Draft RoC Monograph on Trichloroethylene (TCE)

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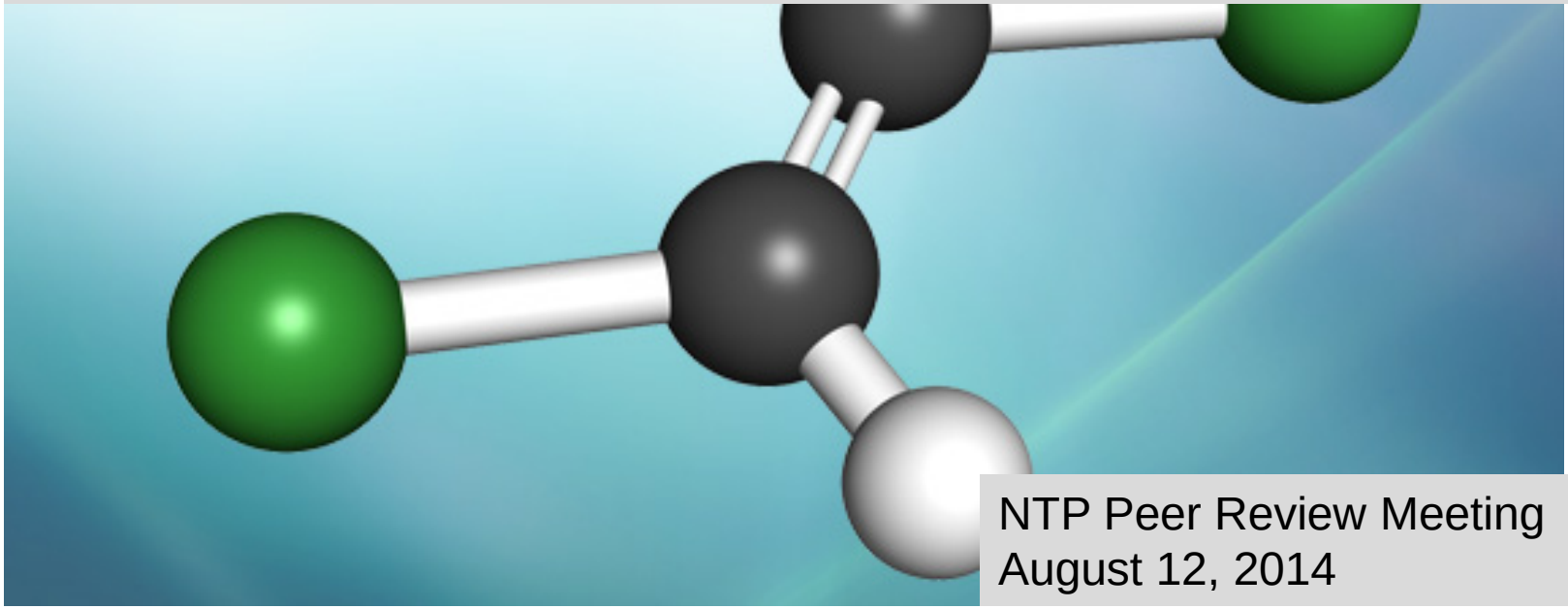
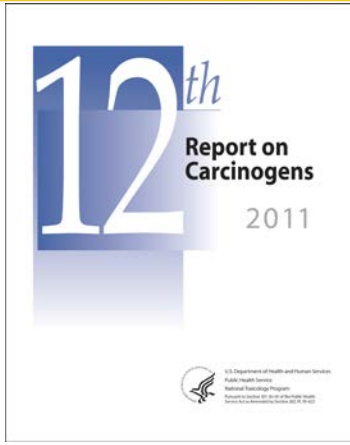


NTP Peer Review Meeting
August 12, 2014

Outline

- Background on the RoC and rationale for selecting TCE as a candidate substance
- RoC process: Current and completed steps
- RoC monograph: Approach and contents
- RoC monograph: Methods
- RoC listing criteria
- Peer review charge
- Next steps

The Report on Carcinogens (RoC) is congressionally mandated



- Public Health Service Act, Section 301(b)(4) (1978, amended 1993)
  - Directs HHS Secretary to publish a list of carcinogens
- Identifies substances that pose a cancer hazard for people in the United States
  - Lists substances as "*known*" or *"reasonably anticipated human carcinogens"*
- National Toxicology Program (NTP) prepares the RoC for the Secretary
- Each edition of the report is cumulative
  - Most recent edition, 12th RoC, was published in June 2011

http://ntp.niehs.nih.gov/go/roc

NTP selected TCE as a candidate substance

- TCE is a chlorinated alkene used primarily as a metal degreaser in the past; recent use is mainly for hydrofluorocarbon production
  - TCE is also ubiquitous in the atmosphere, soil, ground, surface and drinking water, and in food
- Currently listed in the RoC as *reasonably anticipated to be a human carcinogen*
- Adequate database of cancer studies published since the last RoC review

http://ntp.niehs.nih.gov/go/37899

Terminology

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

Process for preparation of the RoC

Nomination and Selection of Candidate Substances

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**)

June 2012

↓ NTP Director

Select candidate substances

Scientific Evaluation of 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

Public Release and Peer Review of Draft RoC Monographs

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)

HHS Approval and Release of Latest Edition of the RoC

Submit recommended listing status for newly reviewed candidate substances

↓ NTP Executive Committee

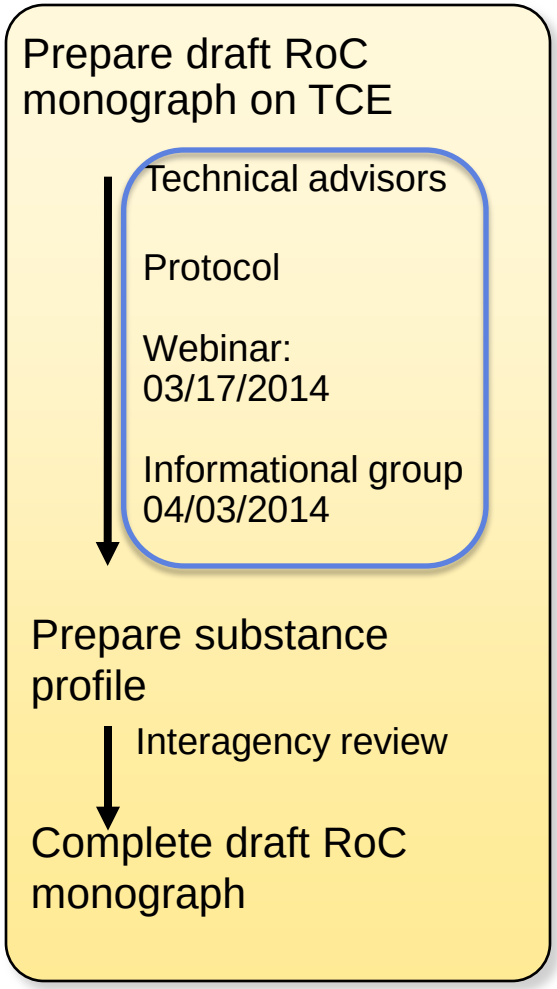
Approval of listing status by Secretary, HHS

(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

Completed steps: Scientific evaluation of TCE



- Public webinar

  "Human Cancer Studies on Exposure to Trichloroethylene (TCE): Methods Used to Assess Exposure and Cancer Outcomes."

- Informational group

  "Evaluation of Trichloroethylene-induced immune effects and their role in its potential carcinogenicity."

TCE draft RoC monograph: Approach

- Three cancer sites: Kidney, liver, and non-Hodgkin lymphoma (NHL) and related subtypes
  - Identified by authoritative reviews as cancers of interest
  - Tissue site concordance in experimental animals
- Evidence in experimental animals
  - No new studies identified that would question the conclusions of the 12th RoC of sufficient evidence
  - Cancer findings included in the mechanistic evaluation but no reevaluation of the level of evidence
- Exposure information was updated in the substance profile
- Mechanistic and other related data
  - Utilizes information from several authoritative reviews supplemented by primary literature for recent or key studies

Sufficient evidence of carcinogenicity from studies in experimental animals (12th RoC, 2011)

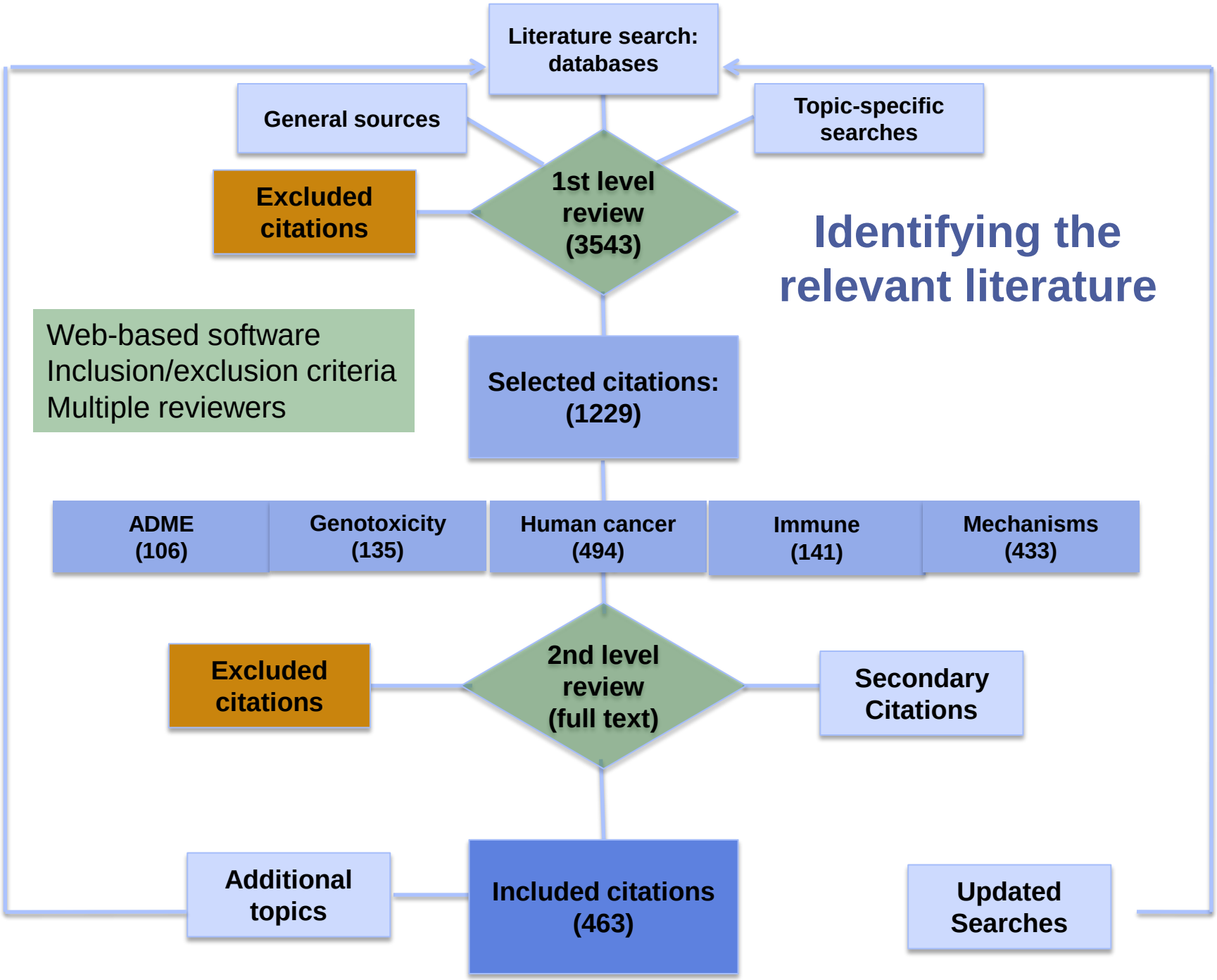
- Trichloroethylene caused tumors in mice and rats at several different tissue sites by two different routes of exposure
  - Liver tumors in mice: inhalation exposure and gavage
  - Lung tumors in mice: inhalation exposure
  - Lymphoma in female mice: inhalation exposure
  - Kidney tumors in male rats: inhalation exposure and gavage
  - Testicular tumors in male rats: inhalation exposure and gavage

Cancer hazard evaluation component contents

ADME/Toxicokinetics	Summary of data on absorption, distribution, and excretion
	More detailed discussion on metabolism
Relevant genetic effects	Genetic and related effects
Human cancer studies	Overview of studies
	Assessment of study quality
Assessments: 3 cancer sites	Human cancer hazard assessment
	Evaluation of mechanistic and related data
Final conclusions	Preliminary level of evidence
	Preliminary listing recommendation
Appendices	Literature search strategy
	Human cancer studies: Study description/quality evaluation
	Evidence-based tables: Genetic and related effects
	Evidence-based tables: Immune effects

Literature search: TCE protocol

Topic	Date/limits
Human exposure	Authoritative reviews Other reviews since 2009
Genotoxicity Mechanisms	Authoritative reviews Primary literature since 2009 and key studies No limits for some issues such as immune effects
Human studies	No time limits


Literature search: databases
General sources
Topic-specific searches
Excluded citations
1st level review (3543)
Identifying the relevant literature
Web-based software
Inclusion/exclusion criteria
Multiple reviewers
Selected citations: (1229)
ADME (106)
Genotoxicity (135)
Human cancer (494)
Immune (141)
Mechanisms (433)
Excluded citations
2nd level review (full text)
Secondary Citations
Additional topics
Included citations (463)
Updated Searches

Assessing study quality and evaluating evidence

- Human cancer studies (protocol)
  - Assessing the quality of the human cancer studies
  - Evaluating the level of evidence for the carcinogenicity of TCE
    - Protocol discusses factors (such as exposure-response relationships, consistency) considered in integrating the evidence across studies for each cancer site and applying the RoC listing criteria
- Mechanistic data
  - Most of the time we have limited data
  - Consideration of whether there are convincing data that a substance operates by a mechanism that would cause cancer in humans
  - Consideration of whether there are compelling data that a substance causes cancer by a mechanism that would not occur in humans

Level of evidence conclusion: Carcinogenicity from studies in humans

RoC listing criteria

- Sufficient evidence from studies in humans*: Causal relationship between exposure to the agent, substance, or mixture, and human cancer
- 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

*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 listing 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

  - Less than sufficient evidence in humans or experimental animals
    - 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

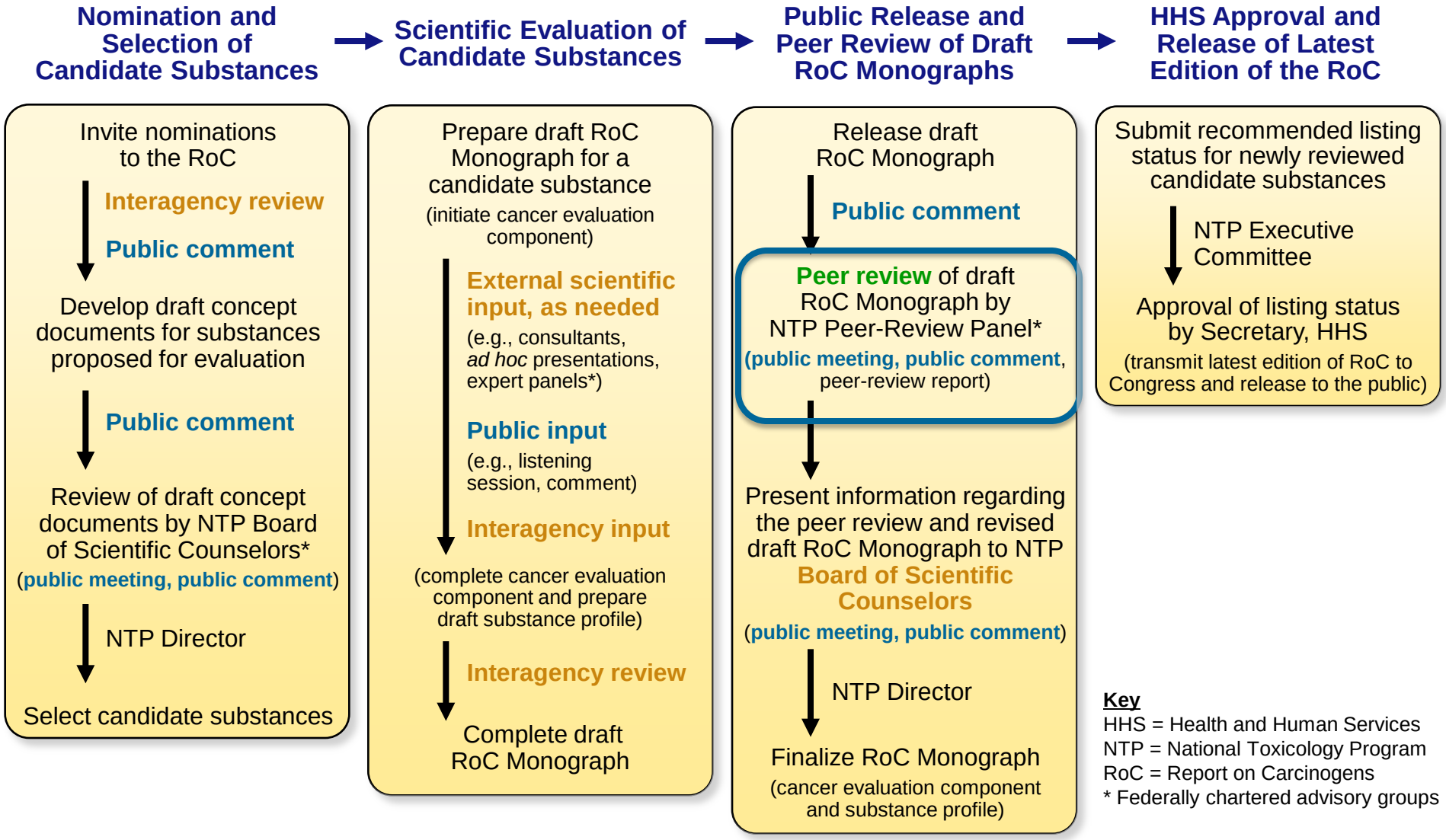
    OR

    - **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.

Current step



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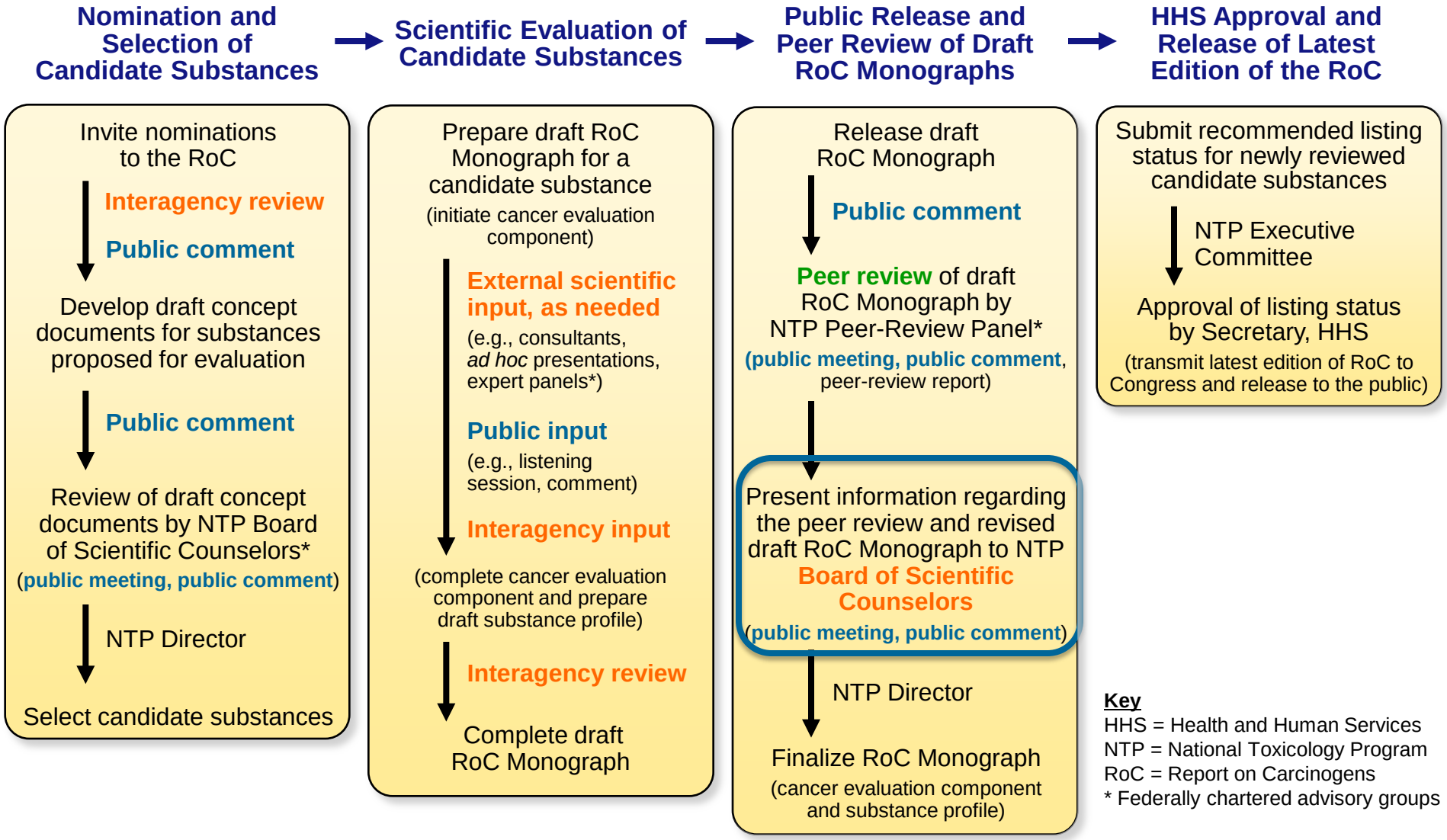
Trichloroethylene peer review

- **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 evidence supports the NTP's preliminary listing decision of the substance in the RoC
- **Actions (votes)**
  - Whether the scientific evidence supports the NTP's conclusion on the level of evidence for carcinogenicity from cancer studies in humans for each cancer site
  - Whether the scientific evidence supports the NTP's preliminary policy decision on the RoC listing status of the substance

Next steps



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