

# Process for Preparing the Draft RoC Monographs for 1-Bromopropane and Cumene

Ruth Lunn, DrPH  
National Institute of Environmental Health Sciences

NTP Peer Review Meeting  
March 21-22, 2013

# The Report on Carcinogens (RoC) is congressionally mandated

- Public Health Services Act, Section 301(b)(4) (1978, amended 1993)
  - Directs HHS Secretary to publish a list of carcinogens biennially
- Preparation of the RoC is delegated to the National Toxicology Program (NTP)
- Each edition of the report is cumulative
- Identifies substances that pose a cancer hazard for people in the United States
  - Lists substances as “*known*” or “*reasonably anticipated human carcinogens*”
  - Hazard identification activity
- Most recent edition, 12<sup>th</sup> RoC, was published in June 2011



# Terminology

- Candidate substance
  - Substance selected for formal review
- Concept document
  - Contains rationale and proposed approach for a substance's review
- Draft RoC monograph consists of two parts
  - Cancer evaluation component – contains the cancer assessment
  - Substance profile – contains the preliminary listing recommendation and key scientific evidence
- Report on Carcinogens
  - Compilation of substance profiles for each listed substance

# Process for Preparation of the RoC

## Nomination and Selection of Candidate Substances



## Scientific Evaluation of Candidate Substances



## Public Release and Peer Review of Draft RoC Monographs



## HHS Approval and Release of Latest Edition of the RoC

Invite nominations to the RoC

**Interagency review**

**Public comment**

Develop draft concept documents for substances proposed for evaluation

**Public comment**

Review of draft concept documents by NTP Board of Scientific Counselors\*  
(**public meeting, public comment**)

NTP Director

Select candidate substances

Prepare draft RoC Monograph for a candidate substance  
(initiate cancer evaluation component)

**External scientific input, as needed**  
(e.g., consultants, *ad hoc* presentations, expert panels\*)

**Public input**  
(e.g., listening session, comment)

**Interagency input**  
(complete cancer evaluation component and prepare draft substance profile)

**Interagency review**

Complete draft RoC Monograph

Release draft RoC Monograph

**Public comment**

**Peer review** of draft RoC Monograph by NTP Peer-Review Panel\*  
(**public meeting, public comment, peer-review report**)

Present information regarding the peer review and revised draft RoC Monograph to NTP **Board of Scientific Counselors**  
(**public meeting, public comment**)

NTP Director

Finalize RoC Monograph  
(cancer evaluation component and substance profile)

Submit recommended listing status for newly reviewed candidate substances

**NTP Executive Committee**

Approval of listing status by Secretary, HHS  
(transmit latest edition of RoC to Congress and release to the public)

### Key

HHS = Health and Human Services

NTP = National Toxicology Program

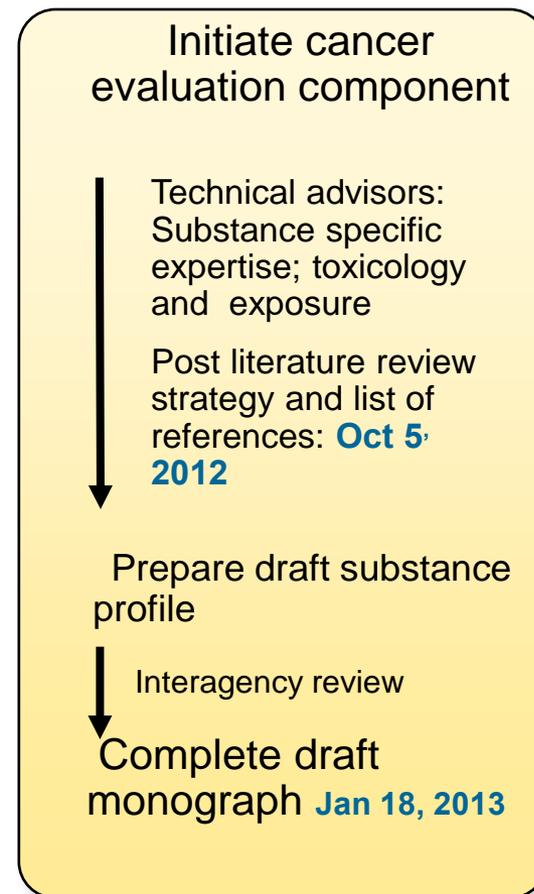
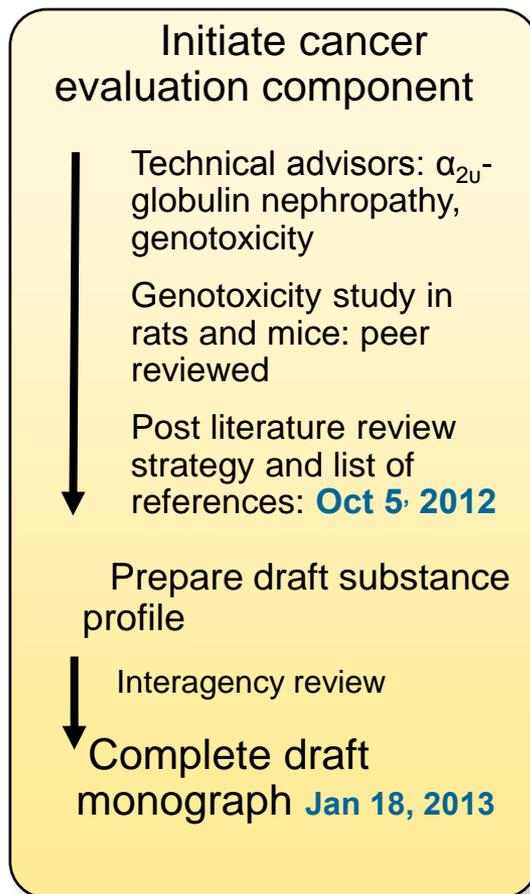
RoC = Report on Carcinogens

\* Federally chartered advisory groups

# 1-Bromopropane (1-BP) and cumene reviews: Completed Steps

## Cumene monograph

## 1-BP monograph



# Monograph contents: 1-Bromopropane and cumene

## Cancer Evaluation Component

Literature-based assessment

Properties and Human Exposure

Disposition and Toxicokinetics

Absorption, distribution, metabolism, excretion

Cancer Studies in Experimental Animals

Other Relevant Data

Genotoxicity, mechanisms

Overall Cancer Evaluation

Appendices

Literature search strategy, data tables, quality questions, background information

## Substance Profile

Listing recommendation

Carcinogenicity: Key studies

Properties

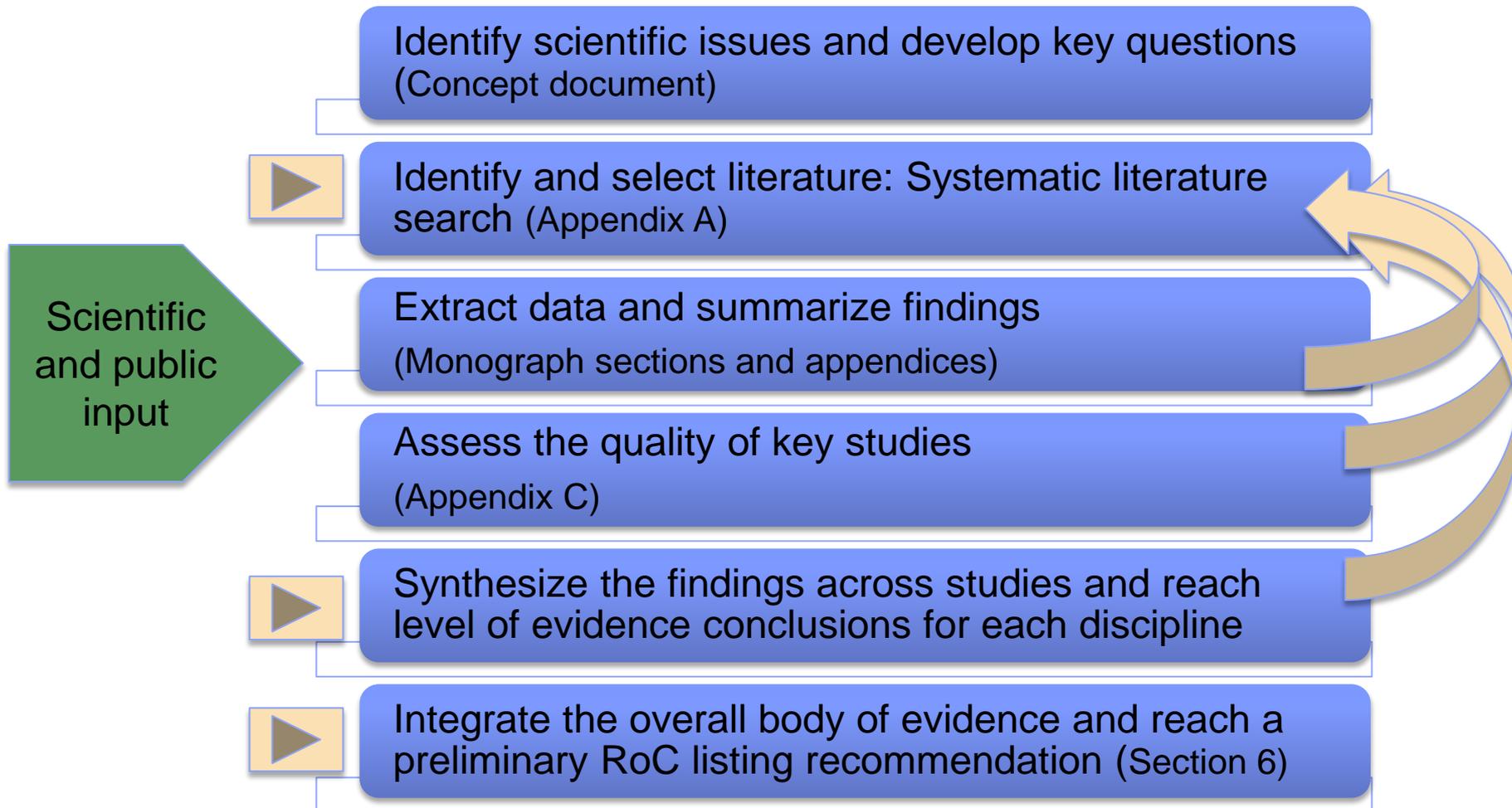
Use

Production

Exposure

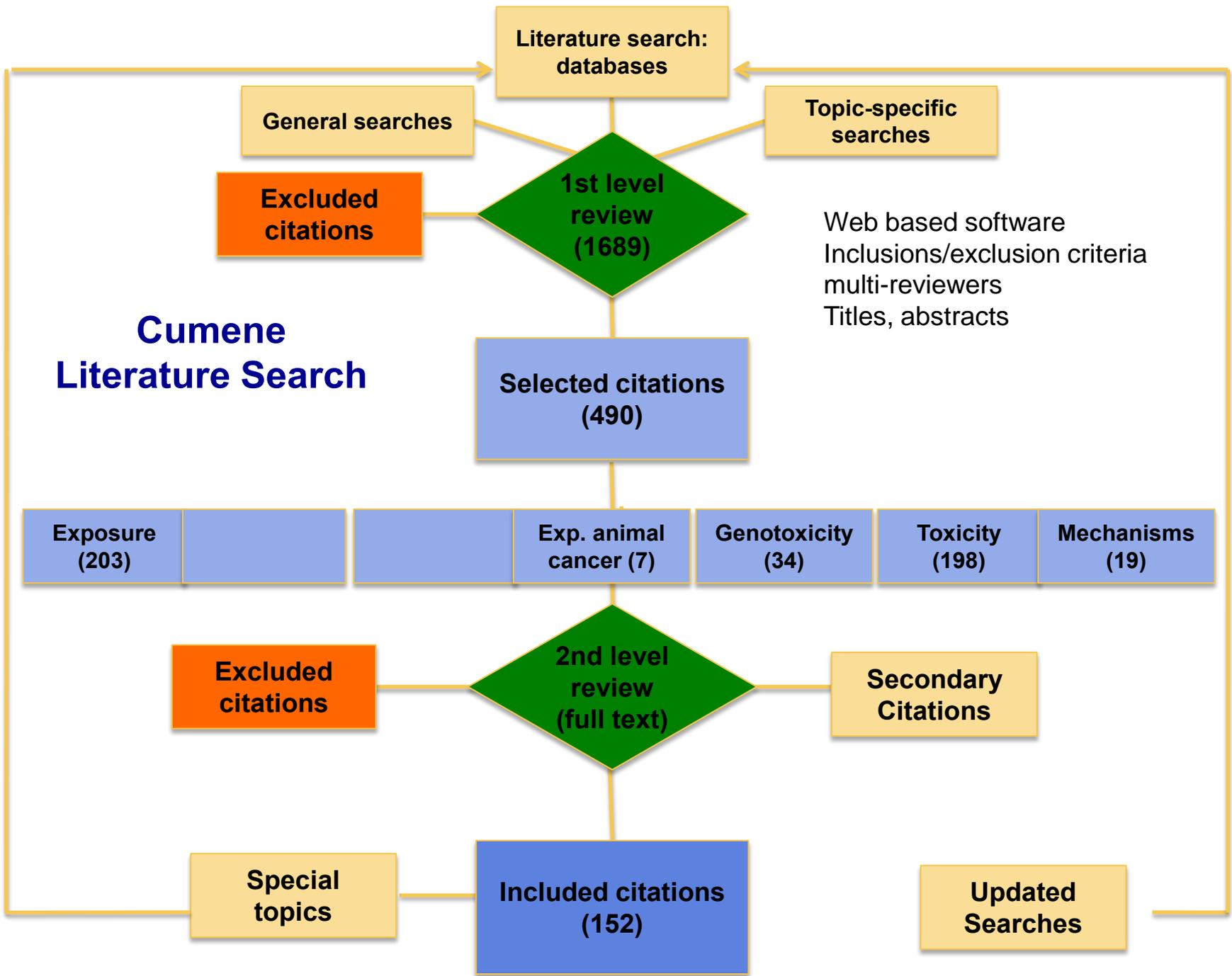
Regulations

# Methods for preparing the cancer evaluation component



# Systematic literature review: Search strategies

- Database searches
  - Searched multiple databases using a search strategy that combined search terms for the substance combined with search terms for the topic
  - Substance search terms: 1-BP or cumene synonyms, metabolites or exposure scenarios (e.g., spray and adhes\*)
  - Topic search terms: combination of multiple terms for specific endpoints (e.g., mutations) for the major topics (animal tumors, exposure, genotoxicity, human epidemiology studies, toxicity and mechanisms)
- General data searches
- QUOSA library searches
- Special topic-focused searches
- Secondary sources



# Cumene Literature Search

Literature search: databases

General searches

Topic-specific searches

1st level review (1689)

Excluded citations

Web based software  
Inclusions/exclusion criteria  
multi-reviewers  
Titles, abstracts

Selected citations (490)

Exposure (203)			Exp. animal cancer (7)	Genotoxicity (34)	Toxicity (198)	Mechanisms (19)
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2nd level review (full text)

Excluded citations

Secondary Citations

Included citations (152)

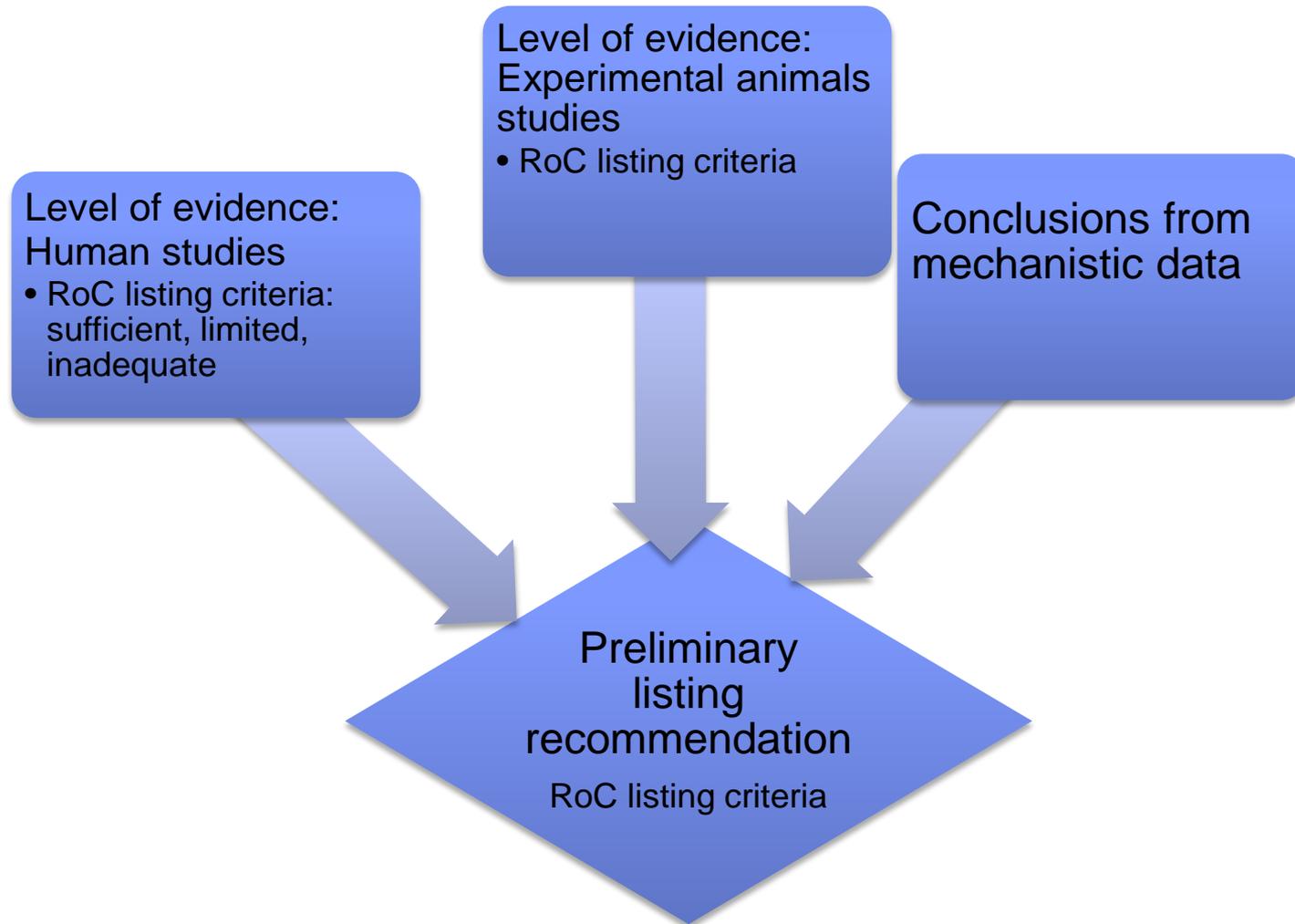
Special topics

Updated Searches

# Significant exposure for U.S. residents

- 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
- Information on exposed numbers of people is usually not available; typically exposure has been inferred from data on the following:
  - Use, production volume, occupational monitoring, environmental (occurrence), estimate intake, and biomonitoring
  - Because cancer has a long latency period, typically past exposure
- Reviewers are asked to use their judgment on whether the exposure information in the draft monographs supports NTP conclusions on U.S. exposure

# Reaching a preliminary listing recommendation



## RoC listing criterion: Sufficient evidence from studies in experimental animals

Increased incidence of malignant and/or a combination of malignant and benign tumors

- In multiple species or at multiple tissue sites
- By multiple routes of exposure
- To an unusual degree with regard to incidence, site, or type of tumor, or age at onset

# Evaluation of mechanistic data

- What are the potential mode of actions (MOA)?
- What is the level of evidence for the potential MOA?
- What evidence do we have in humans?

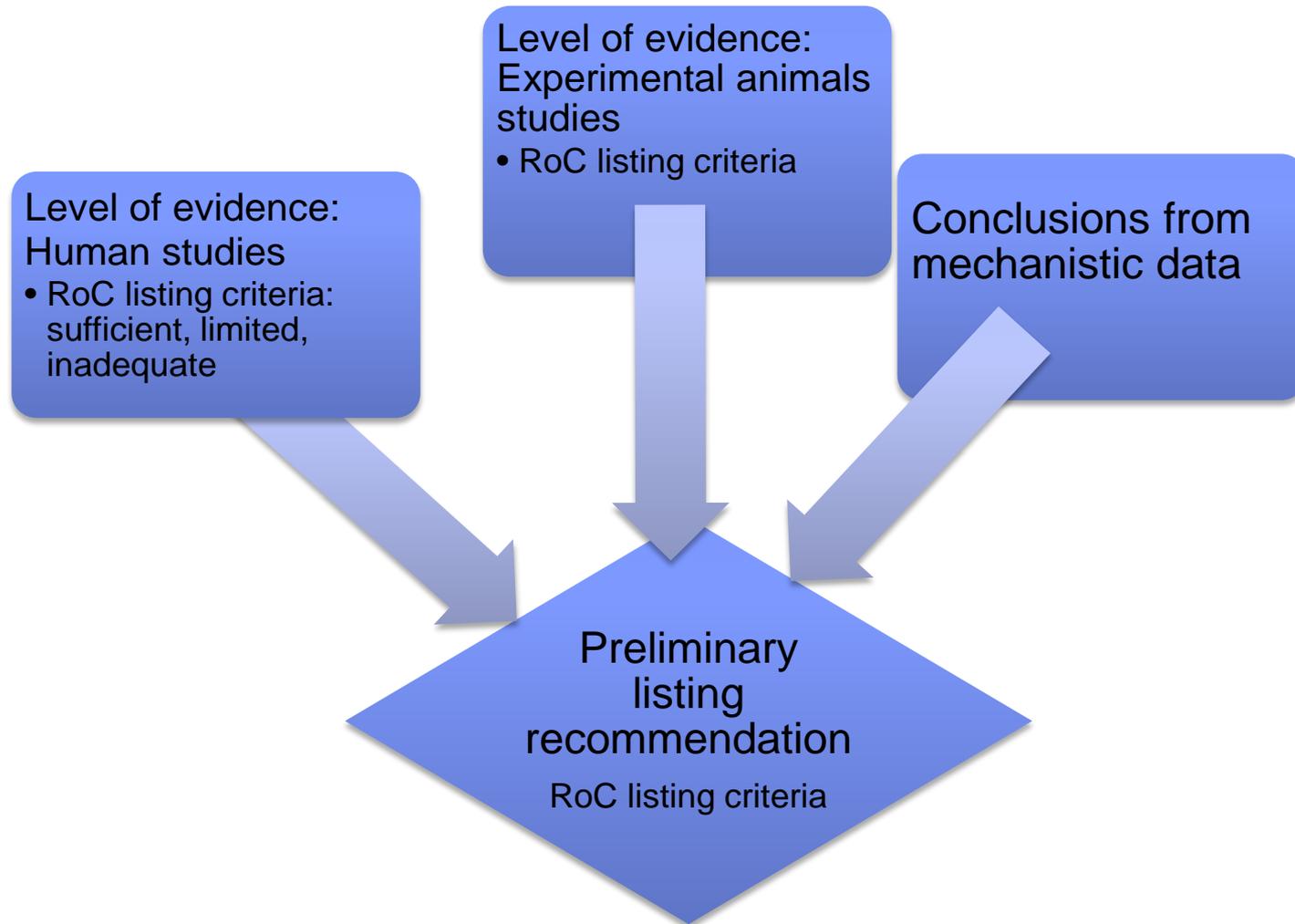


## RoC listing criteria: *Known to be a human carcinogen*

There is sufficient evidence of carcinogenicity from studies in humans\*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

\*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.

# Reaching a preliminary listing recommendation



## RoC Listing Criteria: *Reasonably Anticipated to be Human Carcinogen*

Limited evidence from studies in humans\*

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

OR

Sufficient evidence of carcinogenicity from studies in experimental animals

OR

Less than sufficient evidence in human or experimental animal

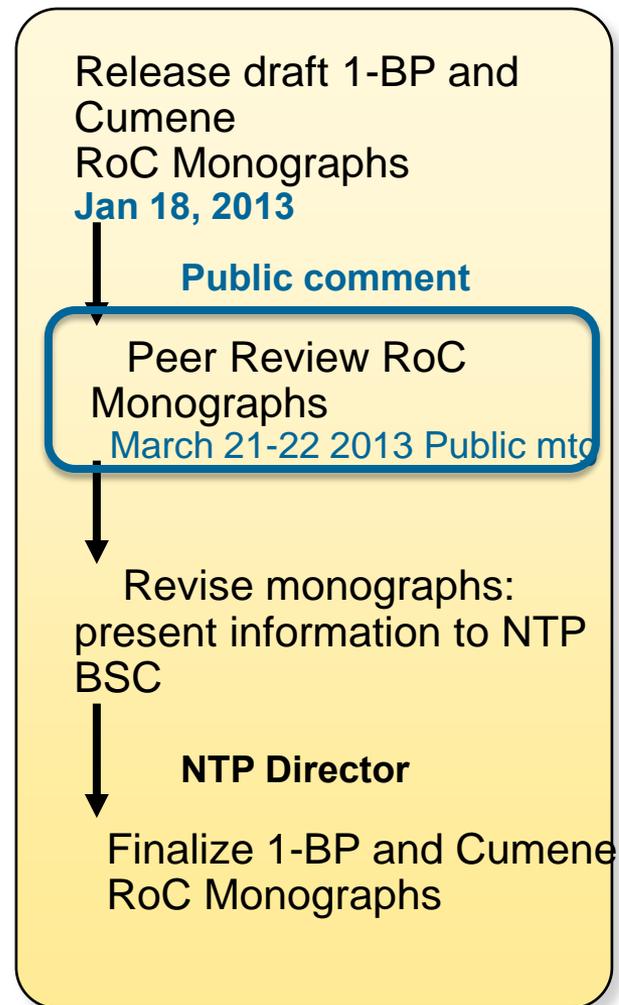
- Agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous RoC as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen,
- **OR** there is **convincing** relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

## RoC Listing Criteria: Guidance (final paragraph)

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are **compelling** data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

# 1-Bromopropane and cumene review: Charge

- To comment on the draft cancer evaluation component, specifically, whether it is technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the listing criteria.
- To comment on the draft substance profile, specifically, whether the scientific justification presented in the substance profile supports the NTP's preliminary policy decision on the RoC listing status of cumene or 1-BP .



## Peer review panel: Actions (votes)

1. Whether the scientific evidence supports the NTP's conclusion on the level of evidence for carcinogenicity from experimental animal studies on cumene or 1-BP
2. Whether the scientific evidence supports the NTP's preliminary listing decision for cumene or 1-BP in the RoC.

# 1-Bromopropane and cumene reviews: Next steps

## Nomination and Selection of Candidate Substances



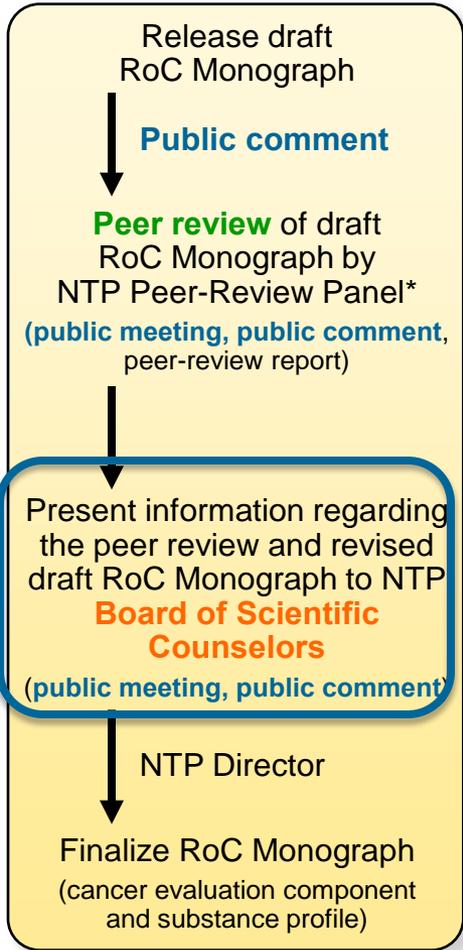
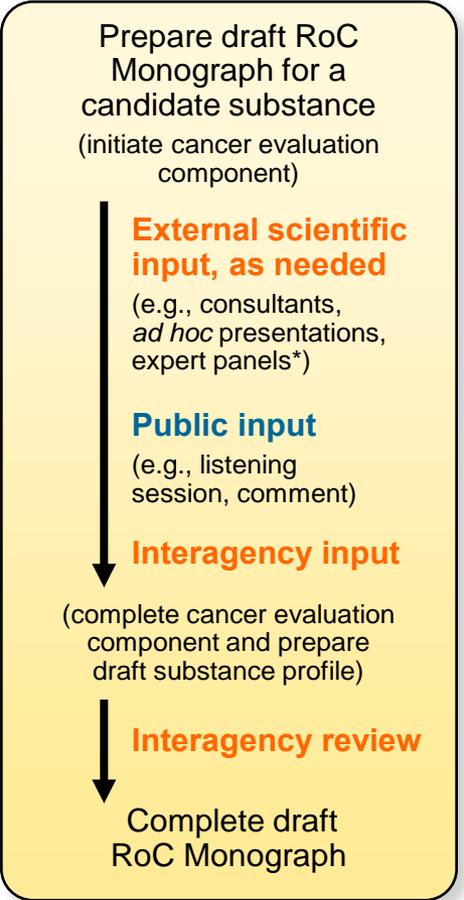
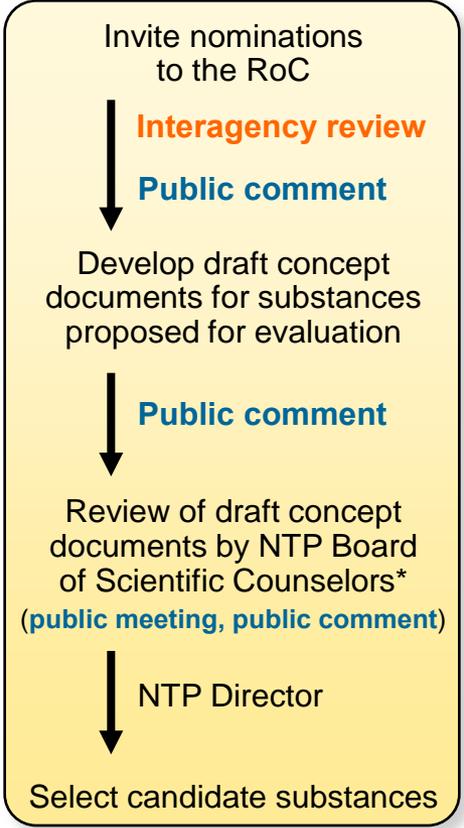
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