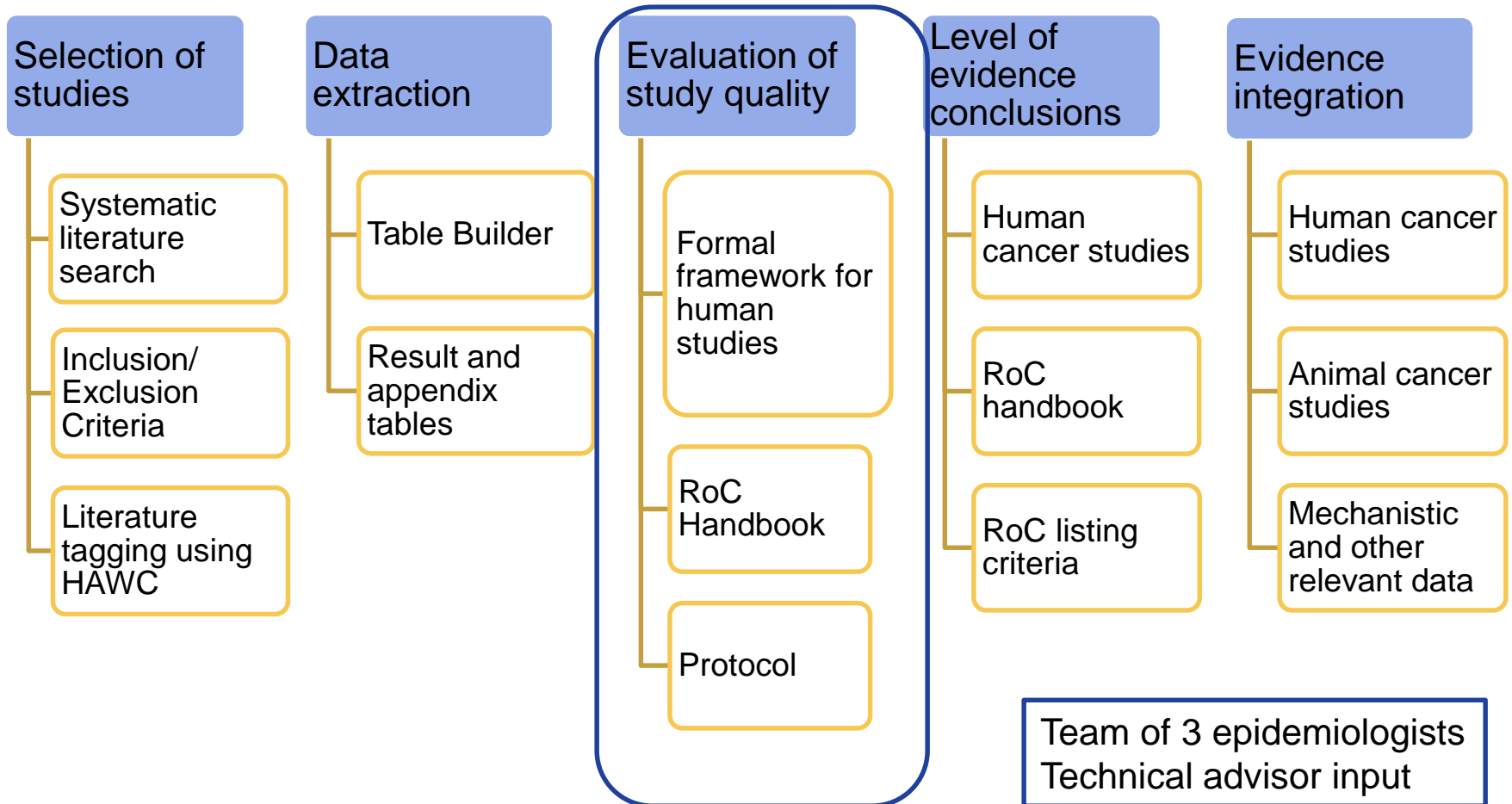
LAN Level 2 - Mechanistic (2018): Literature Tagtree



<b>Reference*</b> Select reference from library Cordina-Duverger et al. (2016)	<b>Additional references</b> Add reference from library • Menegaux et al. (2013)	<b>Study design</b> Case-Control	<b>Location</b> France, Cote d'Or and Ille-
		<b>Enrollment dates</b> 2005-2007	
<b>Population</b>			
<b>Case-control details</b>			
<b>Cases</b>	<b>Population size</b> 975	<b>Response rate</b> 63% of all eligible cases; 71	<b>Selection description</b> Newly diagnosed cases recruited from main cancer hospitals and small public and private
<b>Controls</b>	1,317	76.1%	Eligible controls identified through random selection of 30,000 phone numbers from
<b>Other population descriptors</b> CECILE study; women ages 25-75 tested for ER, PR, and HER2 status	<b>Selection bias rating</b> +++	<b>Bias direction</b> <add>	
<b>Selection bias rationale</b> Selection bias was unlikely as all incident cases in both study areas were recruited; cases were frequency-matched to controls by 10 year age strata and by socioeconomic status (SES)			
<b>Exposure and outcome</b>			
<b>Exposure assessment type</b> questionnaire	<b>Exposure assessment notes</b> In-person interviews collected data on all jobs held for 6+ consecutive mos. For each job, women were asked to report usual work schedules allowing for up to 3 types of	<b>Exposure assessment rating</b> ++	<b>Bias direction</b> <add>
<b>Exposure missing data</b>		<b>Exposure assessment rationale</b> Type of night work (late evening, early morning, overnight), duration in years, average frequency of nights/week, and duration/frequency combinations were assessed; however, due to large differences between night shift systems across occupations, shift rotation, direction and rate of rotation,	



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





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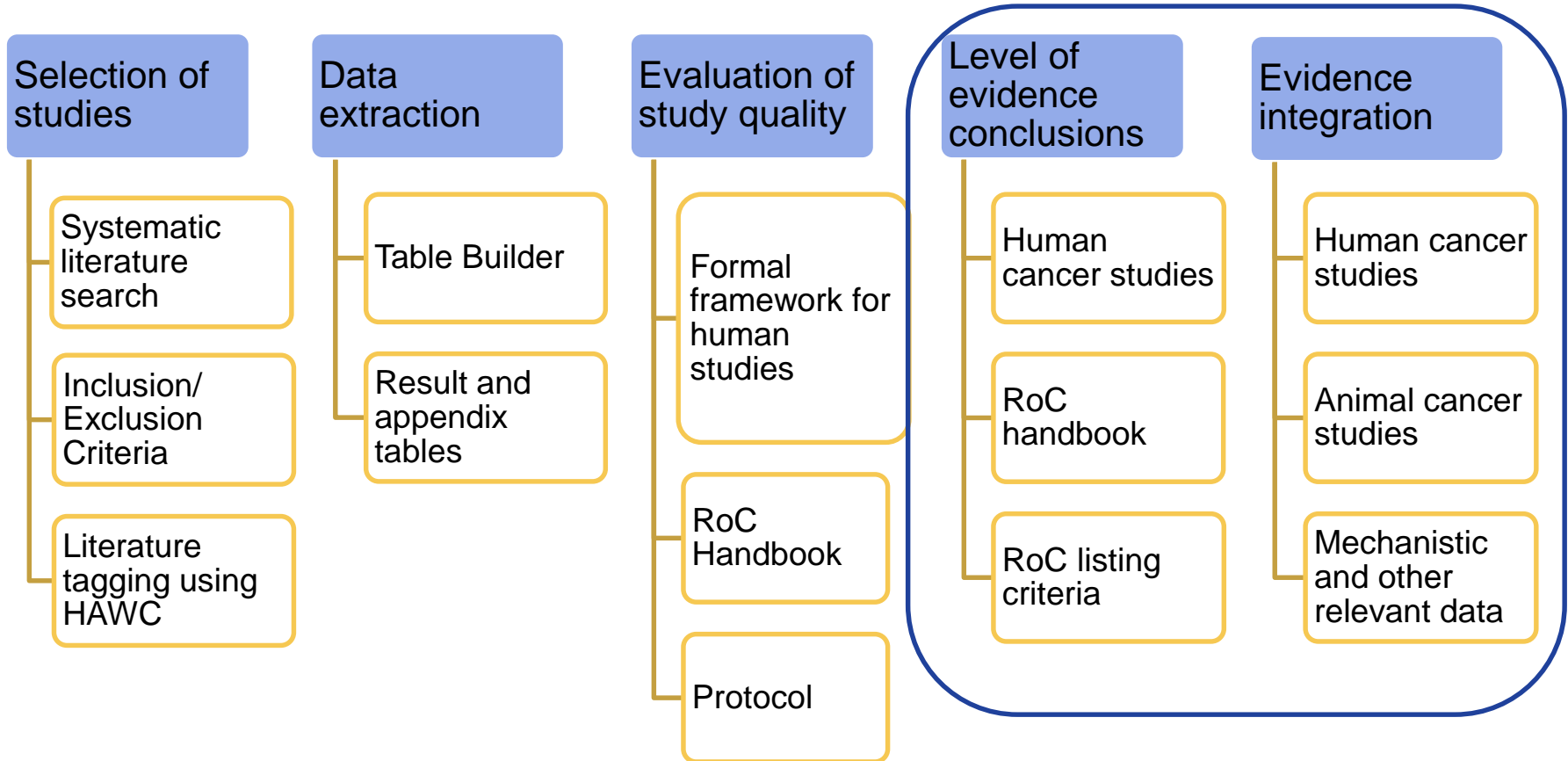
## Reach Cancer Hazard Conclusions

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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 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.





## 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,-Tetrachlordibenzo-p-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

### Section 1

- 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



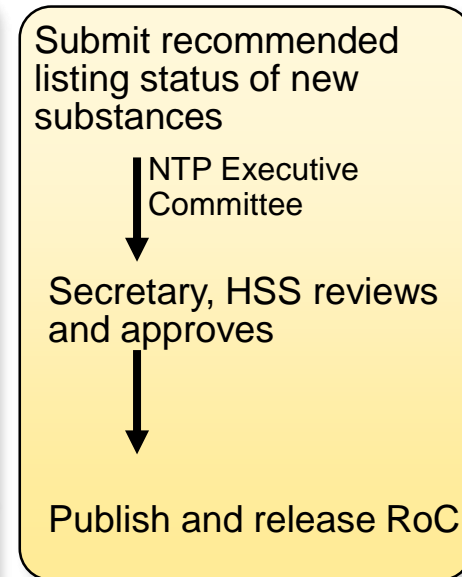
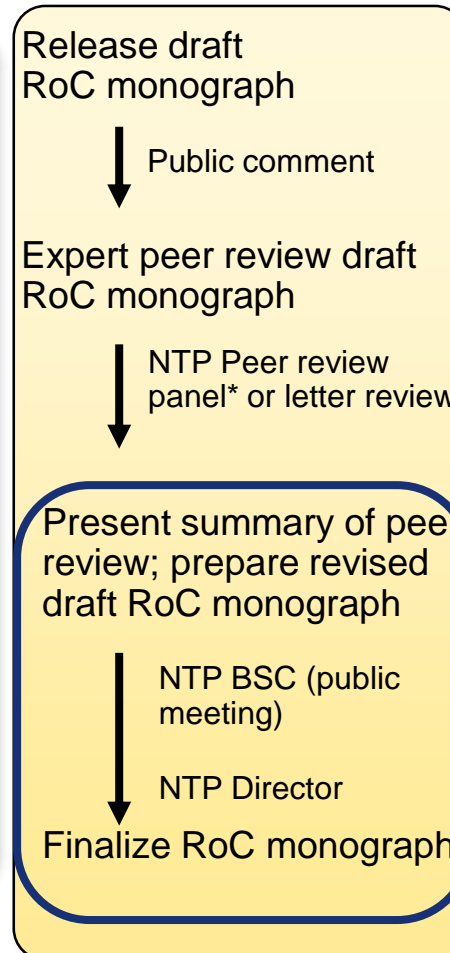
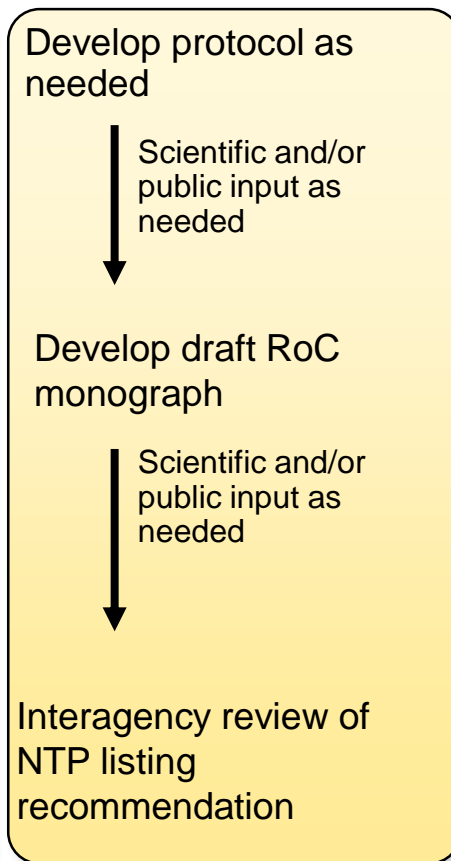
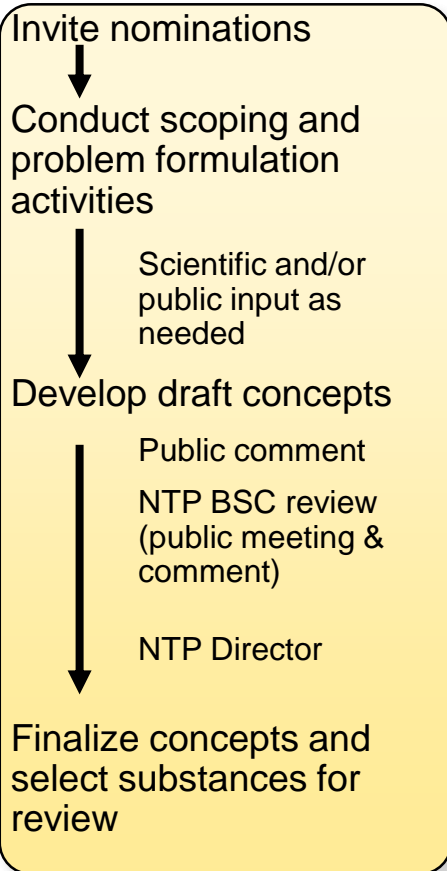
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## **Collaborators**

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**Pam Schwingl (Co-lead)**

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## **Peer Review**

Mary Wolfe

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**Clarification questions?**