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

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National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
December 7–8, 2017
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
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**

<table>
<thead>
<tr>
<th>Mono-haloacetic acids</th>
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<tbody>
<tr>
<td>MCA</td>
<td>MBA</td>
<td>MIA</td>
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<table>
<thead>
<tr>
<th>Di-haloacetic acids</th>
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<tbody>
<tr>
<td>DCA</td>
<td>DBA</td>
<td>DIA</td>
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<table>
<thead>
<tr>
<th>Tri-haloacetic acids</th>
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</thead>
<tbody>
<tr>
<td>TCA</td>
<td>TBA</td>
<td>BDCA</td>
<td>CDBA</td>
<td></td>
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</tbody>
</table>
Assessment of different types of evidence for 13 individual HAAs

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

Read across approaches

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>3 mono HAAs</th>
<th>6 di HAAs</th>
<th>4 tri HAAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Properties (reactivity)</td>
<td>Electrophilicity, pKa</td>
<td></td>
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<tr>
<td>ADME &amp; TK</td>
<td>Comparative data</td>
<td></td>
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<tr>
<td>Animal cancer data</td>
<td>Predicted TD_{50} and BMDs for carcinogenicity</td>
<td></td>
<td></td>
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<tr>
<td>Mechanism</td>
<td>Potencies</td>
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</tbody>
</table>

Overall cancer hazard evaluation

- Animal cancer studies
- ADME and TK
- Mech
- Read-across

RoC Listing Criteria

Preliminary Listing Recommendations

Read Across Approaches
- All 13 HAAs as a class?
- Seven potential subclasses of HAAs?
- Individual HAAs without animal data?
## Haloacetic acid peer-review panel

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

**NTP BSC Liaison:** Daniel Kass
<table>
<thead>
<tr>
<th>Charge</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actions (votes)</td>
<td>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.</td>
</tr>
<tr>
<td>Actions (votes)</td>
<td>Whether the scientific evidence supports the NTP’s conclusions on the level of evidence for carcinogenicity from cancer studies in humans and experimental animals.</td>
</tr>
<tr>
<td>Actions (votes)</td>
<td>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.</td>
</tr>
</tbody>
</table>
The panel agreed unanimously with NTP conclusions

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

* 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

<table>
<thead>
<tr>
<th>Evidence stream</th>
<th>NTP draft recommendation</th>
<th>Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism to a rodent carcinogen and mechanistic data</td>
<td>Chlorodibromoacetic acid is <em>reasonably anticipated to be a human carcinogen.</em></td>
<td>Agree</td>
</tr>
<tr>
<td></td>
<td>Tribromoacetic acid is <em>reasonably anticipated to be a human carcinogen.</em></td>
<td>Agree</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Select substances for evaluation</th>
<th>Prepare draft RoC monographs</th>
<th>Peer review and finalize RoC monographs</th>
<th>Approve and release the RoC</th>
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<tbody>
<tr>
<td>Invite nominations</td>
<td>Develop protocol as needed</td>
<td>Release draft RoC monograph</td>
<td>Submit listing recommendations</td>
</tr>
<tr>
<td>Conduct scoping and problem formulation activities</td>
<td>Scientific and/or public input as needed</td>
<td>Public comment</td>
<td>NTP Executive Committee</td>
</tr>
<tr>
<td>Develop draft concepts</td>
<td>Develop draft RoC monograph</td>
<td>Peer review draft RoC monograph</td>
<td>Approval of listing status by Secretary, HHS</td>
</tr>
<tr>
<td>Public comment</td>
<td>Internal review; NTP listing recommendation</td>
<td>NTP Peer review panel* or letter review</td>
<td>Publish and release RoC</td>
</tr>
<tr>
<td>NTP BSC review (public meeting &amp; comment)</td>
<td>Interagency review of NTP listing recommendation</td>
<td>Prepare revised draft RoC monograph; present response to peer-review report</td>
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<tr>
<td>NTP Director</td>
<td>Finalize concepts and select substances for review</td>
<td>BSC meeting NTP Director</td>
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<tr>
<td></td>
<td>Finalize RoC monograph</td>
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<td>Key</td>
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**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
Ruth Lunn, Director ORoC
Suril Mehta
Amy Wang

ILS, Inc.*
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Ella Darden
Andy Ewens
Jessica Geter
Alton Peters
Tracy Saunders

Technical Advisors and Support
Ron Melnick, Consultant
Grace Patlewicz, US EPA/NCCT
Michael Plewa, Univ. of IL (emeritus)
Susan Richardson, Univ. of SC
Jane Ellen Simmons, US EPA
Scott Auerbach DNTP, NIEHS
Michael Devito, DNTP, NIEHS
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
Canen Byrd

*Contract Support
Questions?