NTP
National Toxicology Program

Report on the Peer Review of the RoC Draft Monograph on Haloacetic Acids Found as Water Disinfection By-products

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NTP Board of Scientific Counselors Meeting
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Haloacetic acids peer-review meeting

Outline

Report on Carcinogens (RoC)

Cancer hazard evaluation of haloacetic acids

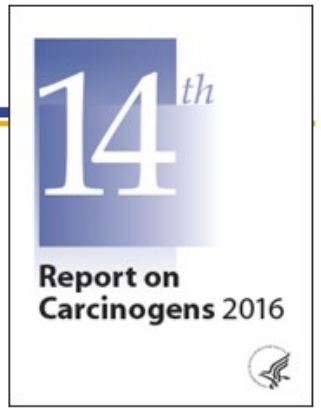
Peer-review meeting and reports

NTP conclusions

Panel recommendations and comments

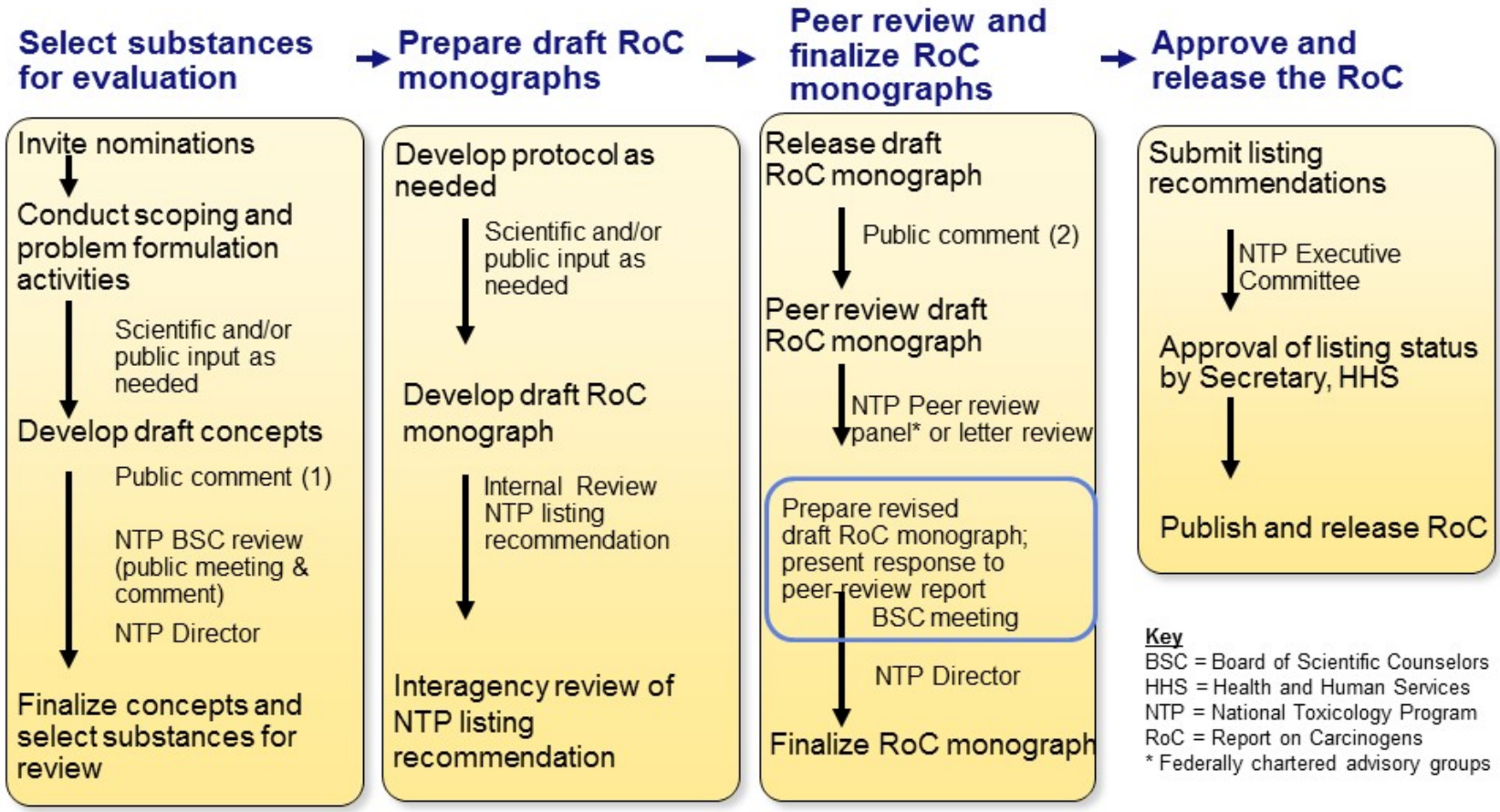
Next steps

The Report on Carcinogens (RoC) is congressionally mandated



- Public Health Service Act, Section 301(b)(4) (1978, amended 1993)
  - Directs Secretary, Health and Human Services (HHS) to publish a list of carcinogens
  - Lists substances as "*known*" or "*reasonably anticipated human carcinogens*"
- Identifies substances that pose a cancer hazard for people in the United States
- Each edition of the report is cumulative
- NTP prepares the RoC for the Secretary, HHS
- http://ntp.niehs.nih.gov/go/roc

Process for Preparation of the RoC



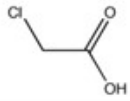
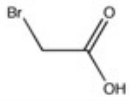
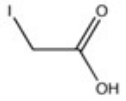
Water disinfection by-products: US exposure

- What are water disinfection by-products (DBPs)?
  - Formed by reaction of vegetative material or other organic materials, such as chemical pollutants, in water with antimicrobial oxidizing agents such as chlorine, chloramine, chlorine dioxide, or with naturally occurring halides.
  - Composition varies with water source, method of disinfection, season of the year.
  - Found in public water supply, including swimming pools and spas.
- More than 80% of U.S. population use disinfected water (with DBPs) from public facilities, most others use private well water
- Over 500 chemicals have been identified.
  - Trihalomethanes: 58% by weight of halogenated by-products.
  - Haloacetic acids: 36% by weight of halogenated by-products.

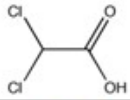
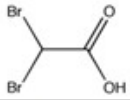
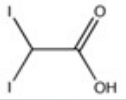
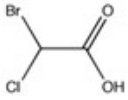
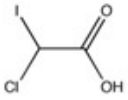
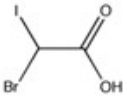
Thirteen haloacetic acids identified

Six haloacetic acids had animal cancer studies

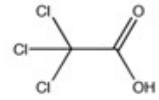
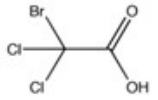
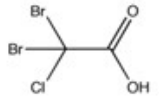
Mono-haloacetic acids

MCA	MBA	MIA
		

Di-haloacetic acids

DCA	DBA	DIA
		
BCA	**CIA**	**BIA**
		

Tri-haloacetic acids

TCA	TBA	BDCA	CDBA
			

Assessment of different types of evidence for 13 individual HAAs

- Properties
- ADME and TK
- Animal cancer studies
- Mechanism

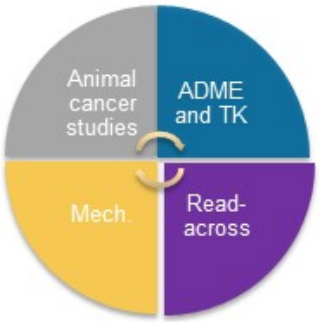
Read across approaches

Endpoint	3 mono HAAs	6 di HAAs	4 tri HAAs
Properties (reactivity)	Electrophilicity, pKa		
ADME & TK	Comparative data		
Animal cancer data	Predicted TDs_{50} and BMDs for carcinogenicity		
Mechanism	Potencies		

Read Across Approaches

- All 13 HAAs as a class?
- Seven potential subclasses of HAAs?
- Individual HAAs without animal data?

Overall cancer hazard evaluation



RoC Listing Criteria

Preliminary Listing Recommendations

Haloacetic acid peer-review panel

Member	Affiliation
Wsihsueh Chiu (Chair)	Texas A&M University
Mathias Attene-Ramos	George Washington University
Julia H. Carter	Wood Hudson Cancer Research Laboratory
Shahid Parvez	Indiana University-Perdue University
Lawrence H. Lash	Wayne State University
Consolato Sergi	University of Alberta
Susan C. Tilton	Oregon State University
Stephen M. Roberts	University of Florida

NTP BSC Liaison: Daniel Kass

Peer-review meeting

Charge	To comment on whether the draft RoC Monograph on Haloacetic Acids Found as Water Disinfection By-Products is technically correct, clearly stated, and objectively presented.
	To provide opinion on whether there is currently or was in the past significant human exposure to haloacetic acids found as water disinfection by-products.
Actions (votes)	Whether the scientific evidence supports the NTP's conclusions on the level of evidence for carcinogenicity from cancer studies in humans and experimental animals.
	Whether the scientific evidence supports the NTP's preliminary policy decisions on the listing status of several haloacetic acids found as water disinfection by-products in the RoC.

The panel agreed unanimously with NTP conclusions

Evidence stream	NTP draft recommendation	Panel
Exposure	Significant U.S. exposure	Concurred
Human cancer studies	Data are *inadequate* to evaluate the relationship between human cancer risk and exposure to haloacetic acids	Agree
Cancer studies in experimental animals	*Sufficient evidence*: Bromochloroacetic acid Bromodichloroacetic acid Dibromoacetic acid Dichloroacetic acid *Insufficient evidence*: Monochloroacetic acid Trichloroacetic acid	Agree*
Listing recommendation (for four haloacetic acids with sufficient evidence)	*Reasonably anticipated to be a human carcinogen*	Agree*

* Each chemical was voted on individually.

Evaluation of TBA and CDBA without cancer data

- Tribromoacetic acid (TBA) and chlorodibromoacetic acid (CDBA) have no animal cancer data, but are metabolized to animal carcinogens.
  - TBA is metabolized to DBA
  - CDBA is metabolized to BCA
- TBA and CDBA have similar mechanistic properties to haloacetic acids that caused tumors in animals.
  - electrophilic
  - oxidative stress
  - DNA damage

The panel agreed unanimously with NTP conclusions

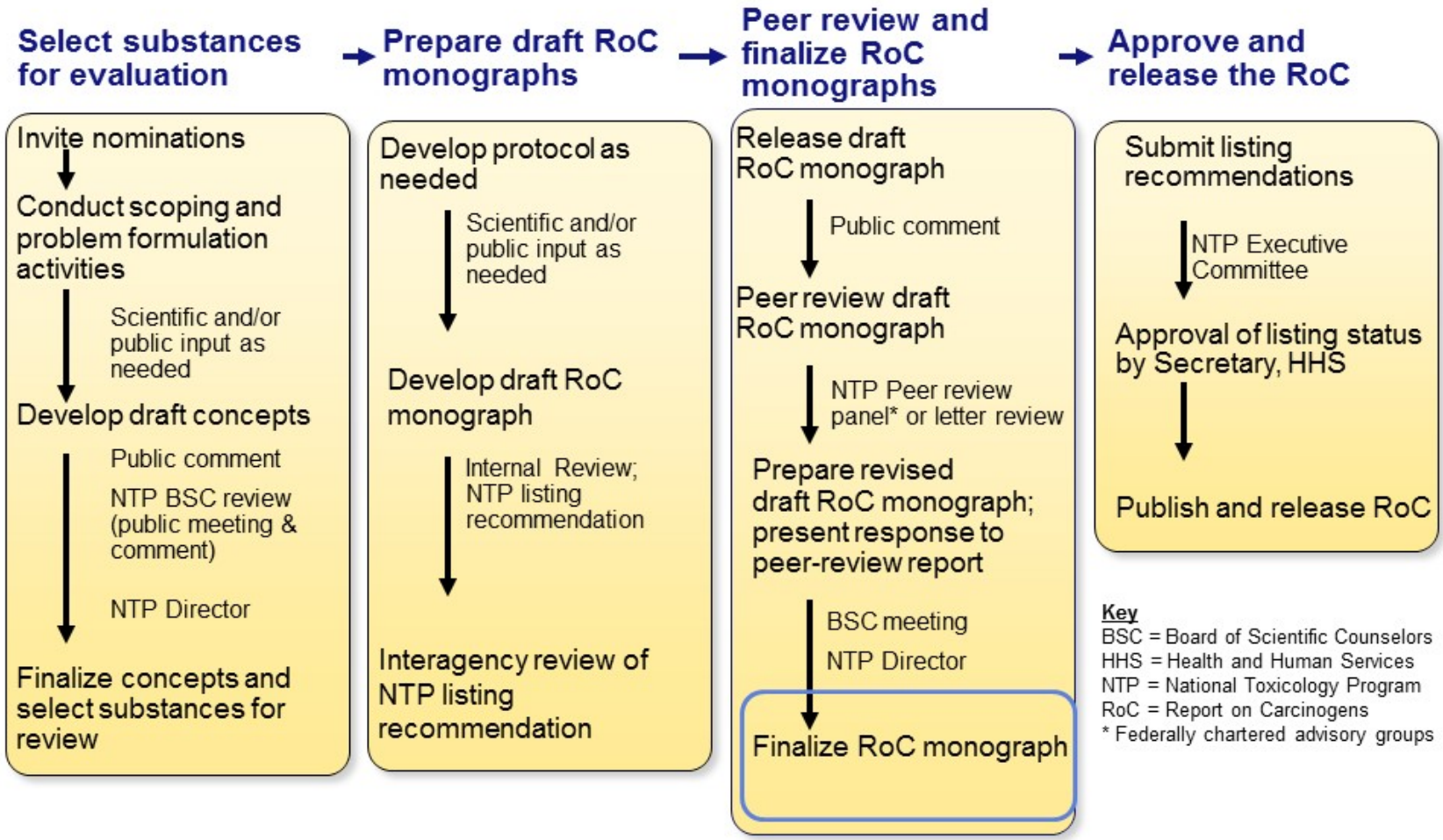
Evidence stream	NTP draft recommendation	Panel
Metabolism to a rodent carcinogen and mechanistic data	Chlorodibromoacetic acid is *reasonably anticipated to be a human carcinogen.*	Agree
	Tribromoacetic acid is *reasonably anticipated to be a human carcinogen.*	Agree

Panel's comments on the draft monograph

Scientific and technical comments to improve monograph

- No major scientific disagreements
- The panel concurred that haloacetic acids could not be evaluated as a class or as subclass(es), although with more mechanistic data this may be possible in the future.
- Substantial revisions
  - Include additional exposure information and references
  - Provide concise synthesis of ADME section
  - Clarify why metabolism to a carcinogen approach is not used for trichloroacetic acid.
- Comments outside the scope of the RoC monographs
  - Describe histology and necropsy process in more detail in text
  - Expand how common or multiple cancer mechanisms would be evaluated across subclasses of haloacetic acids.

Next steps


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
Internal Review; NTP listing recommendation
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
Prepare revised draft RoC monograph; present response to peer-review report
BSC meeting
NTP Director
Finalize RoC monograph
Approve and release the RoC
Submit listing recommendations
NTP Executive Committee
Approval of listing status by Secretary, HHS
Publish and release RoC
Key
BSC = Board of Scientific Counselors
HHS = Health and Human Services
NTP = National Toxicology Program
RoC = Report on Carcinogens
* Federally chartered advisory groups

Acknowledgments

Monograph Preparation

NTP/ORoC

Gloria Jahnke, Co-Project Lead
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Steve Ferguson, DNTP, NIEHS
Andy Shapiro, DNTP, NIEHS

Peer Review Meeting

NTP/Office of Liaison, Policy & Review

Mary Wolfe, Director
Robbin Guy
Anna Lee Mosley (Kelly Services, Inc.)*

ICF, Inc.*

Susan Blaine
Canden Byrd

*Contract Support


Questions?