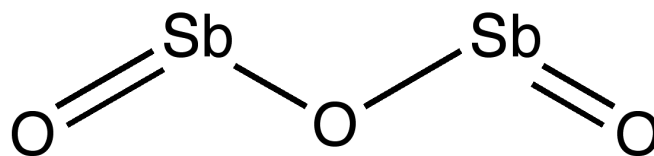


# Process for Preparing the Draft RoC Monograph on Antimony Trioxide



Ruth M. Lunn, DrPH  
Office of the Report on Carcinogens

National Institute of Environmental Health Sciences  
January 24, 2018



# Antimony Trioxide Peer Review Meeting

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## Outline

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Background on Report on Carcinogens (RoC)

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Select antimony trioxide for evaluation for the RoC

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Develop draft RoC monograph

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Evaluate cancer hazards and overview of RoC listing criteria

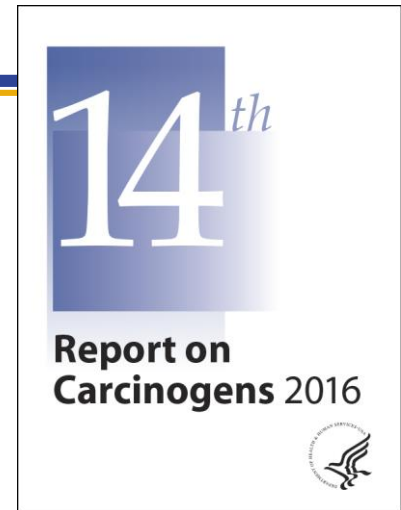
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Next steps



## 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

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

**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

#### Key

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## Process for the Preparation of the RoC

### Select substances for evaluation



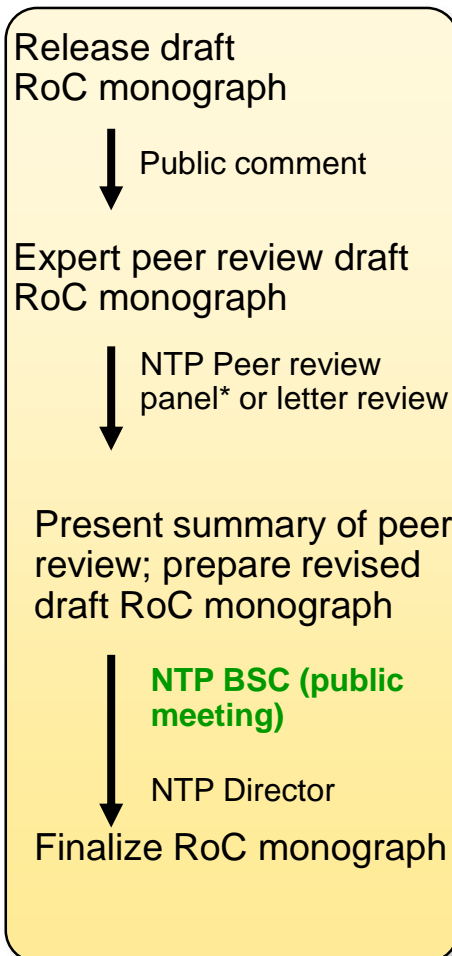
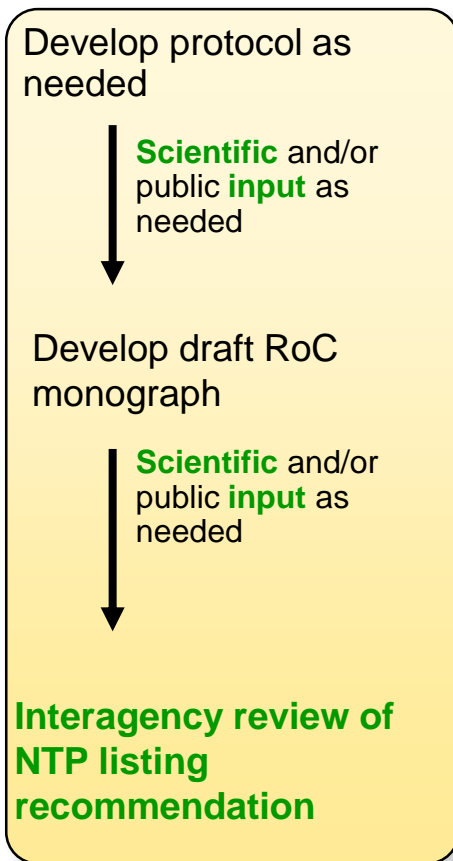
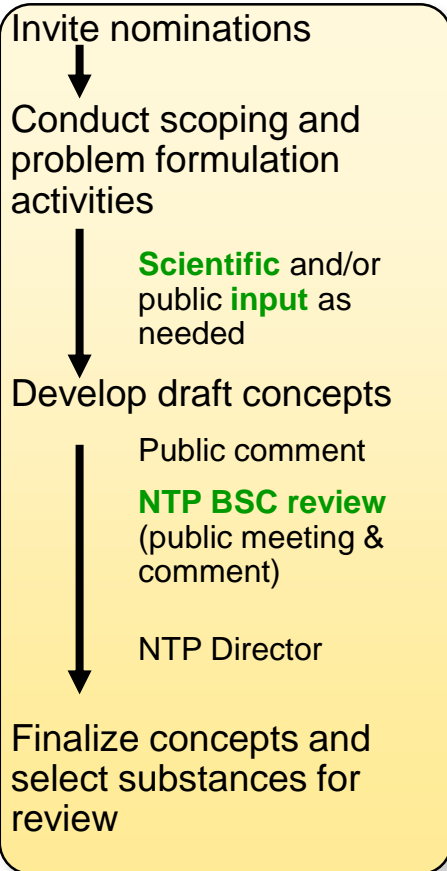
### Prepare draft RoC monographs



### Peer review and finalize RoC monographs



### Publish and release RoC



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# Peer Review: Current Step

## 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  
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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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# Select Antimony Trioxide for Evaluation

## Invite nominations



Conduct scoping and problem formulation activities



Request for Information

September 2016

Develop draft concepts



Public comment  
NTP BSC review  
December 2016

NTP Director

Finalize concepts and select substances for review

RoC Nomination: NIOSH  
Deferred because of  
inadequate database

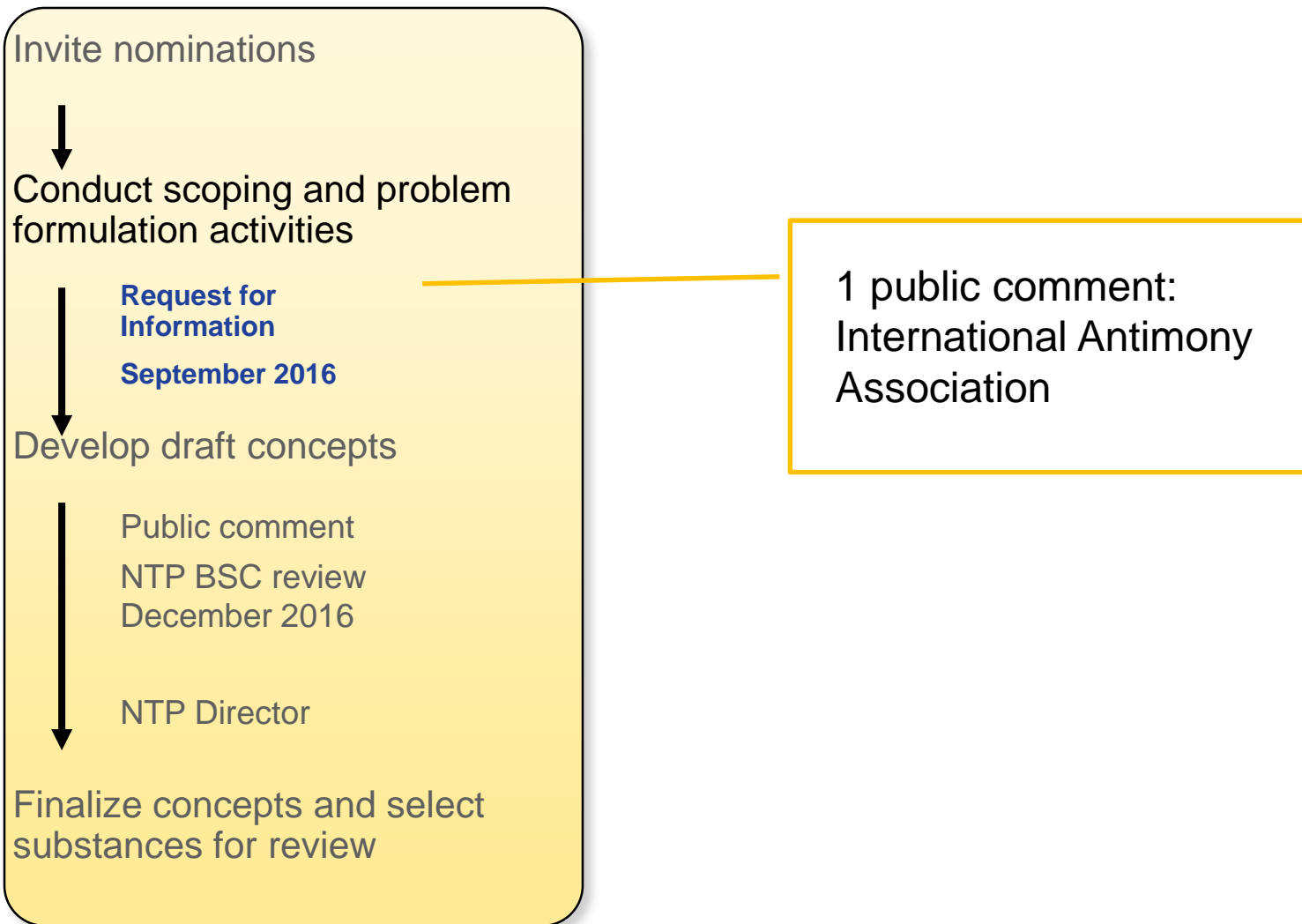
NTP 2-year bioassays  
nomination: CPSC

Draft technical report on  
antimony trioxide was peer  
reviewed in 2016 and  
finalized in 2017





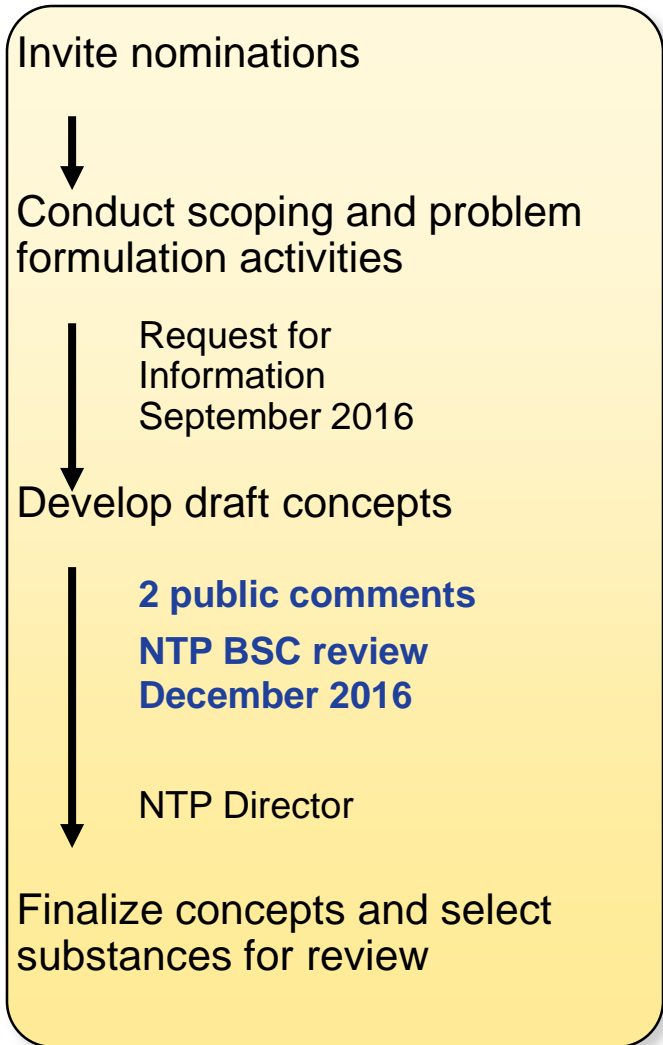
# Select Antimony Trioxide for Evaluation





# Select Antimony Trioxide for Evaluation

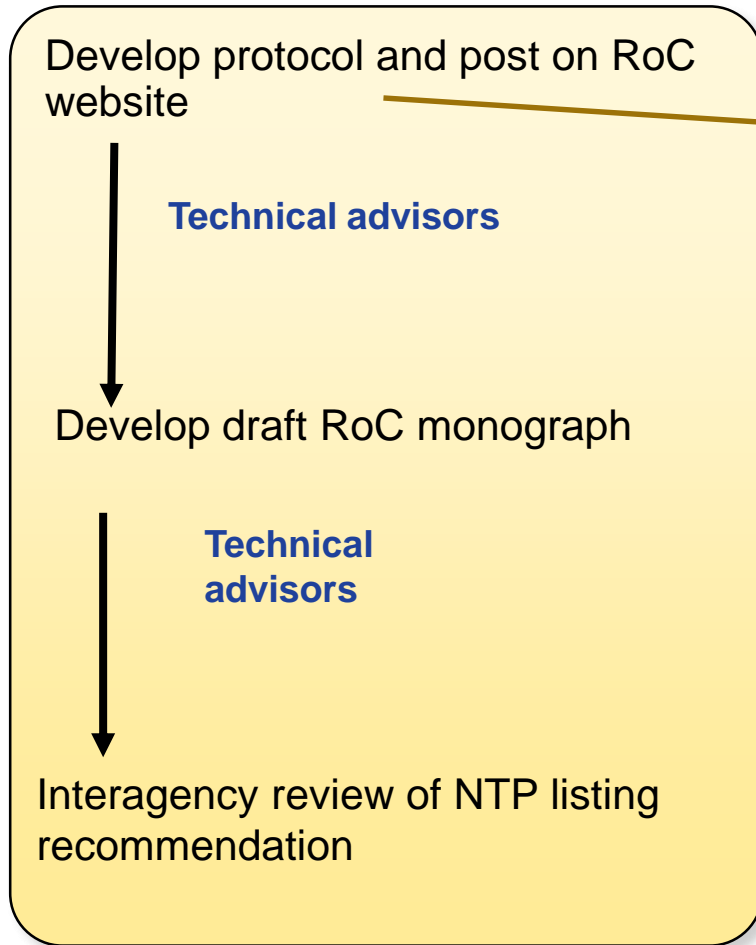
## Potential public health concern



- Adequate database of cancer studies in experimental animals
- Evidence for occupational exposure in the United States
- Interest reinitiated by 2016 NTP technical report on 2-year bioassays



## Process for preparing draft monograph on antimony trioxide



Methods for preparing the monograph such as approaches for evaluating study quality and integrating data



## Research Questions

- Are or were a significant number of people in the United States exposed to antimony trioxide?
- Is antimony trioxide known or reasonably anticipated to be a human carcinogen (as defined by the RoC listing criteria)?

## Scope of the monograph

- Antimony trioxide is converted *in vitro* and *in vivo* to other antimony forms and vice versa
- Information on other antimony compounds may help inform the potential carcinogenicity of antimony trioxide



# Prepare Draft RoC Monograph

## Evaluate whether a significant number of U.S. residents are exposed to antimony trioxide

### 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 2)

- Past and present exposure inferred using data on consumption, use, environmental and occupational exposure
- Workers are typically exposed to high levels
- Not a formal exposure assessment

### Reviewer instructions

- Use their judgment as to whether the exposure information in the draft monograph supports the NTP conclusion that a significant number of U.S. residents are exposed to antimony trioxide



## Research Questions

- Are a significant number of people in the United States exposed to antimony trioxide?
- Is antimony trioxide *known or reasonably anticipated to be a human carcinogen* (as defined by the RoC listing criteria)?

## Scope of the monograph

- Antimony trioxide is converted *in vitro* and *in vivo* to other antimony forms and vice versa
- Information on other antimony compounds may help inform the potential carcinogenicity of antimony trioxide
- Inadequate database on other antimony compounds to evaluate the potential carcinogenicity



# Evaluate Cancer Hazards

## Framework for evaluating research question

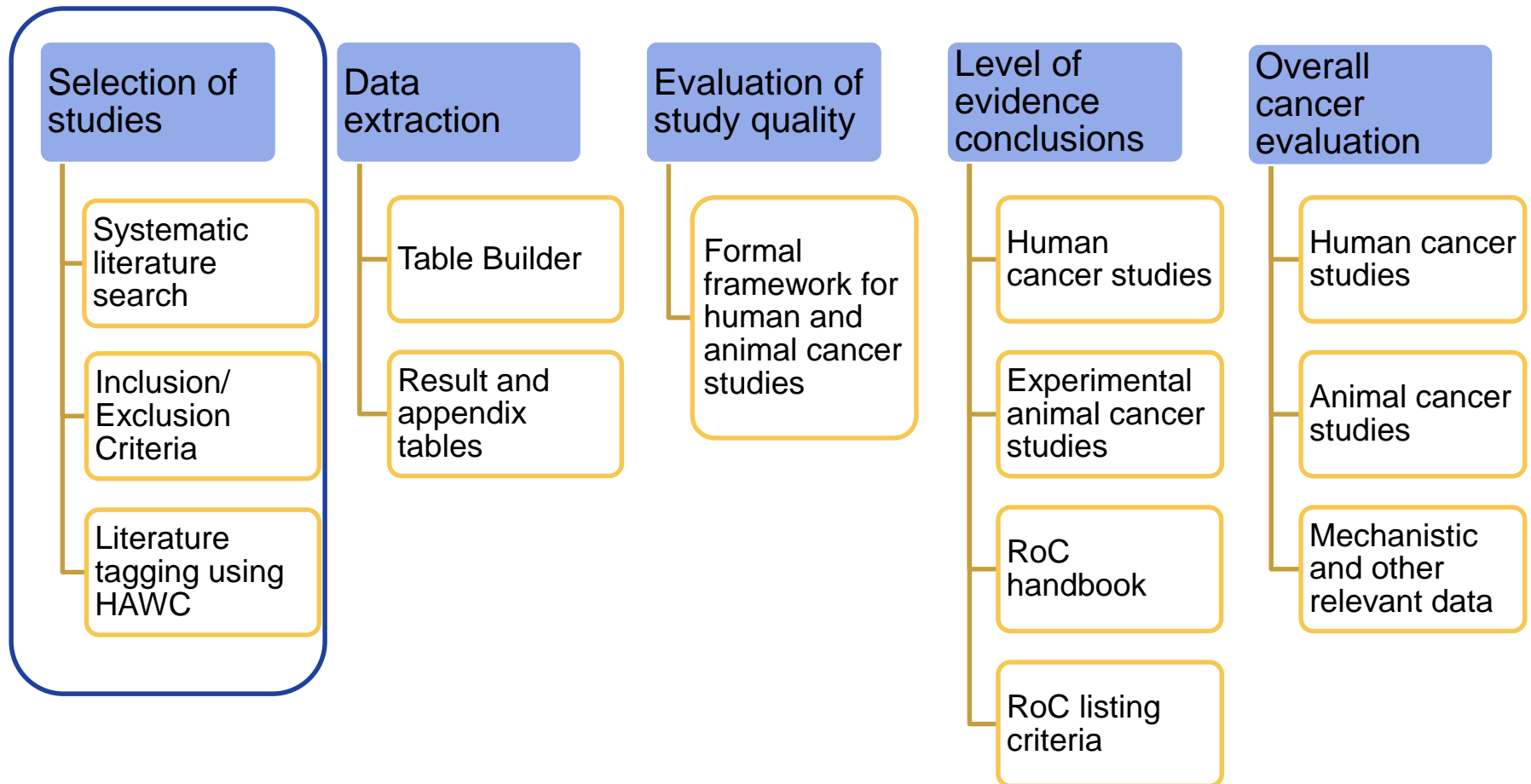
Scientific evidence stream	Exposure	Outcome
<b>Primary evidence</b>		
Experimental animal studies	Antimony trioxide	All reported neoplasms
Human epidemiology studies	Antimony trioxide and other antimony compounds	Lung and stomach cancer
<b>Supporting evidence (mechanistic and other relevant data)</b>		
Experimental animal studies	Antimony (III) compounds	Carcinogenicity and biological effects related to carcinogenicity or toxicity
Human studies	Antimony (III) compounds	Biological effects related to carcinogenicity or toxicity
<i>In vitro</i> studies	Antimony (III) compounds	Biological effects related to carcinogenicity or toxicity

Analogous to "PECO" Statement, P = population replaced by evidence stream, E = exposure, O = outcome, C= comparator – unexposed for all evidence streams, O = outcome



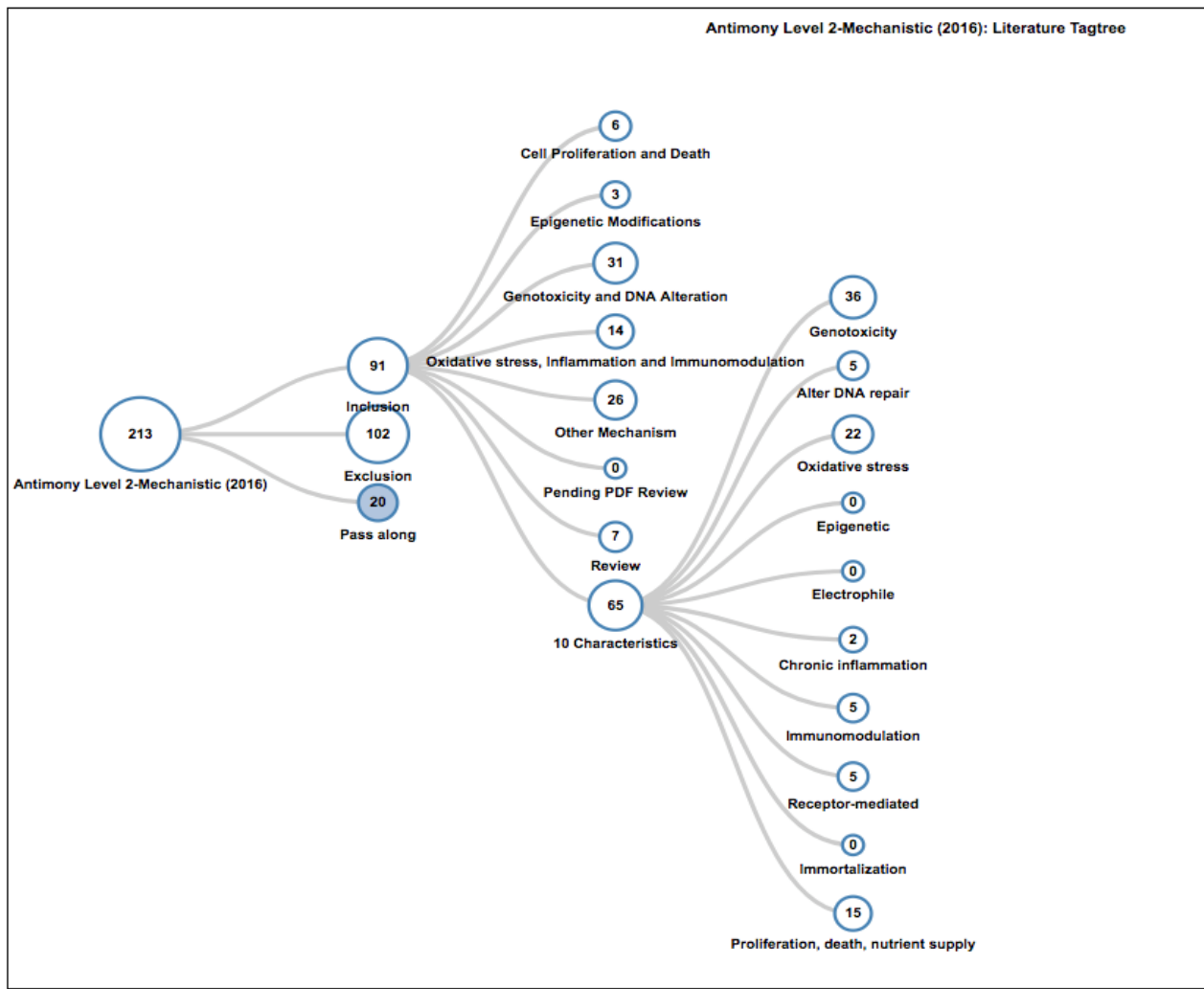
# Evaluate Cancer Hazards

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





# Literature tagging was done using HAWC

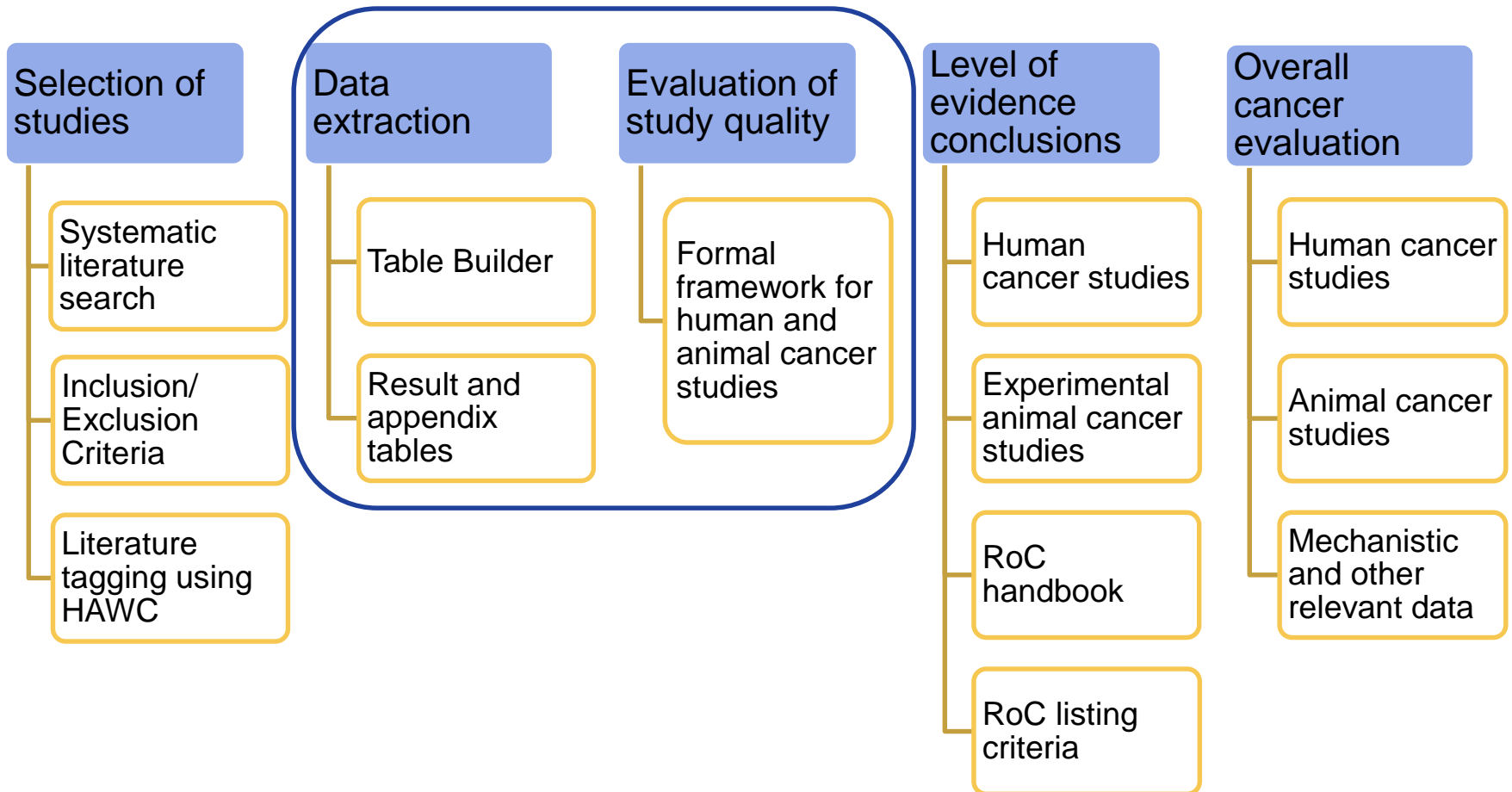


Health Assessment Workspace Collaborative: On line collaborate workspace  
<https://hawcproject.org>



# Evaluate Cancer Hazards

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



# Data was systematically extracted and study quality is assessed using a web-based management system

NTP animal evidence Special characters

Hover-over field labels for more descriptive text. Fields marked with an asterisk (\*) are required.

General information

Reference\*  Additional references  Data class

NTP 2017\*

Study design

Exposure

Agent  Purity

Dosing route  Vehicle

Dosing regimen

Chemical characterization

Bias rating  Bias direction

Bias rationale

Dosing regimen

Bias rating  Bias direction

Bias rationale

Exposure duration sensitivity

Bias rating  Bias direction

Bias rationale

Dose/response sensitivity

Bias rating  Bias direction

Bias rationale

Outcome

Confounding

Analysis and reporting

Study judgment

Tables developed for both animal and human cancer studies

Accordion design for each study element

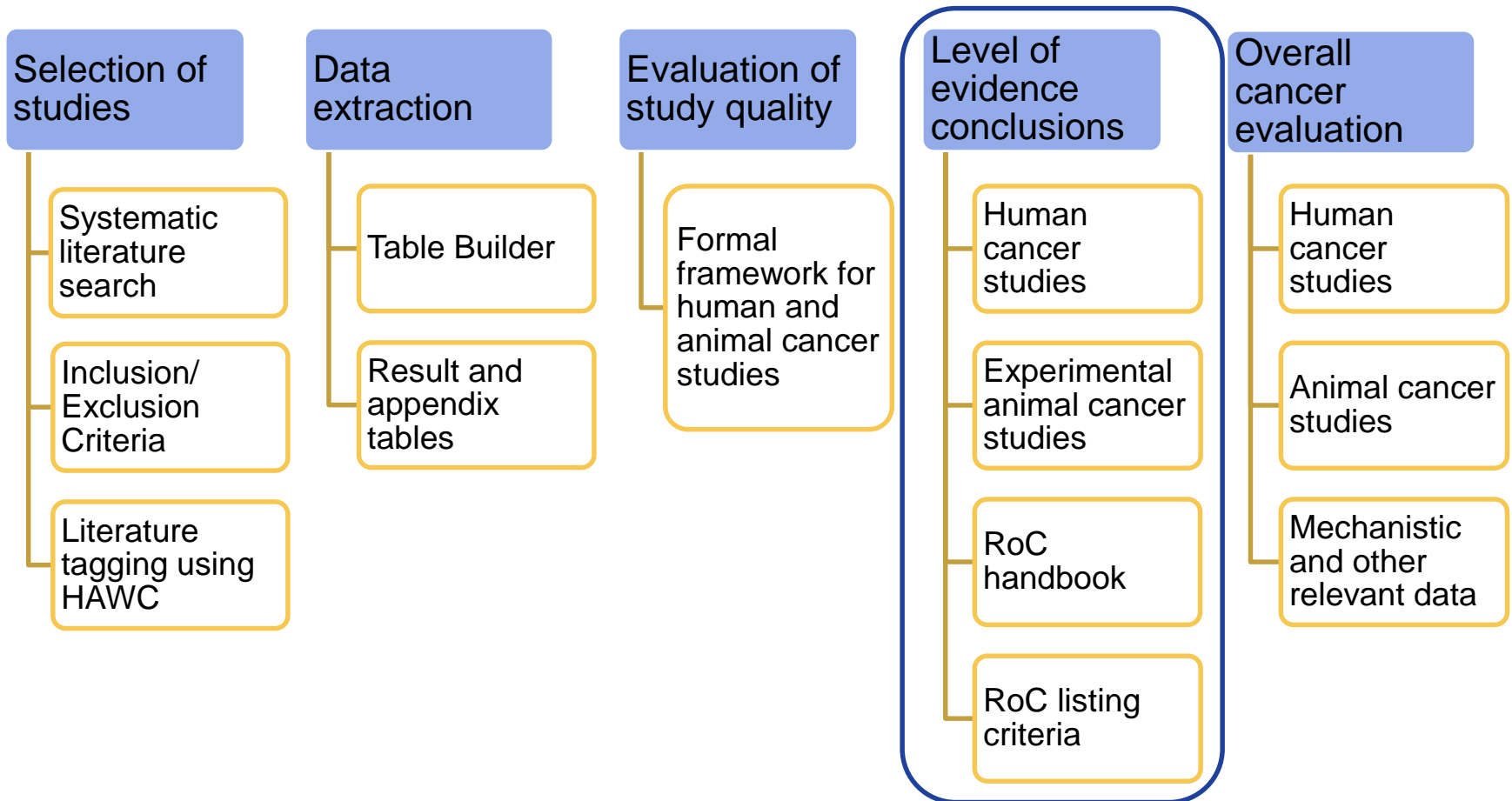
Result modules

Output into Word tables or Excel



# Evaluate Cancer Hazards

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





## Reach level of evidence from studies in experimental animals

### Sufficient evidence

- Increased incidence of malignant and/or a combination of malignant and benign tumors
  - In multiple species or at multiple tissue sites  
OR
  - By multiple routes of exposure  
OR
  - To an unusual degree with regard to incidence, site, or type of tumor, or age at onset



## 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

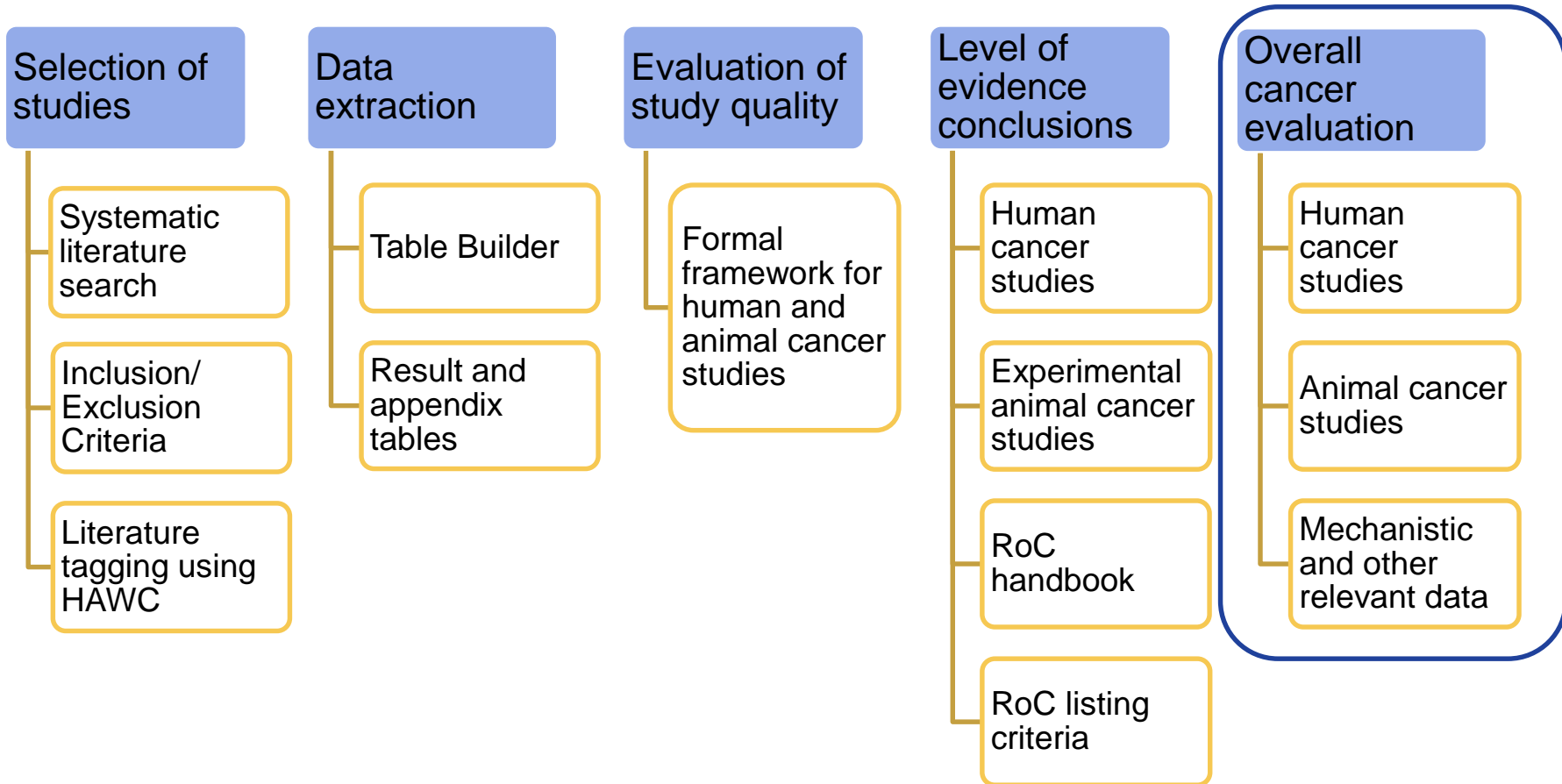
- Causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded

\*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.



# Evaluate Cancer Hazards

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





# 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.





## Process for the Preparation of the RoC

### Select substances for evaluation



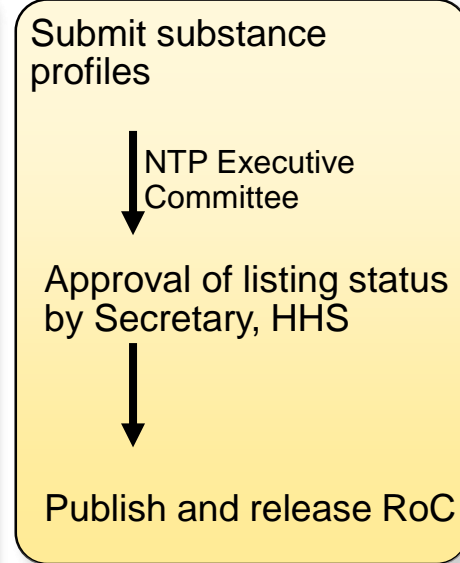
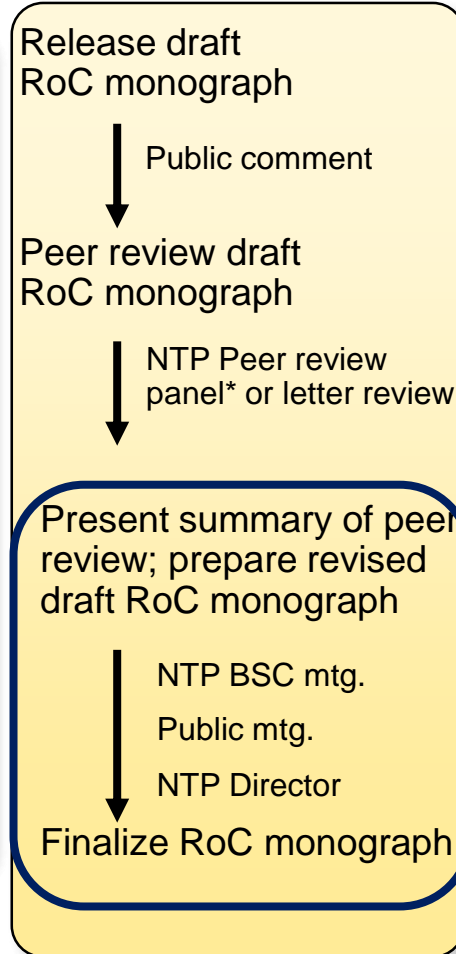
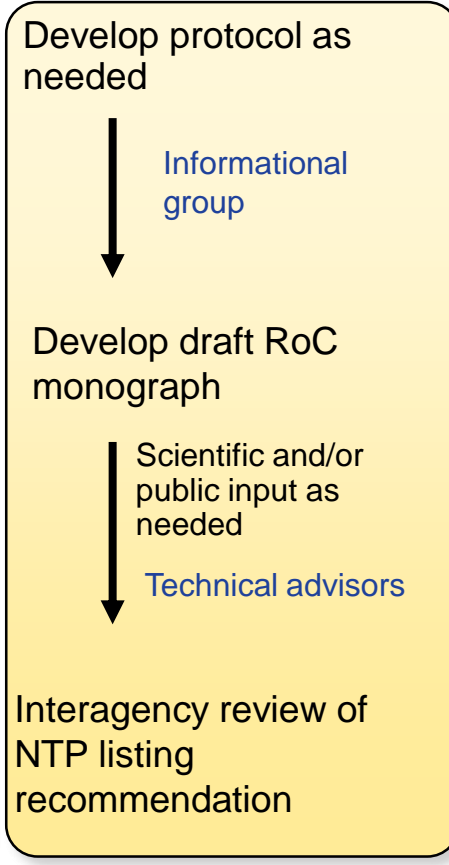
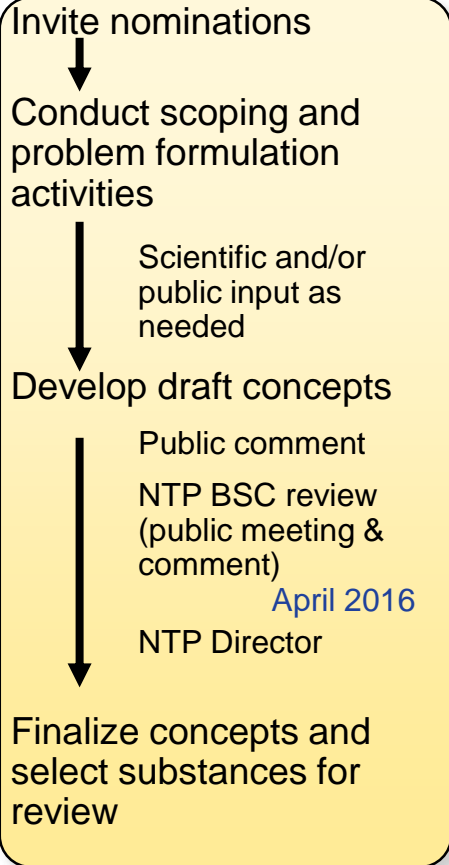
### Prepare draft RoC monographs



### Peer review and finalize RoC monographs



### Approve and release the RoC



#### Key

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\* Federally chartered advisory groups

# Acknowledgments

## Monograph Preparation

### ORoC/DNTP/NIEHS

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Ruth Lunn

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Alton Peters (ILS)

Whitney Arroyave (ILS)

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Susan E. Blaine (ICF)

Canden N. Byrd (ICF)

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### Other Support

Susan Dakin (contractor\*)

Andy Shapiro (DNTP/NIEHS): Table builder and HAWC

\*Contract Support



## Charge

Comment on whether the Draft RoC Monograph on Antimony Trioxide is technically correct, clearly stated, and objectively presented.

Provide opinion on whether there is currently or was in the past significant human exposure to antimony trioxide.

## Actions (votes)

Whether the scientific evidence supports the NTP's conclusions on the level of evidence for carcinogenicity from cancer studies in animals and human for antimony trioxide.

Whether the scientific evidence supports NTP's preliminary policy decision on the listing status of antimony trioxide in the RoC.