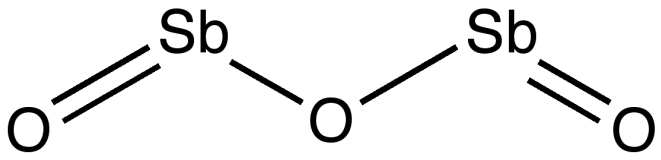
NTP
National Toxicology Program

Process for Preparing the Draft RoC Monograph on Antimony Trioxide



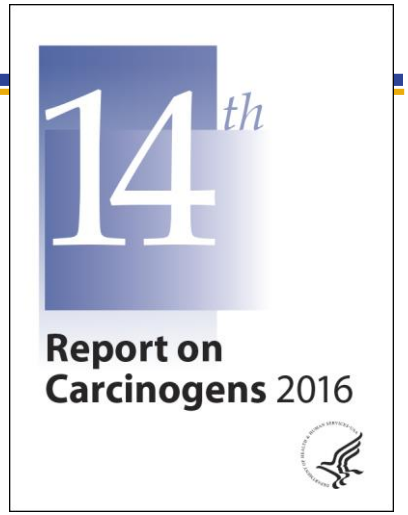
Ruth M. Lunn, DrPH
Office of the Report on Carcinogens

National Institute of Environmental Health Sciences
January 24, 2018

Outline

- Background on Report on Carcinogens (RoC)
- Select antimony trioxide for evaluation for the RoC
- Develop draft RoC monograph
- Evaluate cancer hazards and overview of 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

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

Develop draft RoC monograph

↓ Scientific and/or public input as needed

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

↓ NTP BSC (public meeting)

↓ NTP Director

Finalize RoC monograph

Publish and release RoC

Submit recommended listing status of new substances

↓ NTP Executive Committee

Secretary, HSS reviews and approves

↓

Publish and release RoC

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

Opportunity for Public Comment

Process for the Preparation of the RoC

Select substances for evaluation

Invite nominations

↓

Conduct scoping and problem formulation activities

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Develop draft concepts

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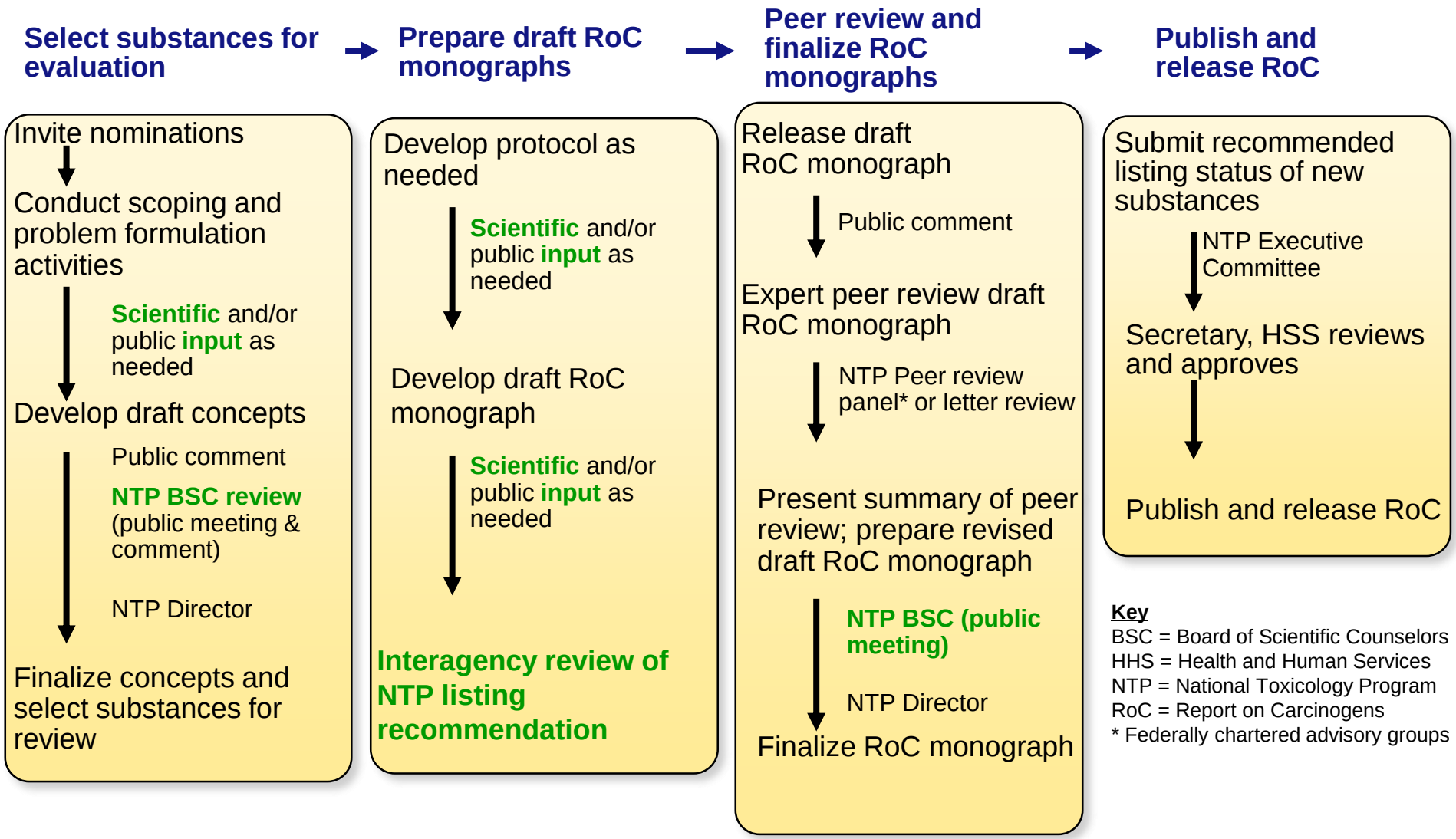
Process for the Preparation of the RoC



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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

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

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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

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

1 public comment:
International Antimony Association

Select Antimony Trioxide for Evaluation

Potential public health concern

Invite nominations

↓

Conduct scoping and problem formulation activities

↓ Request for Information September 2016

Develop draft concepts

↓ **2 public comments**
NTP BSC review December 2016

↓ NTP Director

Finalize concepts and select substances for review

- 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

Develop protocol and post on RoC website

Technical advisors

Develop draft RoC monograph

Technical advisors

Interagency review of NTP listing recommendation

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

Prepare Draft RoC Monograph

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

Evaluate Cancer Hazard

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

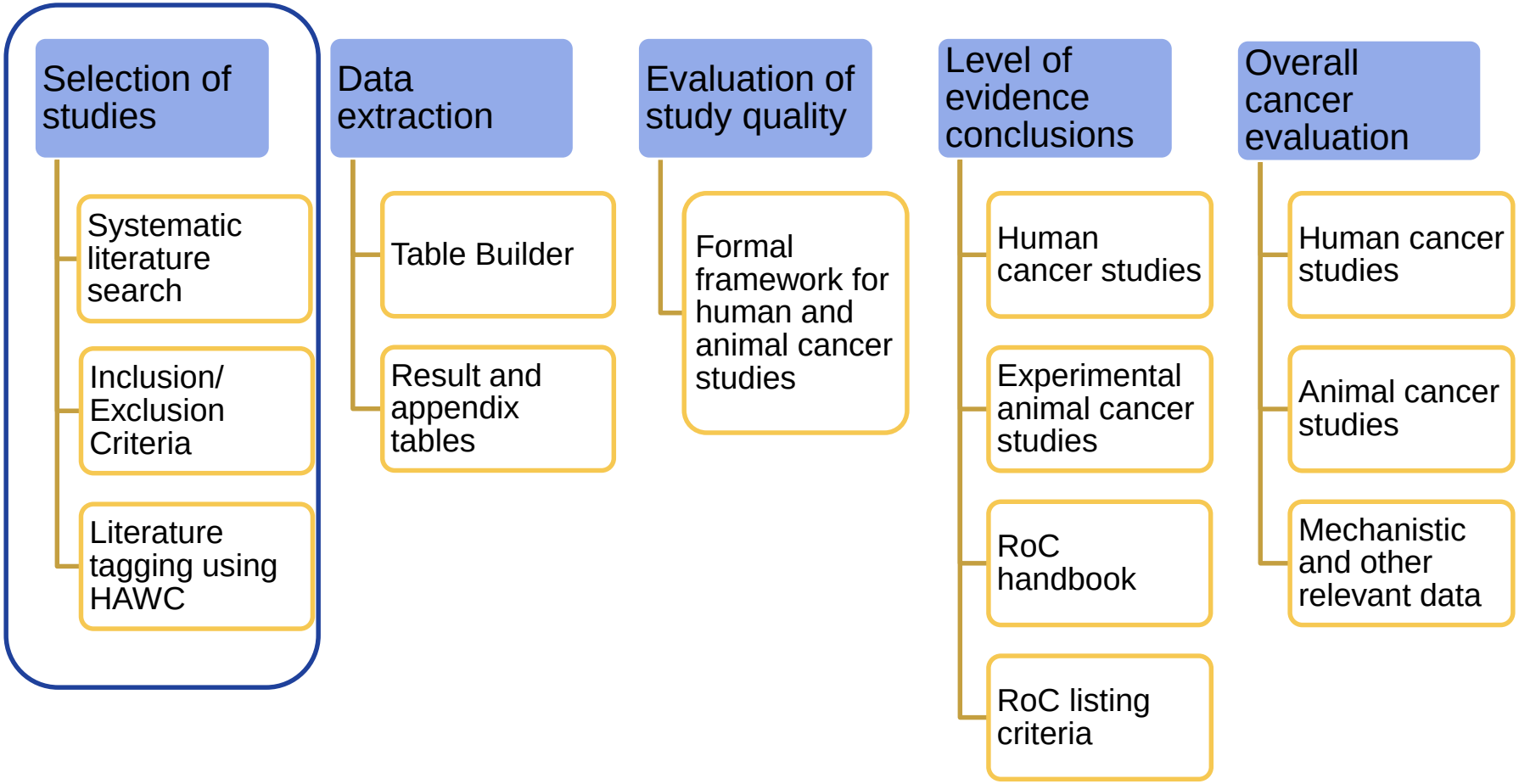
Framework for evaluating research question

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

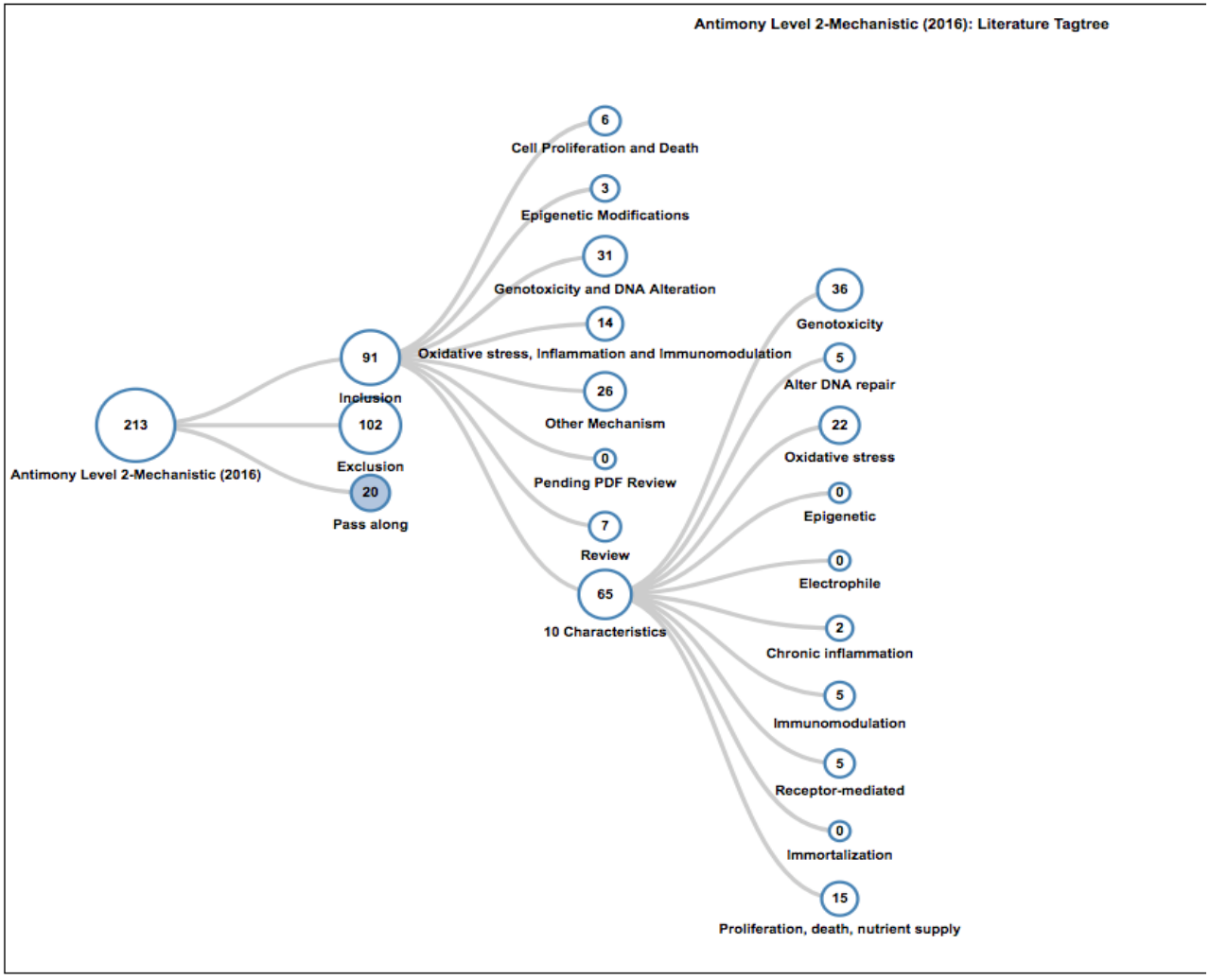
Analogous to ”PECO” Statement, P = population replaced by evidence stream, E = exposure, O = outcome, C= comparator – unexposed for all evidence streams, O = outcome

Evaluate Cancer Hazards

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



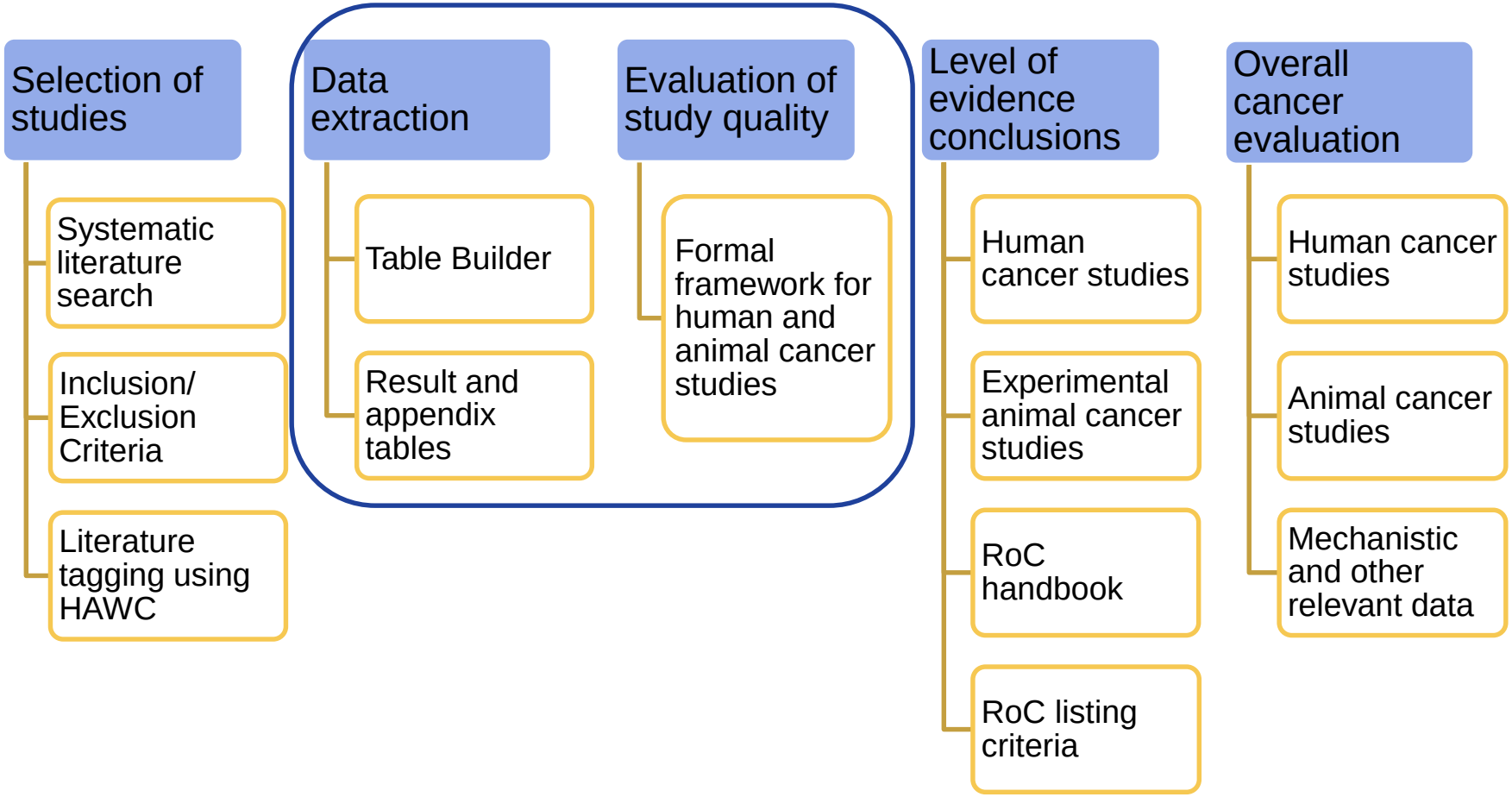
Literature tagging was done using HAWC



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

Tables developed for both animal and human cancer studies

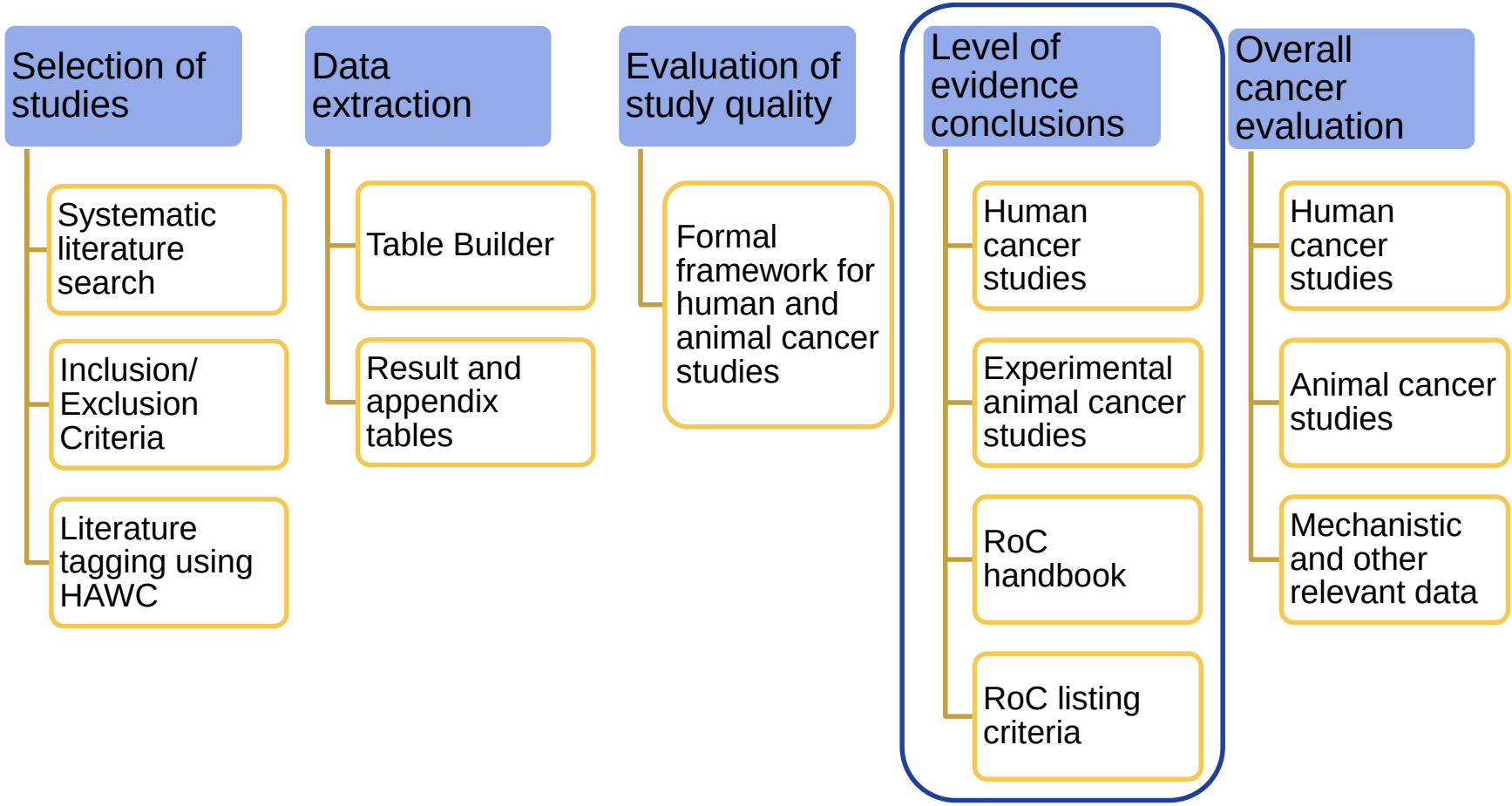
Accordion design for each study element

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

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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

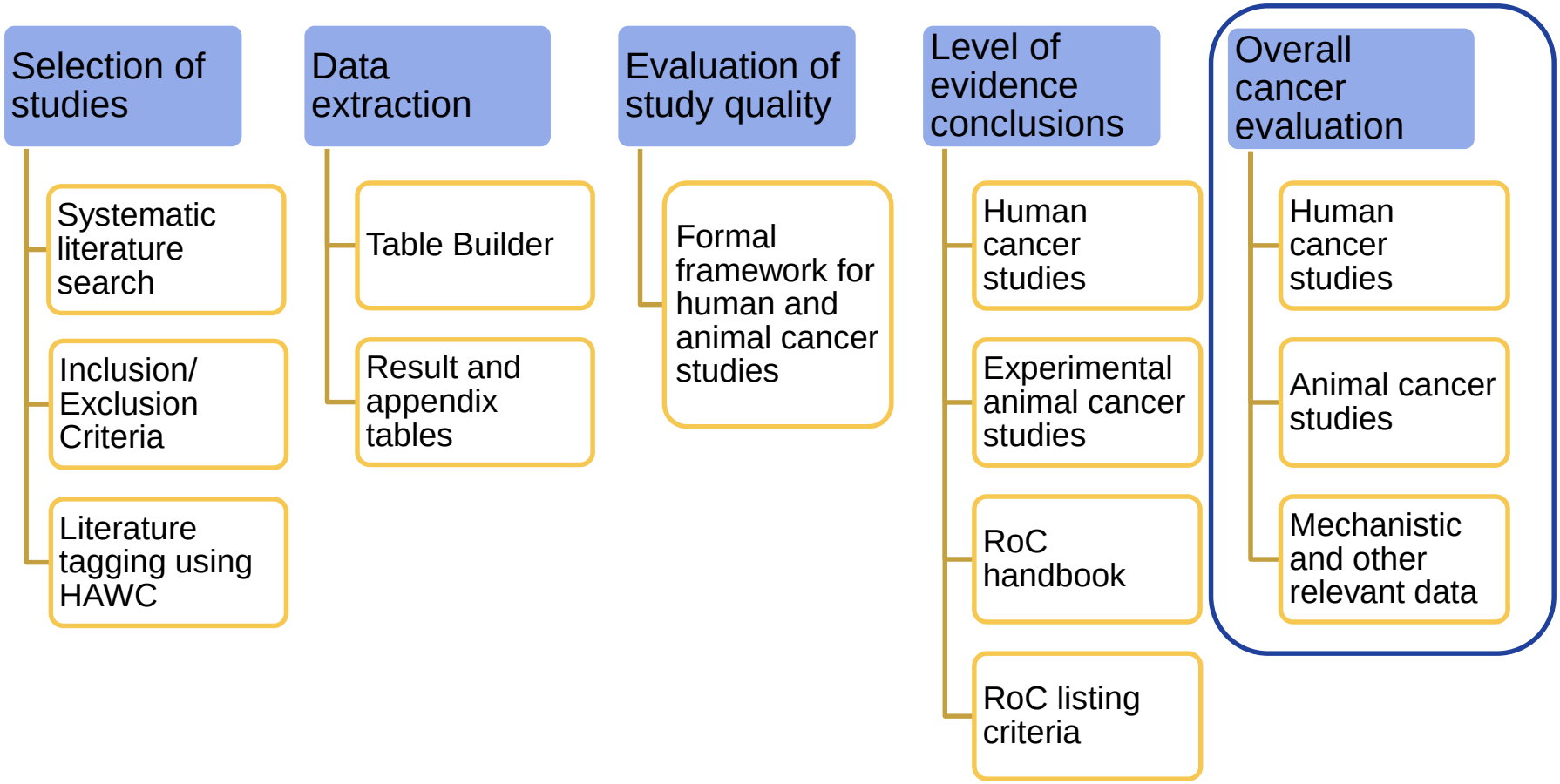
Limited evidence

- 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.

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.

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Process for the Preparation of the RoC

Select substances for evaluation

Invite nominations

↓

Conduct scoping and problem formulation activities

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Develop draft concepts

↓ Public comment

↓ NTP BSC review (public meeting & comment)

April 2016

↓ NTP Director

Finalize concepts and select substances for review

Prepare draft RoC monographs

Develop protocol as needed

↓ Informational group

Develop draft RoC monograph

↓ Scientific and/or public input as needed

↓ Technical advisors

Interagency review of NTP listing recommendation

Peer review and finalize RoC monographs

Release draft RoC monograph

↓ Public comment

Peer review draft RoC monograph

↓ NTP Peer review panel* or letter review

Present summary of peer review; prepare revised draft RoC monograph

↓ NTP BSC mtg.

↓ Public mtg.

↓ NTP Director

Finalize RoC monograph

Approve and release the RoC

Submit substance profiles

↓ NTP Executive Committee

Approval of listing status by Secretary, HHS

↓

Publish and release RoC

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Acknowledgments

Monograph Preparation

ORoC/DNTP/NIEHS

Amy Wang, Project Lead
Gloria Jahnke
Ruth Lunn
Suril Mehta

ILS and ICF, Inc.*

Sandy Garner (ILS)
Andy Ewens (ILS)
Joanne Trgovcich (ICF)
Alton Peters (ILS)
Whitney Arroyave (ILS)
Ella Darden (ILS)
Jessica Jeter (ILS)
Tracy Saunders (ILS)

Peer Review Meeting

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Government Agencies

Linda M. Sargent (CDC)
Kristina M. Hatlelid (CPSC)
Melanie C. Buser (ATSDR)
Yin-tak Woo (EPA)

Other Support

Susan Dakin (contractor*)
Andy Shapiro (DNTP/NIEHS): Table builder and HAWC

*Contract Support

Peer Review Meeting

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.