

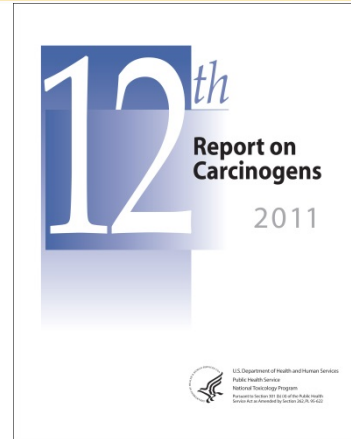
Preparation of the Draft RoC Monographs: *ortho*-Toluidine Pentachlorophenol and By-Products of its Synthesis

Ruth Lunn, DrPH
National Institute of Environmental Health Sciences

NTP Peer Review Meeting
December 12-13, 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
- Preparation of the RoC is delegated to the National Toxicology Program (NTP)
- Identifies substances that pose a cancer hazard for people in the United States
 - Lists substances as “*known*” or “*reasonably anticipated human carcinogens*”
- Each edition of the report is cumulative
 - Most recent edition, 12th 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 scientific evidence that is key to the recommendation
- 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

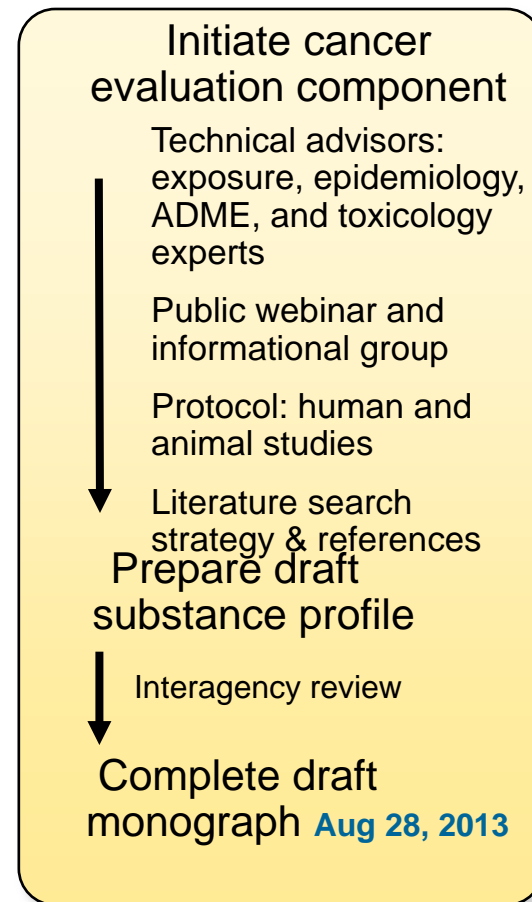
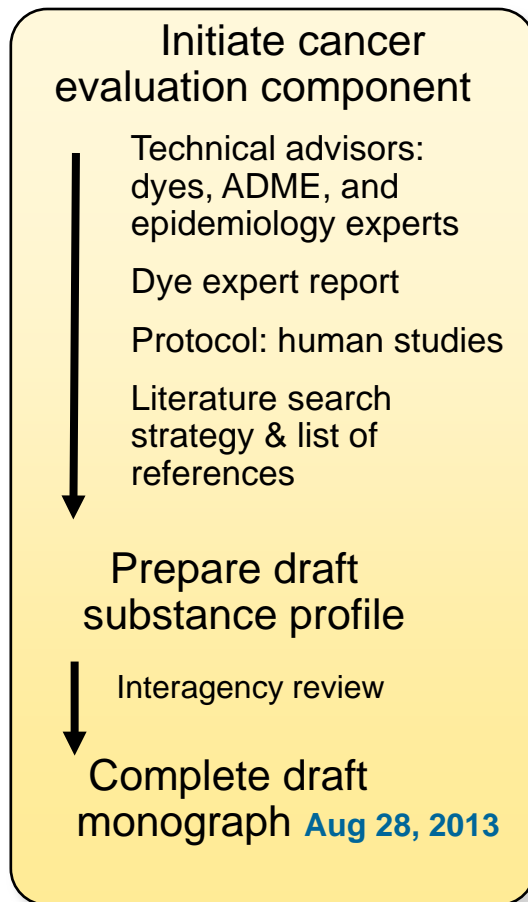
RoC = Report on Carcinogens

* Federally chartered advisory groups

ortho-Toluidine and pentachlorophenol* reviews: Completed steps

ortho-toluidine monograph

pentachlorophenol monograph



*Includes by-products of its synthesis

Monograph contents: *o*-Toluidine and pentachlorophenol

Cancer evaluation component

Literature-based assessment

Properties and Human Exposure

Disposition and Toxicokinetics

Absorption, distribution, metabolism, excretion

Cancer Studies in Humans

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

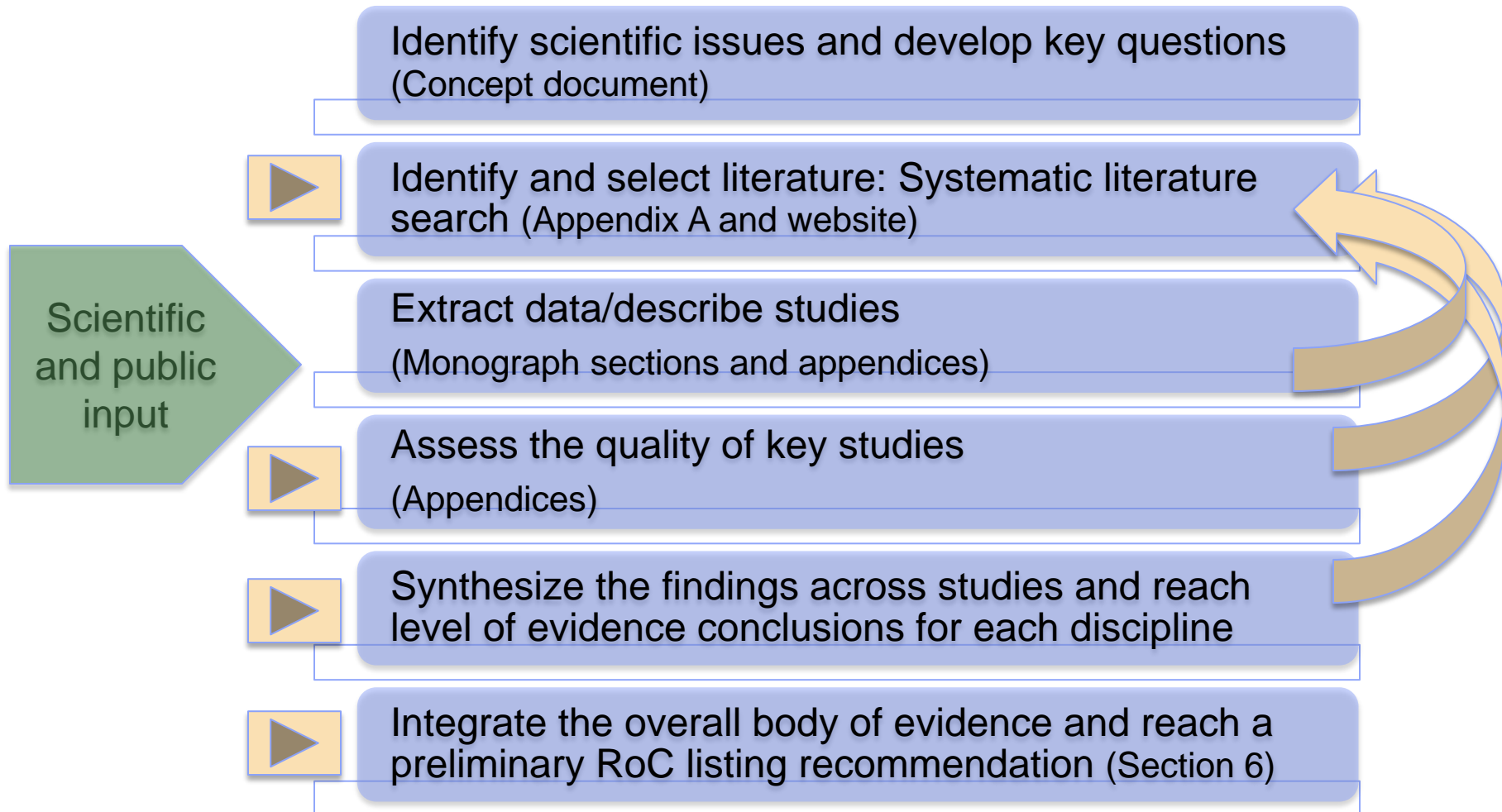
Use

Production

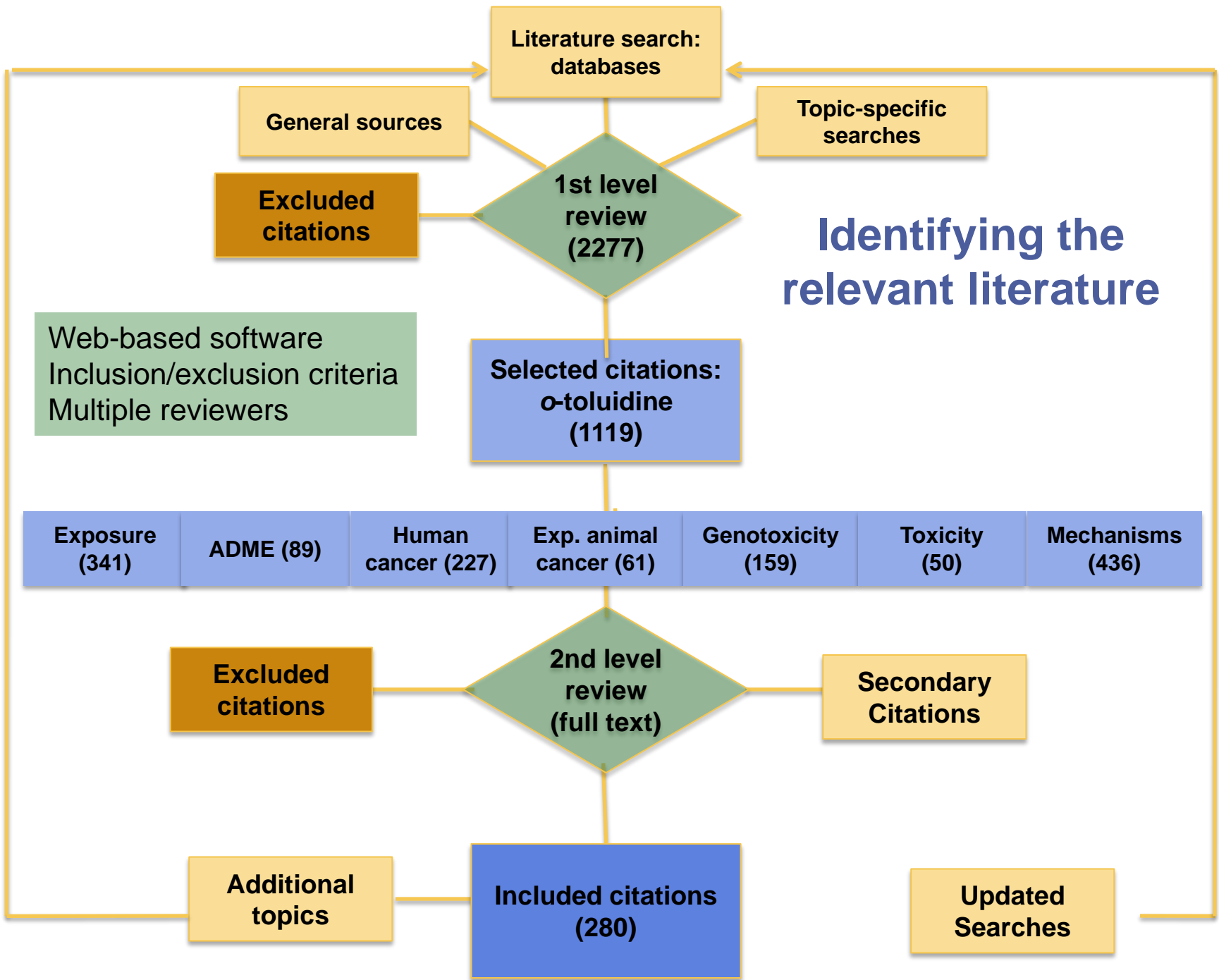
Exposure

Regulations

Preparing the cancer evaluation component



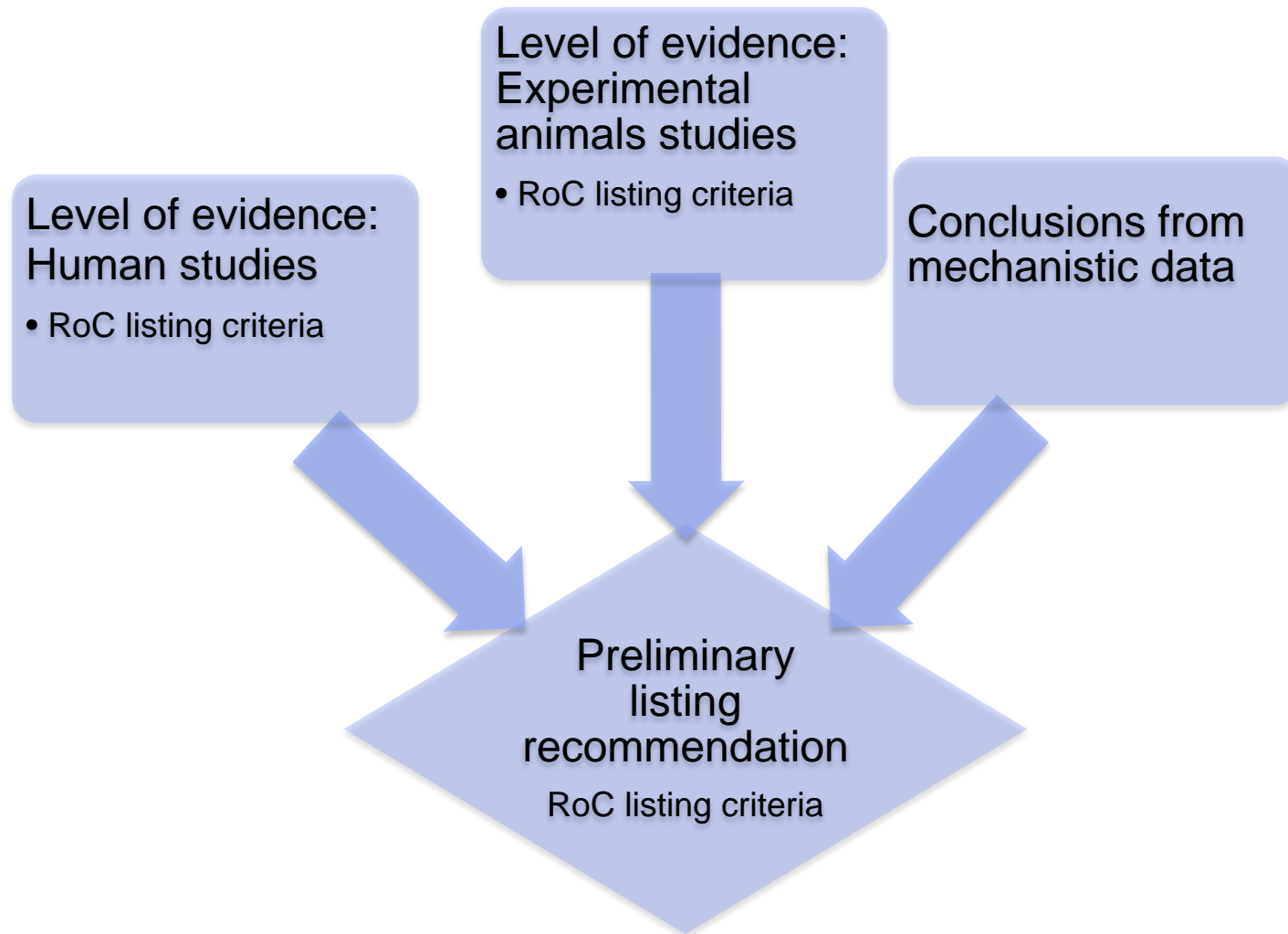
Identifying the relevant literature



Assessing study quality

- Methods developed for evaluating study quality for the cancer studies in humans and experimental animals (Appendices)
- Protocols posted on each candidate substance's website
 - Human cancer studies for both substances
 - Cancer studies in experimental animals for pentachlorophenol

Reaching a preliminary listing recommendation



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

Reaching a level of evidence conclusion of 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

Reaching a level of evidence carcinogenicity conclusion from studies in experimental animals

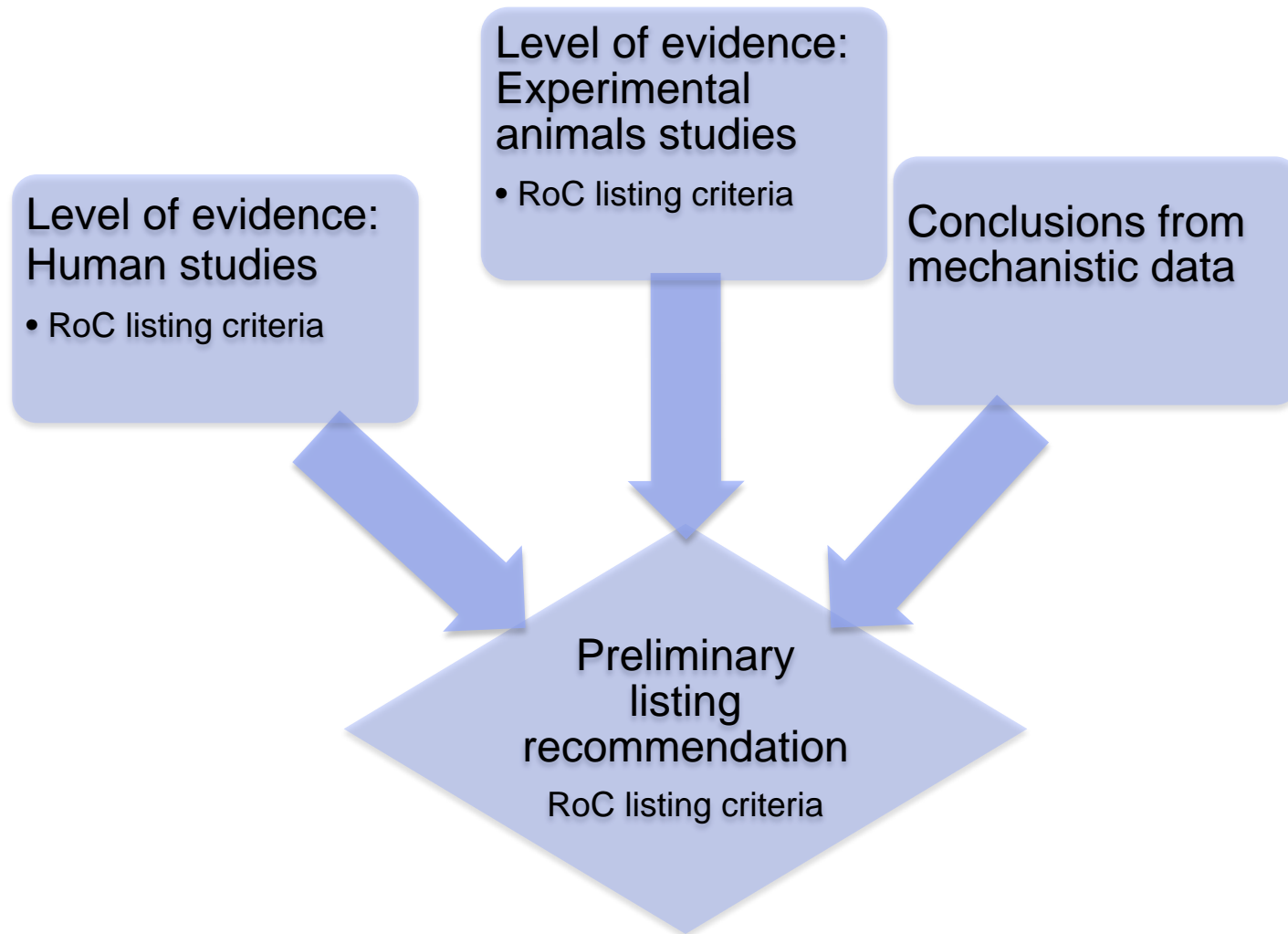
Sufficient evidence from studies in experimental animals defined by RoC listing criteria

- 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

Evaluating and using the mechanistic data

- What are the potential mechanisms?
- Does the agent belong to a well-defined, structurally related class of substances whose members are listed in the RoC?
- What evidence do we have in humans and animals?
- How do we use mechanistic data?
 - Most of the time we have limited data
 - Is there convincing data that a substance operates by a mechanism that would cause cancer in humans?
 - Is there compelling data that a substance causes cancer by a mechanism that would not occur in humans?

Reaching a preliminary listing recommendation



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.

ortho-Toluidine and pentachlorophenol reviews: Current step

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

***ortho*-Toluidine and pentachlorophenol peer reviews**

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

- Whether the scientific evidence supports the NTP's conclusion on the level of evidence for carcinogenicity from cancer studies in humans
- Whether the scientific evidence supports the NTP's conclusion on the level of evidence for carcinogenicity from experimental animal studies
- Whether the scientific evidence supports the NTP's preliminary policy decision on the RoC listing status of the substance

ortho-Toluidine and pentachlorophenol reviews: Next steps

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