Process for Preparing the Draft RoC Monograph on Haloacetic Acids Found as Water Disinfection By-Products

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Outline

Background on Report on Carcinogens (RoC)

Select HAAs for evaluation for the RoC

Draft RoC monograph

Reach RoC conclusions and RoC listing criteria

Next steps
The Report on Carcinogens (RoC) is congressionally mandated

- Identifies substances that pose a cancer hazard to people residing in the United States
  - Two listing categories: known and reasonably anticipated to be a human carcinogen

- Substance profile is written for each listing
  - Listing status, scientific information key to listing and data on properties, uses, production, exposure, and regulations to limit exposure

- Each edition of the report is cumulative

- NTP prepares the RoC for the Secretary of the Department of Health and Human Services using a four-part formal process and established listing criteria

http://ntp.niehs.nih.gov/go/roc
Process for the Preparation of the RoC

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
  - Public comment
  - NTP BSC review
  - Public mtg.
  - NTP Director
  - Interagency review of NTP listing recommendation

Peer review and finalize RoC monographs
- Release draft RoC monograph
  - Scientific and/or public input as needed
  - Peer review draft RoC monograph
    - NTP Peer review panel* or letter review
  - Present summary of peer review; prepare revised draft RoC monograph
    - NTP BSC mtg.
    - Public mtg.
    - NTP Director
    - Finalize RoC monograph

Approve and release the RoC
- Submit substance profiles
  - 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

https://ntp.niehs.nih.gov/go/rocprocess
Nearly everyone in the United States is potentially exposed to HAAs found as drinking water disinfection by-products (DBPs).

Some human studies report a potential association with urinary bladder cancer with chlorinated water exposure.

Large database of experimental cancer and mechanistic studies.

Some DBPs are listed in the RoC but HAAs have not been evaluated.

Regulations are for specific DBPs.
Develop protocol

Informational group: External and government scientists

Develop draft RoC monograph

Technical advisors: External and government scientists

Interagency review of NTP listing recommendation

Methods for preparing the monograph such as approaches for evaluating study quality and integrating data

Discussed approaches to determine if HAAs could be evaluated as a chemical class, or a subclass.
Draft RoC Monograph on HAAs Found as Water DBPs

Objective

- Evaluate relevant scientific information, assess its quality, apply RoC listing criteria to the information, and reach a listing status recommendation
- Evaluate individual (13) HAAs, HAAs as one class, HAAs as several subclass(es)

Contents

- Background and methods
- Monograph sections: Human exposure, carcinogenicity, and other relevant information
- Substance profiles
- Appendices (separate document): Study quality and result tables

https://ntp.niehs.nih.gov/go/790113
Evaluate whether a significant number of U.S. residents are exposed to HAAs

**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.

**Evaluate data (Section 2)**
- Number of people served by public water supply
- Levels of HAAs in water
- Not a formal exposure assessment

**Reviewer instructions**
- Use their judgment as to whether the exposure information in the draft monograph supports the NTP conclusion that a significant number of U.S. residents are exposed to HAAs
Type of evidence: Individual HAAs (Section 1 to 6)

Properties (Section 1)
- Defines class of 13 HAAs and how members of the class differ

ADME and TK (Section 3)
- Informs MOAs
- Informs evaluation of HAAs without cancer data

Animal cancer studies (Section 4)
- Cancer assessments of 6 individual HAAs
- Informs evaluation of HAAs without cancer data

Mechanism (Section 6)
- Identifies biological effects, patterns (potencies) across events, and potential MOAs

Evidence integration: Class/subclass assessments (Section 7)

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<tr>
<th>Endpoint</th>
<th>3 mono HAAs</th>
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<tbody>
<tr>
<td>Properties (reactivity)</td>
<td>Electrophilicity, pKa</td>
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<td>TK</td>
<td>Comparative data</td>
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<td>Biological effects</td>
<td>Potencies</td>
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<td>Animal cancer data</td>
<td>Predicted TDs_{50} and BMDs for carcinogenicity</td>
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Read-across like approaches
- 13 HAAs as a class?
- Subclasses of HAAs?
- Individual HAAs?

Overall cancer hazard evaluation (Section 8)
- Animal cancer studies
- ADME and TK
- Read-across
- Mech.
- Preliminary Listing Criteria
- Recommendations
- RoC Listing Criteria
RoC Listing Criteria: Two 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
- Belongs to well-defined structurally related class of substances listed in the RoC or demonstrates convincing mechanistic evidence

Conclusions based on scientific judgment considering all relevant information such as chemical structure, metabolism, pharmacokinetics, genetic effects, and mechanisms of action.

Level of evidence from studies in experimental animals

Sufficient evidence

- 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
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  - April 2016
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Acknowledgments

Monograph Preparation

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Peer Review Meeting

NTP/Office of Policy, Liaison & Review
Mary Wolfe, Director
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ICF, Inc.*
Susan Blaine
Canden Byrd

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Questions?