Evaluation of HAAs as a Class or Subclass(es)

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HAAs as a Class or Subclass(es)

Outline

- **Class**
  - All 13 HAAs as a potential class

- **Subclasses**
  - 7 Potential subclasses

- **Analogues (metabolism)**
  - Individual untested HAAs (carcinogenicity)
Can all 13 HAAs be Considered a Class?

Approach and methods

- Conduct read across-like analysis
  - Informed by previous sections of the monograph
  - Compared potency values for biological effects
- Evaluate published QSARs for biological effects
- Evaluate QSAR modeling to predict carcinogenicity
## Biological effects varied with number and type of halogens

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Mono-HAAs</th>
<th>Di-HAAs</th>
<th>Tri-HAAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Properties (reactivity)</td>
<td>Electrophilicity ($E_{\text{LUMO}}$), pKa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism &amp; Toxicokinetics</td>
<td>Comparative data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanistic data</td>
<td>Comparative data: potency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal cancer data</td>
<td>Br-HAAs more cancer sites than Cl-HAAs TD$_{50}$ and BMDLs for quantitative assessment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Potency of biological effects increased** (*in vitro*)
  - with decreasing number of halogens
  - with increasing halogen size

- **these trends are related to chemical properties**

- **Limitations/challenges**
  - no well defined mechanism for HAA carcinogenicity
  - cancer potency metric

* Graphical representation (Table 7-1) in the Monograph captures all data evaluated
Published QSAR models successfully predicted effects related to the characteristics of carcinogens

- Predicted potency for **oxidative stress** and **genetic damage** in cultured mammalian cells for 12 HAAs
- Predicted potency of **neural tube defects** in mouse embryo cultures (*ex vivo*) for 10 HAAs
- These models were based on pKa and $E_{\text{LUMO}}$
  - pKa relates to bioavailability/transport
  - $E_{\text{LUMO}}$ relates to intrinsic activity/covalent interaction with macromolecules
Published QSAR models successfully predicted effects related to the characteristics of carcinogens

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Could we develop a similar QSAR model to predict carcinogenicity?
Empirical animal data results

- Br-HAAs were associated with more cancer sites than Cl-HAAs
- MCA was not carcinogenic

Modeled cancer potency estimates did not show the expected trends

- Published Benchmark Dose Low (BMDL, mg/kg/day)
- Predicted Toxic Dose 50 (TD$_{50}$, mg/kg/day)
  - MCA was predicted to be carcinogenic
HAAs as a Subclass(es)

Outline

- Class
  - All 13 HAAs as a potential class

- Subclasses
  - 7 Potential subclasses

- Analogues (metabolism)
  - Individual untested chemicals
Evaluate Seven Potential Subclasses

Approach and Methods

• Same general approach as with all 13 HAAs

• Considered 7 smaller groups based on number and type of halogens
  - Subclasses include tested and non-tested chemicals for animal carcinogenicity
  - Evaluate the confidence for read across
    • Are there testing data for at least one member of the subclass?
    • Are there testing data for HAAs containing the principal halogen(s) within the subclass?
    • Does the subclass contain any HAAs tested in animals and found not to cause tumors?
    • Are there other similarity criteria (e.g., metabolism, chemical, biological)?
<table>
<thead>
<tr>
<th>Subclass</th>
<th>Members*</th>
<th>Confidence as a potential category for read across</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-HAAs</td>
<td>MCA, MBA, MIA</td>
<td>No</td>
</tr>
<tr>
<td>Di-HAAs</td>
<td>DCA, DBA, BCA,</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>DIA, CIA, BIA</td>
<td></td>
</tr>
<tr>
<td>Tri-HAAs</td>
<td>TCA, BDCA, CDBA,</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>TBA</td>
<td></td>
</tr>
<tr>
<td>CI-HAAs</td>
<td>MCA, DCA, BCA,</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>CIA, TCA</td>
<td></td>
</tr>
<tr>
<td>Br-HAAs</td>
<td>BA, DBA, BCA, BIA</td>
<td>Low/moderate</td>
</tr>
<tr>
<td></td>
<td>TBA, BDCA, CDBA</td>
<td></td>
</tr>
<tr>
<td>I-HAAs</td>
<td>IA, DIA, CIA, BIA</td>
<td>No</td>
</tr>
<tr>
<td>Br-Di-/Tri-HAAs</td>
<td>DBA, BCA, BIA,</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>BDCA, CDBA, TBA</td>
<td></td>
</tr>
</tbody>
</table>

* Red = rodent carcinogens, blue = not carcinogenic, black = no animal carcinogenicity data
Example evaluation

<table>
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<th>Members*</th>
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<tr>
<td>Br-Di-/Tri-HAAs</td>
<td>DBA, BCA, BIA, BDCA, CDBA, TBA</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

- Testing data for 3 members: DBA, BCA, BDCA
- No testing data for any iodinated HAAs
- CDBA and TBA are metabolized to tested HAAs
- Two untested chemicals (CDBA, TBA) have similar properties as tested chemical (BDCA)

Conclusion: Read across to BIA is too uncertain without a defined mechanism of action and/or animal carcinogenicity data for an iodinated HAA.
Outline

- Class
  - All 13 HAAs as a potential class

- Subclasses
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- Analogues (metabolism)
  - Individual untested chemicals
Evaluate Individual Untested HAAs

Subclass evaluation informed potential “read-across” for two tri-HAAs without cancer data (CDBA and TBA)

- Metabolism data and analogue approach
- Metabolites and analogues are known animal carcinogens
- Supporting mechanistic data
Tri-HAAs Metabolized to Di-HAAs

- Tri-HAAs with both Cl and Br always lose a Br
- Br loss from Tri-HAA corresponds 1:1 to Di-HAA formation
- Br substitution for Cl enhances metabolism
- TBA and CDBA: no animal cancer data but are metabolized to animal carcinogens
- No other microsomal metabolites identified

<table>
<thead>
<tr>
<th>No. of Bromines</th>
<th>Parent</th>
<th>Relative extent of metabolism</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>TCA</td>
<td></td>
<td>DCA</td>
</tr>
<tr>
<td>1</td>
<td>BDCA</td>
<td></td>
<td>DCA</td>
</tr>
<tr>
<td>2</td>
<td>CDBA</td>
<td></td>
<td>BCA</td>
</tr>
<tr>
<td>3</td>
<td>TBA</td>
<td></td>
<td>DBA</td>
</tr>
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</table>
### All Tested Br-HAAs are Rodent Carcinogens

<table>
<thead>
<tr>
<th>Species/Tumor type</th>
<th>Tested chemicals</th>
<th>Untested chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BCA</td>
<td>DBA</td>
</tr>
<tr>
<td>Rats</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>MCL</td>
<td>–</td>
<td>✔</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Mammary</td>
<td>✔</td>
<td>–</td>
</tr>
<tr>
<td>Skin</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mice</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Liver</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Lung</td>
<td>–</td>
<td>✔</td>
</tr>
<tr>
<td>Harderian gland</td>
<td>–</td>
<td>–</td>
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✔ = tumor site, – = not a tumor site
CDBA and TBA are metabolized to rodent carcinogens

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# Other Supporting Data

CDBA and TBA are similar (properties/effects) to BDCA

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<td>✓</td>
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<td>-</td>
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<tr>
<td>Skin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Mice</strong></td>
<td>✓</td>
<td>✓</td>
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<tr>
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<td>✓</td>
</tr>
<tr>
<td>Lung</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>Harderian gland</td>
<td>-</td>
<td>-</td>
</tr>
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## CDBA and TBA are predicted to be rodent carcinogens

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CDBA and TBA have chemical properties and biological effects similar to that of BDCA that caused cancer in experimental animals

- Electrophiles
- Oxidative stress
- DNA damage

These properties and effects are relevant to humans
HAAs as a Class or Subclass(es)

Summary

Class
- All 13 HAAs as a potential class: No

Subclasses
- 7 Potential subclasses: No

Analogues (metabolism)
- Individual untested HAAs (carcinogenicity): Yes
Questions?
Comment on the methods and approaches for evaluating haloacetic acids as a class or subclass.

Comment on the assessment and NTP’s conclusion that the available data are inadequate to evaluate haloacetic acids as a class.

Comment on the assessment and NTP’s conclusion that the available data are inadequate to evaluate haloacetic acids as a subclass or subclasses (based on number or type of halogen substitutions).

Comment on the assessment and NTP’s conclusion that metabolism data and read across principles can be applied to two haloacetic acids (CDBA and TBA) without cancer data.