



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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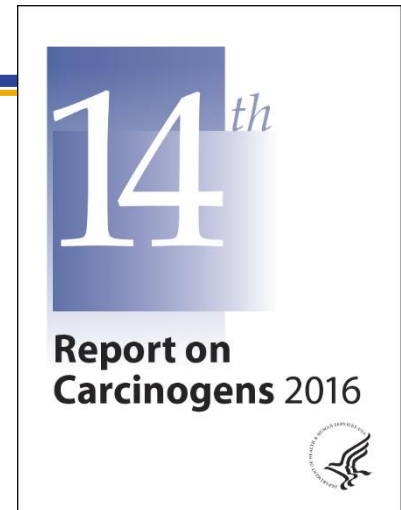
- RoC listing criteria

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





Four-Part Process

Process for the Preparation of the RoC

Select substances for evaluation



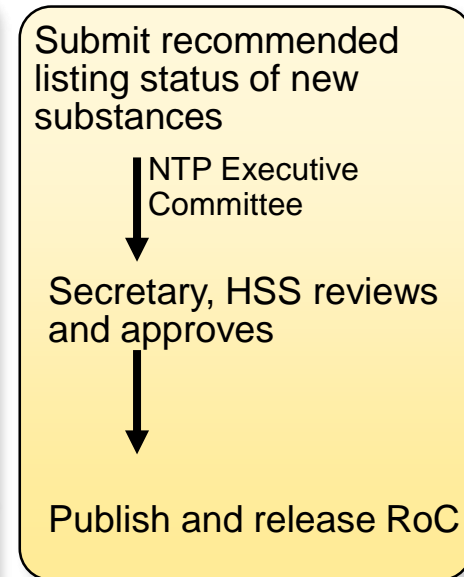
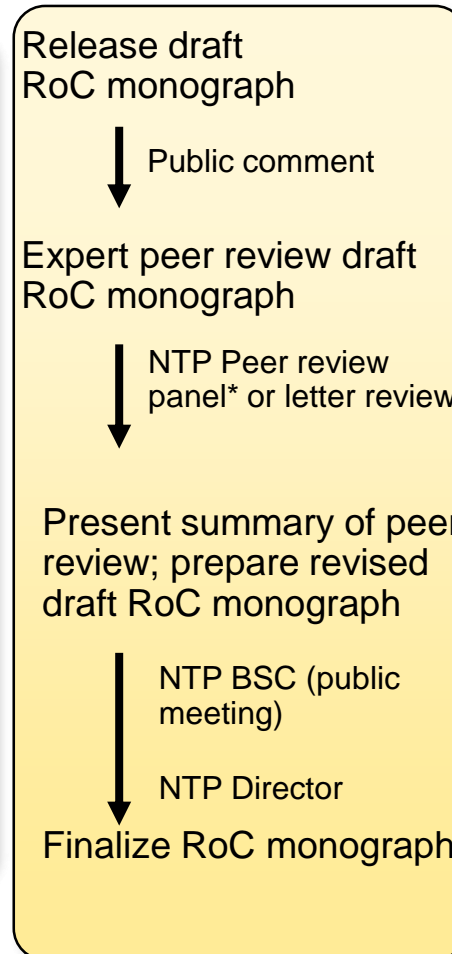
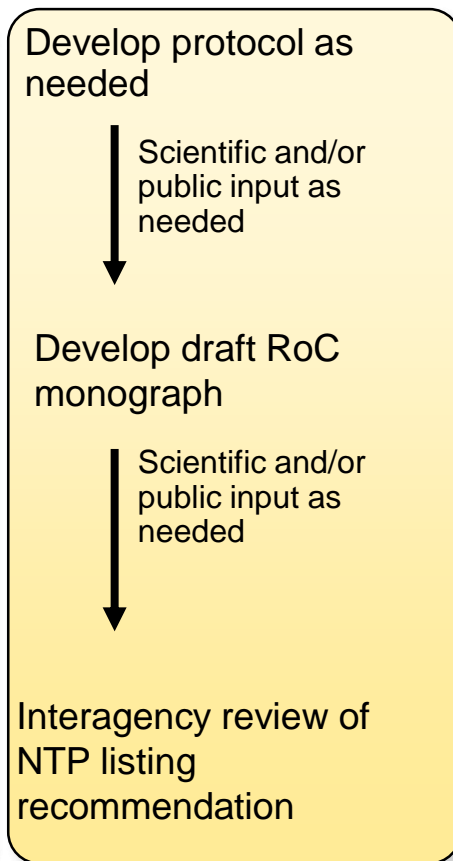
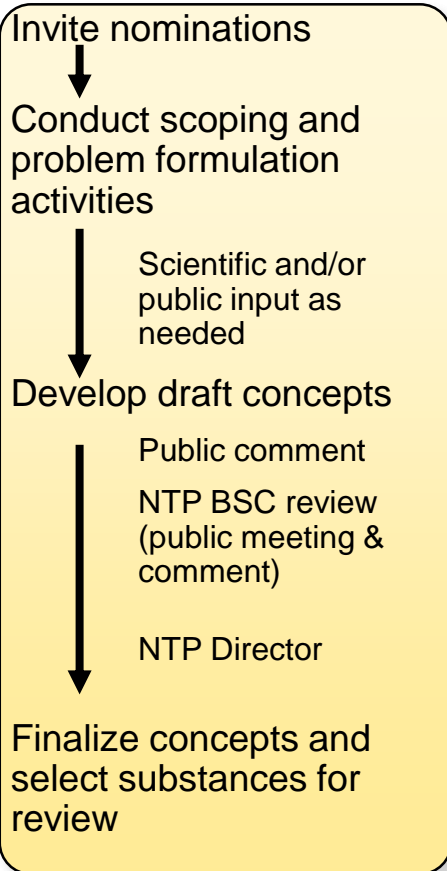
Prepare draft RoC monographs



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

↓
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Process for the Preparation of the RoC

Select substances for evaluation



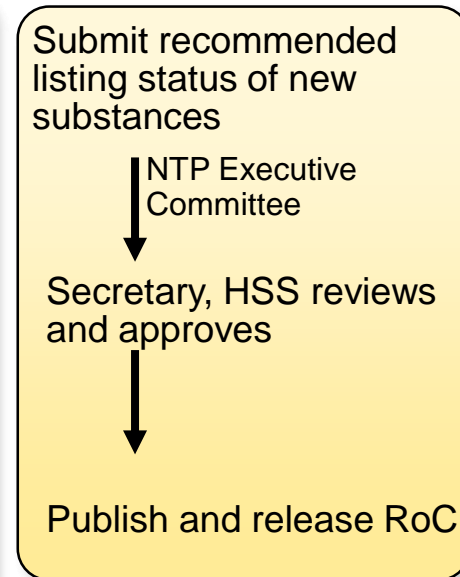
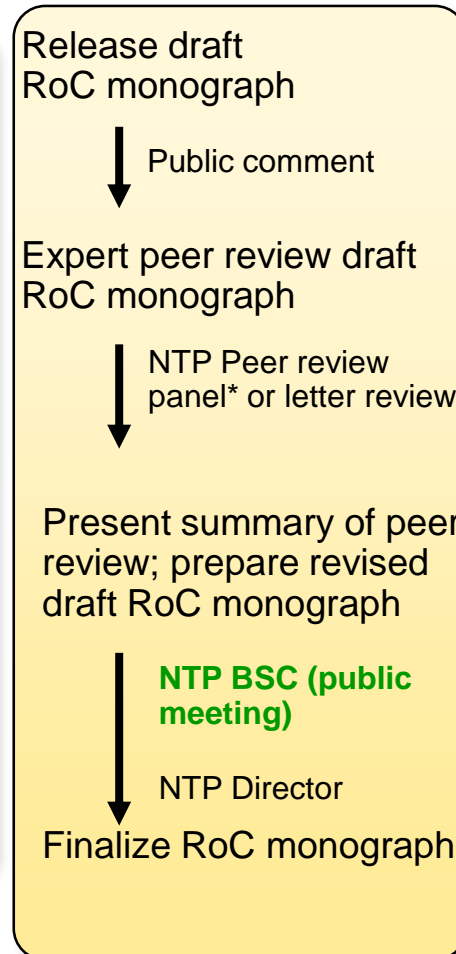
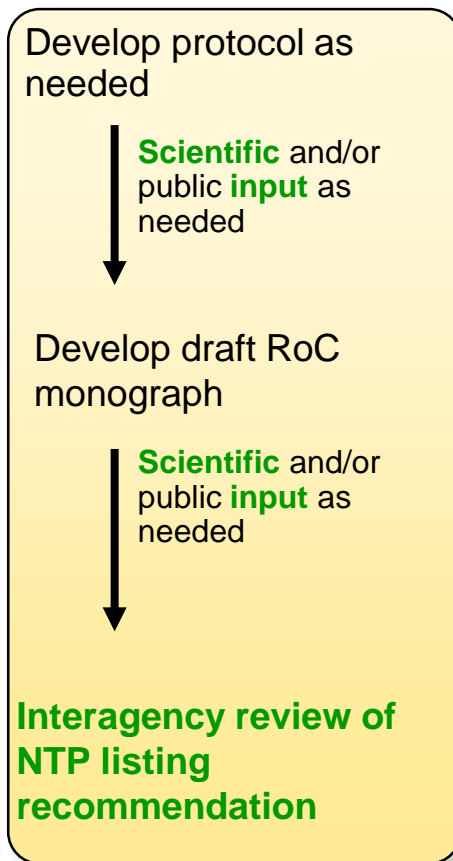
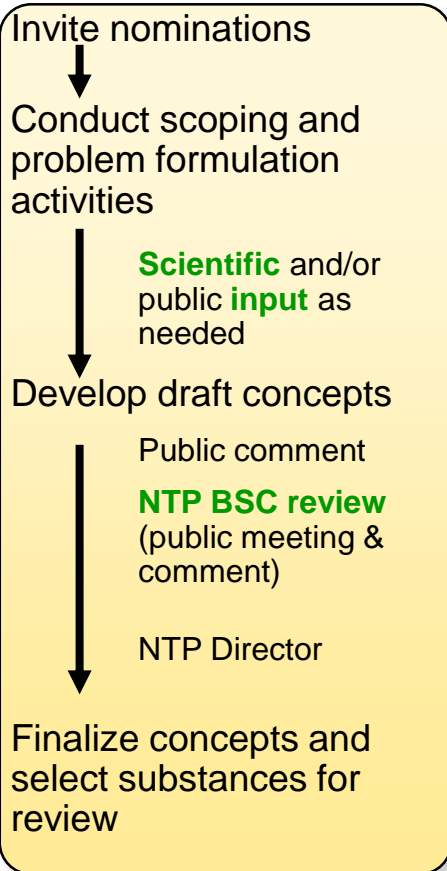
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Peer Review: Current Step

Process for the Preparation of the RoC

Select substances for evaluation



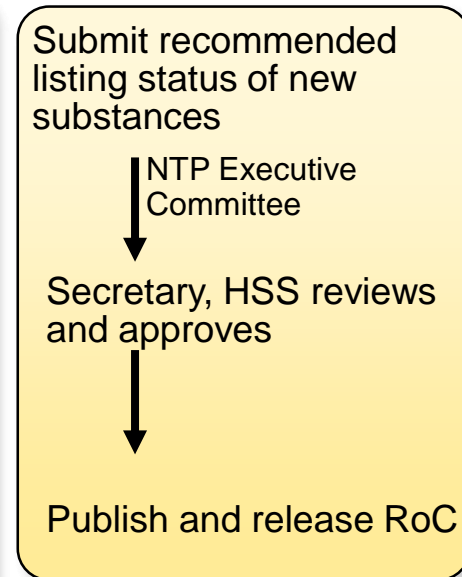
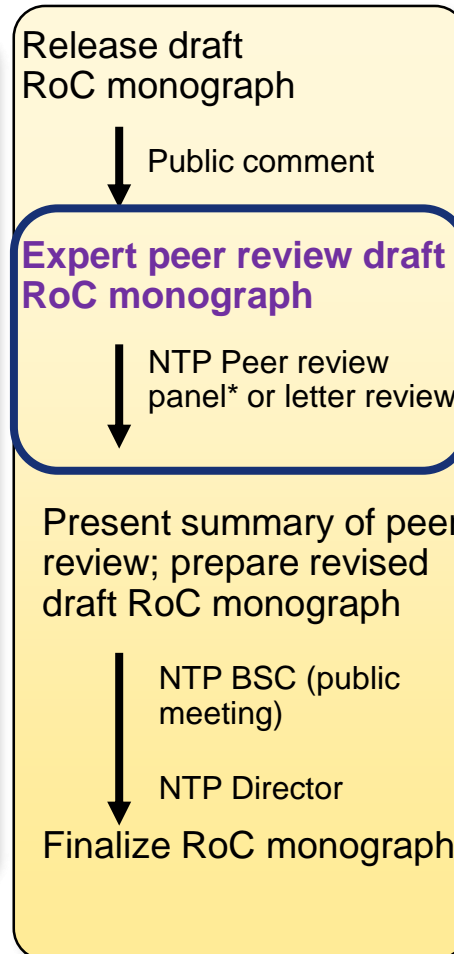
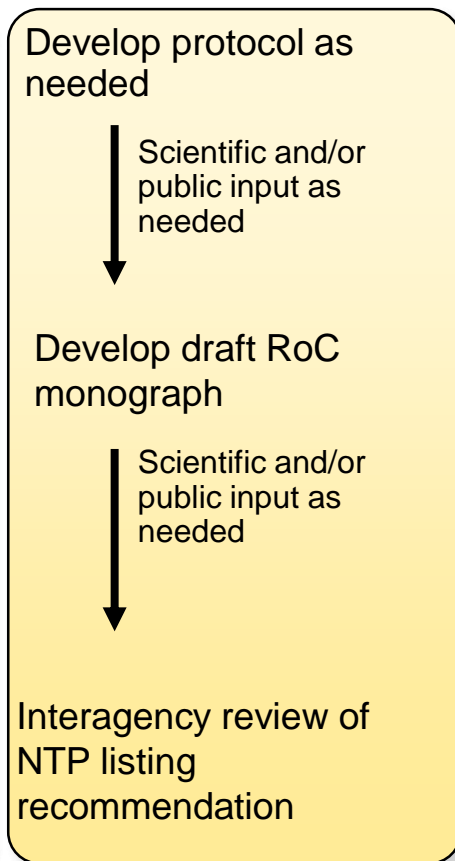
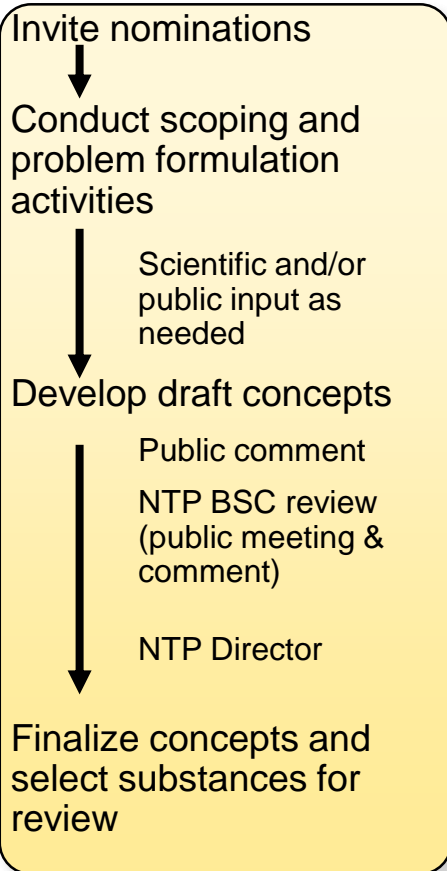
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Select Substances for Evaluation

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



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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

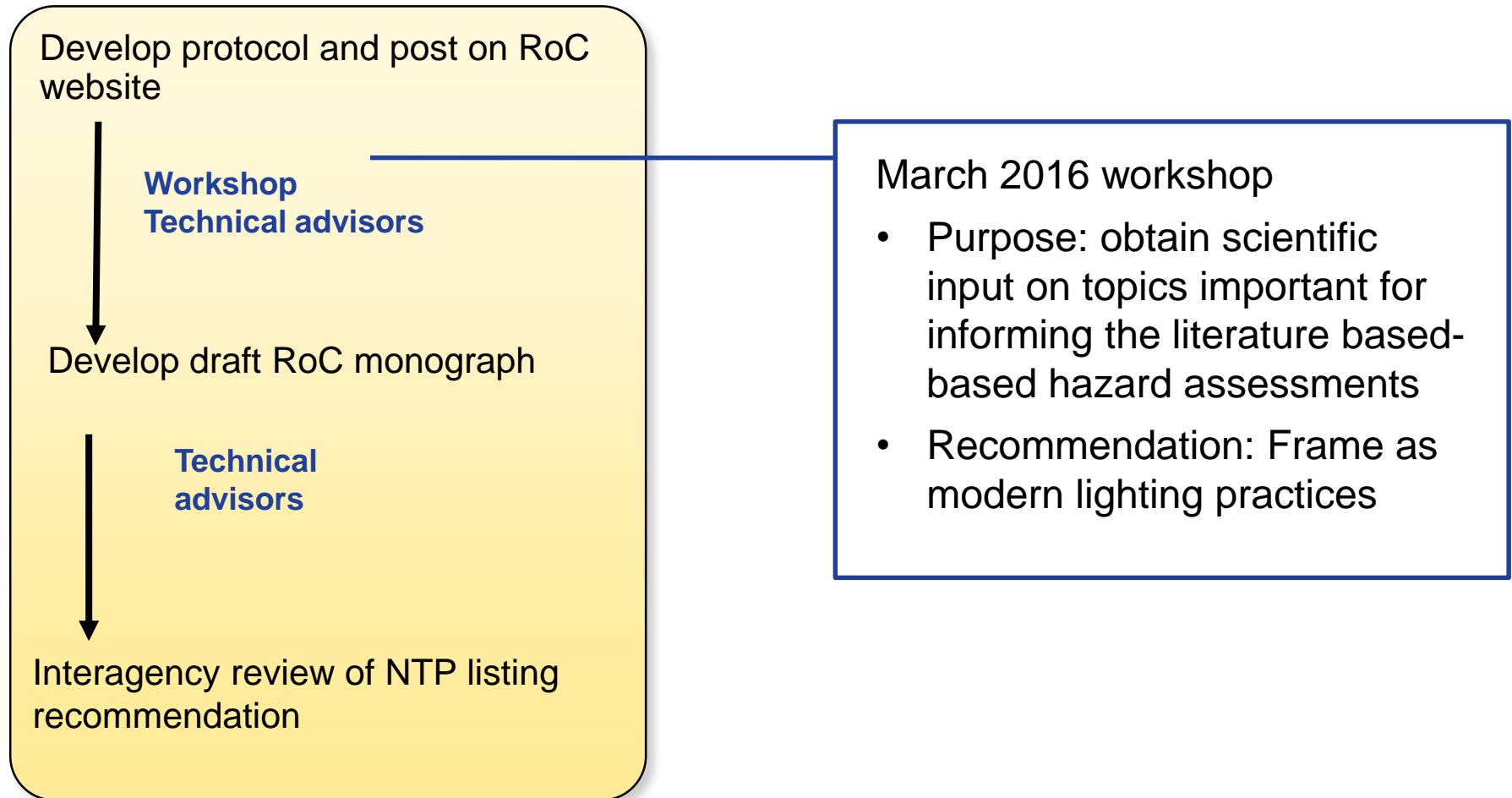
- RoC listing criteria

Next steps



Prepare Draft RoC Monograph

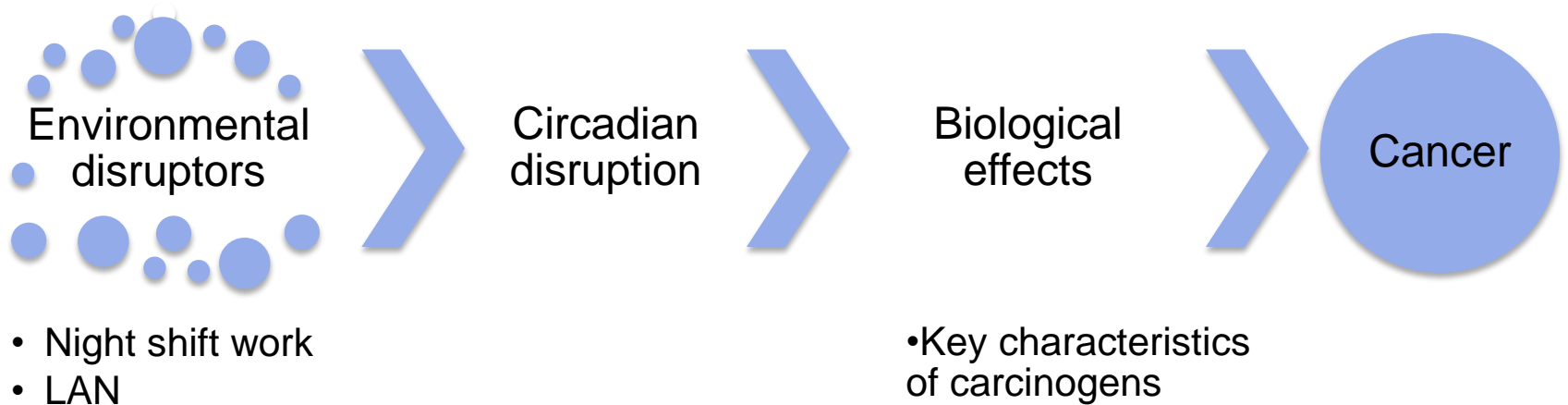
Process for preparing draft monograph on LAN and night shift work





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 stream	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



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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



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



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	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



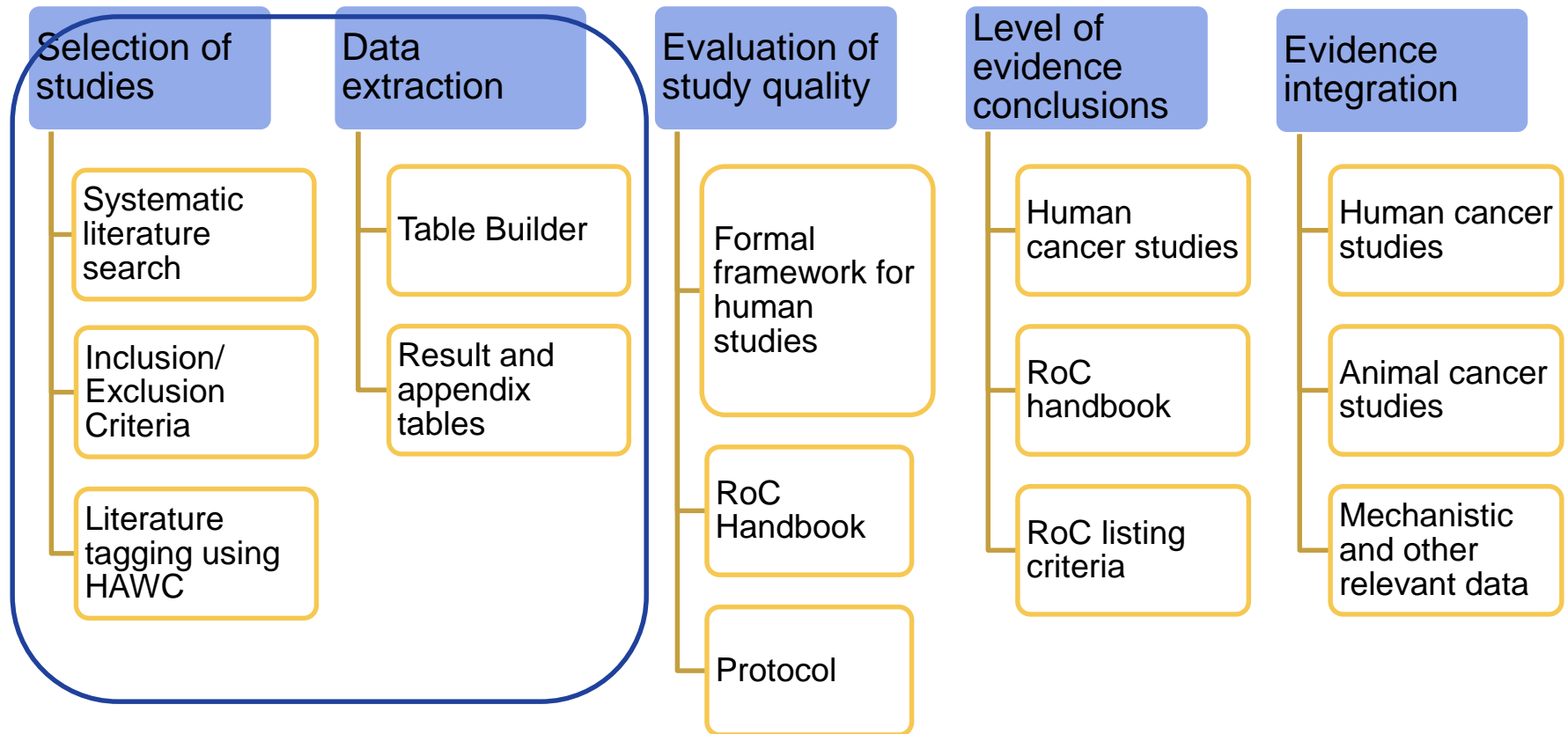
Cancer

Grey: intermediate effects; CD = circadian disruption

Section 6



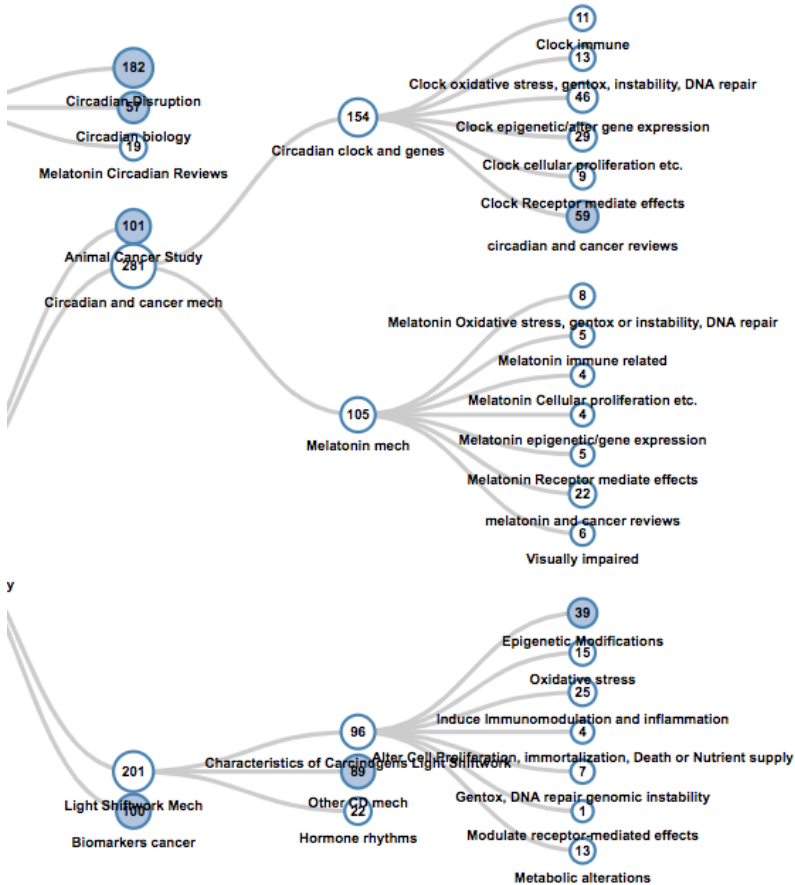
Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria





Literature tagging and data extraction

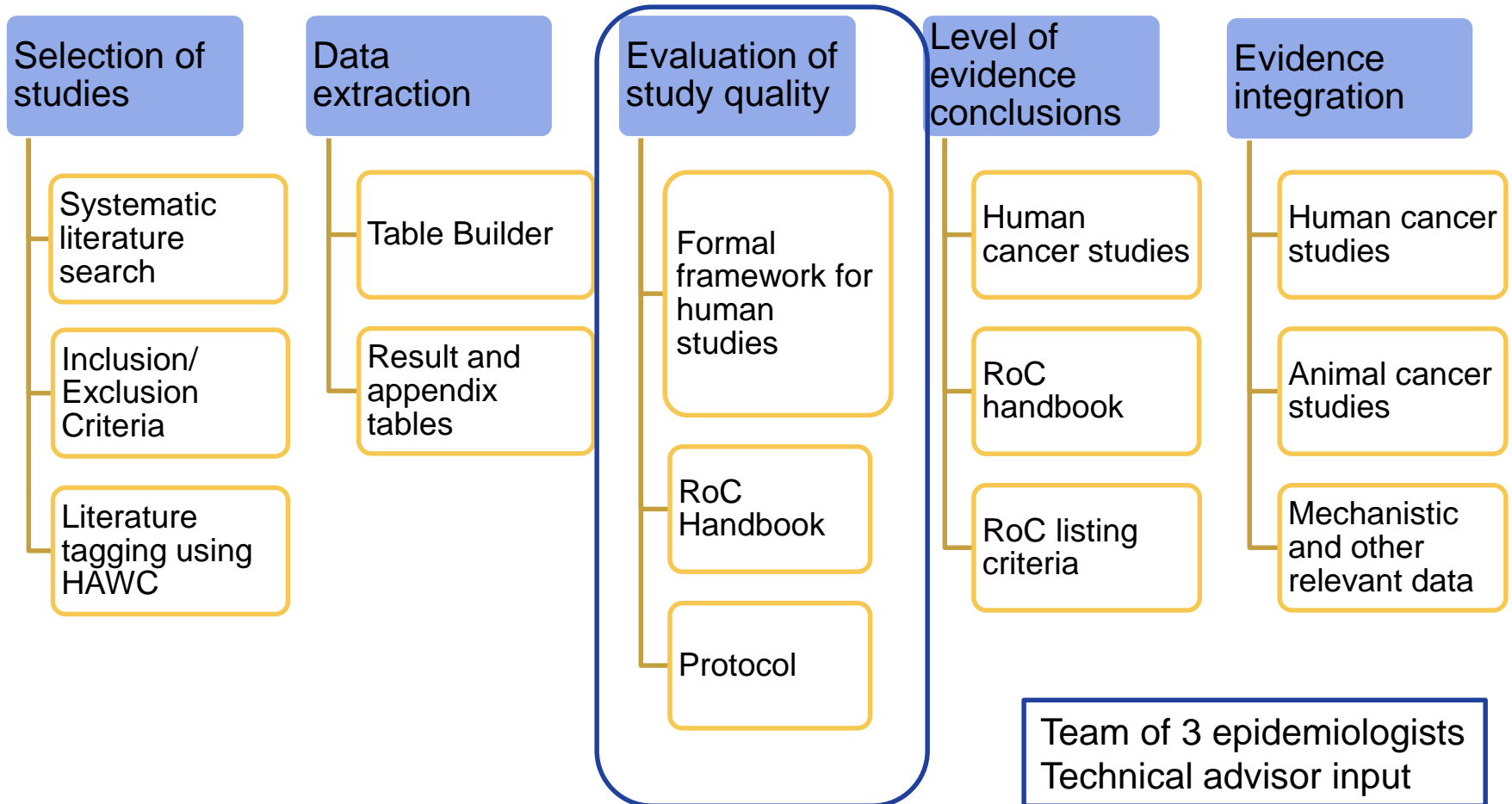
LAN Level 2 - Mechanistic (2018): Literature Tagtree



Reference* Select reference from library Cordina-Duverger et al. (2016)	Additional references Add reference from library • Menegaux et al. (2013)	Study design Case-Control	Location France, Cote d'Or and Ille-1
		Enrollment dates 2005-2007	
Population			
Case-control details			
Cases	Population size 975	Response rate 63% of all eligible cases; 71	Selection description Newly diagnosed cases recruited from main cancer hospitals and small public and private
Controls	1,317	76.1%	Eligible controls identified through random selection of 30,000 phone numbers from
Other population descriptors CECILE study; women ages 25-75 tested for ER, PR, and HER2 status	Selection bias rating +++	Bias direction <add>	Selection bias rationale 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)
Exposure and outcome			
Exposure assessment type questionnaire	Exposure assessment notes 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	Exposure assessment rating ++	Bias direction <add>
Exposure missing data		Exposure assessment rationale 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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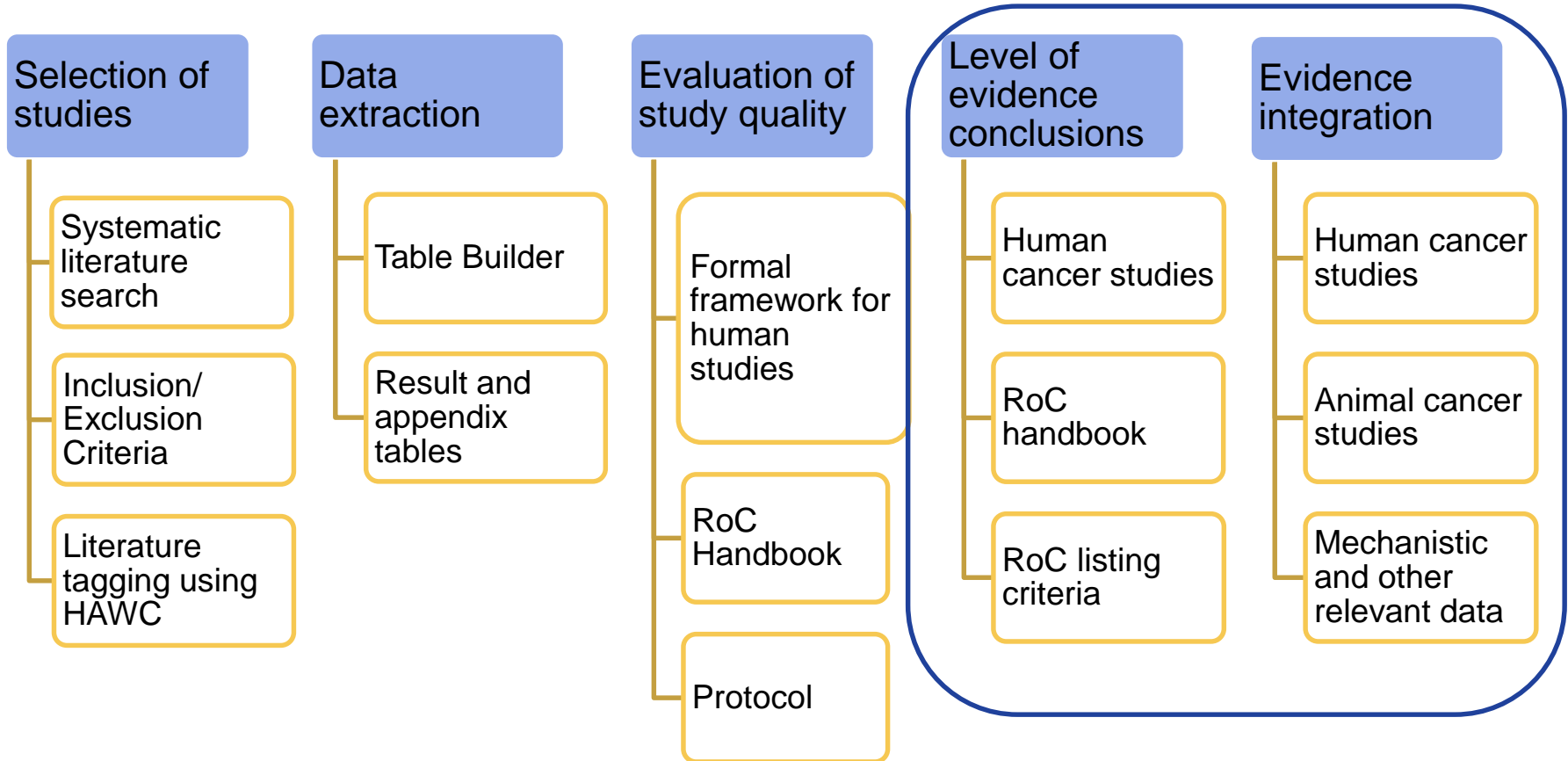
Reach Cancer Hazard Conclusions

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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



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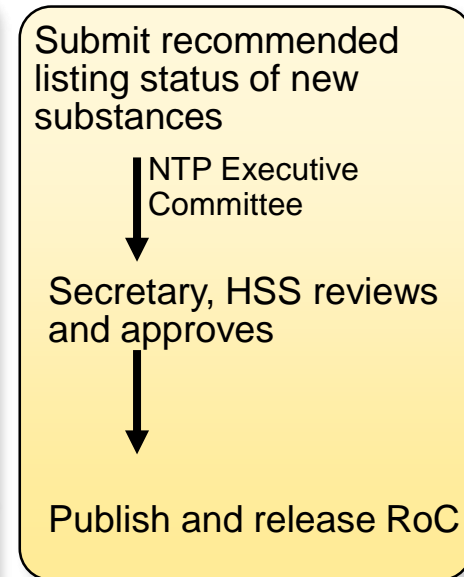
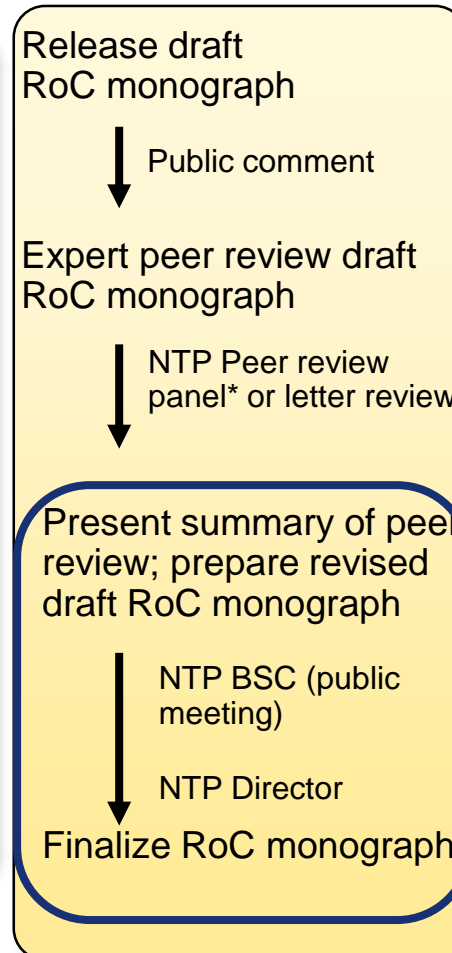
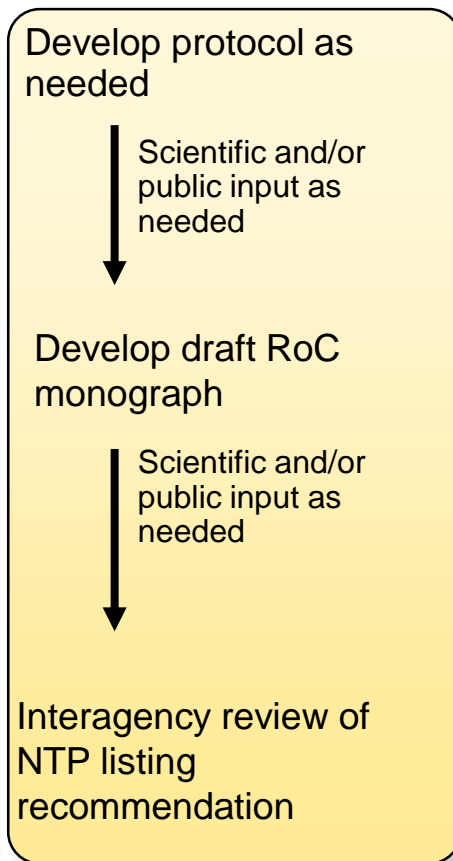
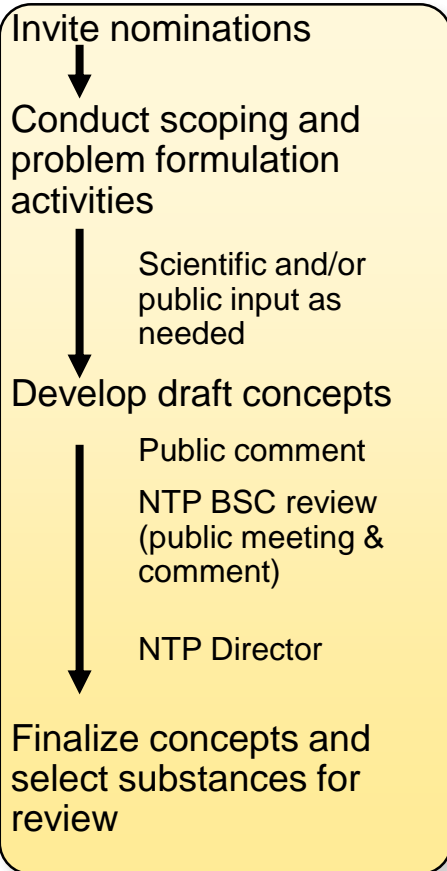
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Collaborators

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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Ella Darden

Jessica Geter

Lara Handler

Tracy Saunders

Peer Review

Mary Wolfe

ICF Staff



Clarification questions?