



NTP

National Toxicology Program

Report on the Draft RoC Monograph Peer-Review Panel Meeting March 21-22, 2013

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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

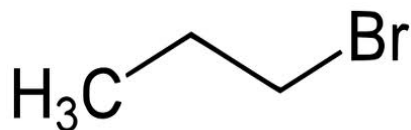
NTP BSC Meeting: Objective

- To provide the BSC with information regarding the peer review of the draft RoC monographs for 1-bromopropane and cumene (March 21-22, 2013 Meeting). For each substance, this includes information on:
 - Steps in the review process, public comments and development of the RoC monograph.
 - Peer review-panel meeting, including the members, charge and the panel's recommendations (Panel Report).
 - NTP response to the panel recommendations.

1-Bromopropane and cumene

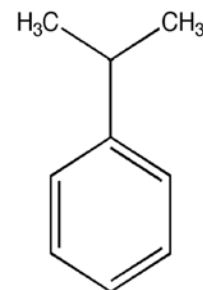
- 1-Bromopropane

- Brominated hydrocarbon used in a variety of industries: primarily as a vapor degreaser for electronics and metals, solvent cleaner using aerosolized adhesives, spot cleaner for textiles, and dry cleaning.
- Project leader: Diane Spencer, MS



- Cumene

- Volatile liquid with a gasoline-like odor, primarily used in the synthesis of acetone and phenol.
- Also a component of fossil fuels, crude oil, coal tar, gasoline; found in cigarette smoke.
- Project leader: Gloria Jahnke DVM, DABT



Key steps in the review of 1-bromopropane and cumene

Selection of Candidate Substances

FR. Public comments: Nominated substances

FR. Public comments: Draft concepts

BSC Meeting: Draft concepts

• Jan 20, 2012

• Apr 20, 2012

• Jun 21, 2012

Scientific Evaluation: Candidate Substances

Post (website): preliminary references

FR. Public comment: Draft monographs

• Oct 5, 2012

• Jan 18, 2013

Peer Review: Draft RoC Monographs

Peer Review Mtg: Draft monographs

• Mar 21-22, 2013

Technical advisors

Cumene: α_{2U} - Globulin nephropathy, genotoxicity
1-BP: Toxicology & exposure

Internal reviews: NTP and Interagency review

FR = *Federal Register Notice*

Public comments

- Multiple opportunities for public comments

	Number of comments	
	Cumene	1-BP
• Nomination	0	1
• Draft concept (written or oral)	0	0
• Draft monograph (written)	2	2
• Draft monograph (oral)	0	1
• Post peer-review meeting	1	0

- Time was set aside at the peer-review meeting to discuss scientific issues raised in the public comments

Monograph contents

Cancer Evaluation Component

Literature-based assessment

Properties and Human Exposure

Disposition and Toxicokinetics

Human Cancer Studies (no studies)

Cancer Studies in Experimental Animals

Other Relevant Data

Overall Cancer Evaluation

Appendices

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

Substance Profile

Listing recommendation

Carcinogenicity: Key studies

Properties

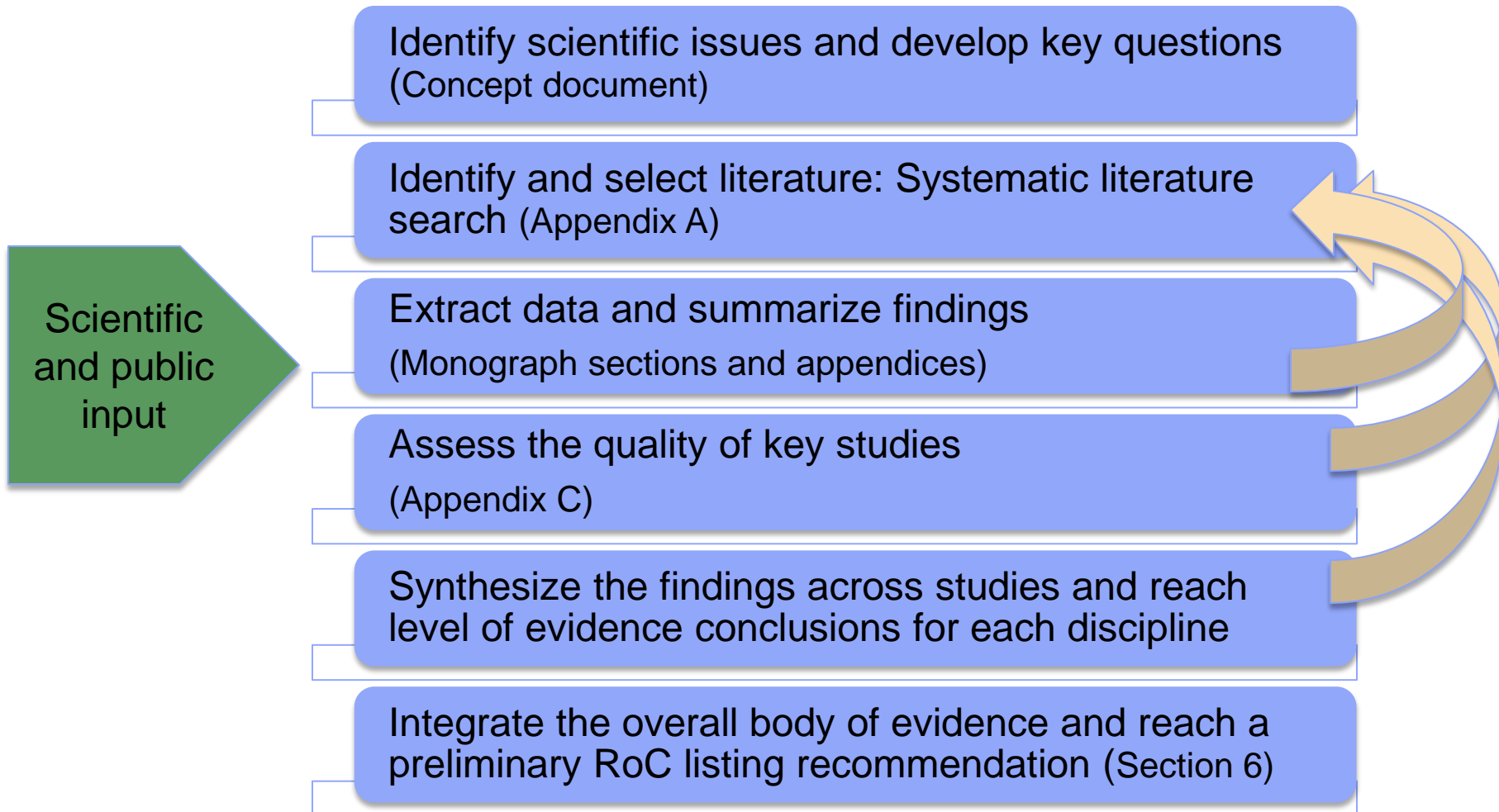
Use

Production

Exposure

Regulations

Methods for preparing the cancer evaluation component



RoC conclusions: Level of evidence and evaluation of mechanistic data

- Level of evidence conclusions in humans based on RoC listing criteria: inadequate, limited, sufficient
 - No human cancer studies available for either substances
- Level of evidence conclusions in experimental animals based on RoC listing criteria: sufficient, not sufficient.
- Mechanistic data considerations (most cases limited data)
 - Compelling data that a substance causes cancer by a mechanism that would not occur in humans.
 - Convincing data that a substance operates by a mechanism indicating that it would cause cancer in humans.

RoC conclusions: Preliminary listing recommendation

- *Known to be a human carcinogen*
 - Sufficient evidence of carcinogenicity from studies in humans (convincing mechanistic data can contribute to the evaluation).
- *Reasonably anticipated to be a human carcinogen*
 - Limited evidence of carcinogenicity from studies in humans.
 - Sufficient evidence of carcinogenicity from studies in experimental animals.
 - Convincing mechanistic data.

1-Bromopropane and Cumene Peer-Review Panel

Member	Affiliation
Lucy Anderson, PhD, DABT (Chair)	Consultant for Biomedical Sciences and Toxicology
Leo Thomas Burka, PhD	Independent Consultant
Michael Elwell, DVM, PhD	Covance Laboratories Inc
Terry Gordon, PhD	New York University School of Medicine
Lawrence H. Lash, PhD	Wayne State University School of Medicine
Stephen Nesnow, PhD	Independent Consultant
Wayne T. Sanderson PhD, CIH	University of Kentucky
Mary Jane K. Selgrade, PhD	ICF International
Paul A. White, PhD	Health Canada

Peer-review panel: Charge and actions for each draft monograph (1-bromopropane and cumene).

- 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 the substance.
- Actions (votes)
 - Whether the scientific evidence supports the NTP's conclusion on the level of evidence for carcinogenicity from experimental animal studies of the substance.
 - Whether the scientific evidence supports the NTP's preliminary listing decision for the substance in the RoC.

Peer-review report and NTP responses

- Peer-review report
 - Recommendations concerning NTP's draft conclusions and scientific issues supporting the recommendations (e.g., mainly actions).
 - Scientific and technical peer-review comments to improve the technical accuracy, clarity, and objectivity of the monograph (charge questions).
 - Over, all the Panel liked the structure of the monographs, which is new to the process.
- Revised draft monographs
 - NTP revised the draft monographs for cumene and 1-bromopropane based on the peer review comments.
- NTP response to the peer-review report
 - NTP addressed both types of comments in its response.
 - Provides the NTP's rationale for accepting/not accepting peer review recommendations.

1-Bromopropane (1-BP): Actions

NTP conclusions in draft monograph	Panel Report	NTP Response to Panel Report
Significant number of persons in the United States are exposed to 1-BP.	Panel agreed (no vote).	NTP concurs.
Sufficient evidence of carcinogenicity from studies in experimental animals: skin tumors in male rats, large intestine tumors in female and male rats, and lung tumors in female mice.	Panel agreed (8 yes, 0 no, 0 abstentions) that the scientific evidence supports NTP level of evidence conclusion.	NTP concurs.
Preliminary listing recommendation: <i>reasonably anticipated to be a human carcinogen.</i>	Panel agreed (8 yes, 0 no, 0 abstentions) with NTP preliminary policy recommendation.	NTP concurs.

Cumene: Actions

NTP conclusions in draft monograph	Panel Report	NTP Response to Panel Report
Significant number of persons in the United States are exposed to cumene.	Panel agreed (no vote).	NTP concurs.
Sufficient evidence of carcinogenicity from studies in experimental animals.	Panel agreed (8 yes, 0 no, 0 abstentions) that the scientific evidence supports NTP level of evidence conclusion but disagreed with the tumor sites.	NTP concurs with revised tumor sites.
Preliminary listing recommendation: <i>reasonably anticipated to be a human carcinogen.</i>	Panel agreed (8 yes, 0 no, 0 abstentions) with NTP preliminary policy recommendation.	NTP concurs.

Cumene: Tumor sites providing sufficient evidence in experimental animals

Tumor sites	Panel votes
NTP's conclusions in draft monograph: lung tumors in male and female mice, liver tumors in female mice, and renal tumors in male rats.	4 yes, 5 no, 0 abstentions; chair broke the tie No votes: uncertainty about the role of α 2u-globulin in producing all of the kidney tumors in male rats.
Panel's proposal for tumors sites contributing to sufficiency of carcinogenicity in experimental animals: lung tumors in male and female mice and liver tumors in female mice.	7 yes, 1 no, 0 abstentions; no vote thought there was no compelling evidence that cumene could not cause kidney tumors in humans.
Panel's proposal for tumor sites providing supporting evidence: renal tumors in male rats and benign nasal tumors in male and female rats.	8 yes, 0 no, 0 abstentions.

1-Bromopropane and cumene reviews: Next steps

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