Draft RoC Monograph on Haloacetic Acids Found as Water Disinfection By-Products

Evaluation of HAAs as a Class or Subclass(es)

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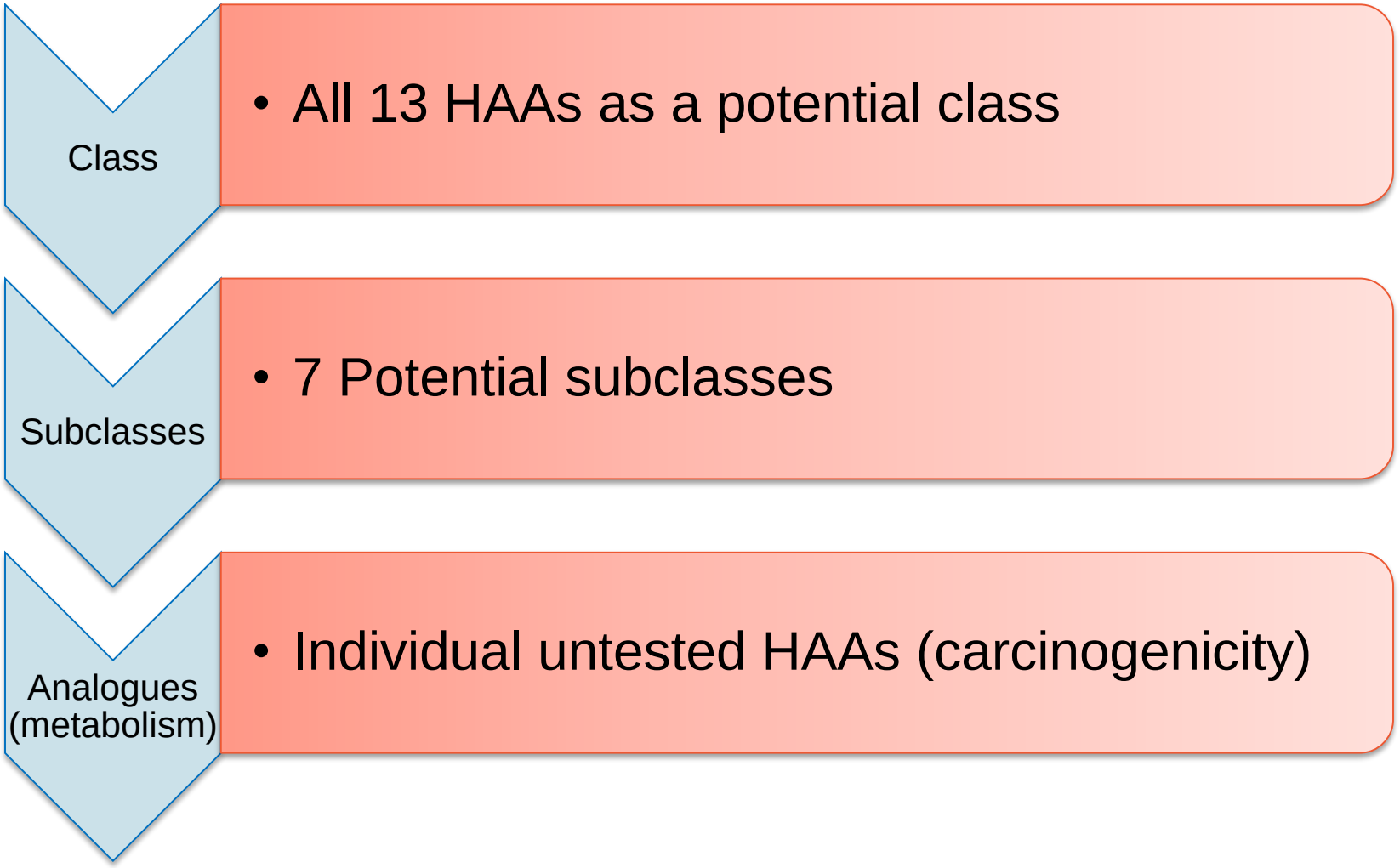
HAAs as a Class or Subclass(es)

Outline



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

Conduct Read-Across Analysis

Biological effects varied with number and type of halogens

Endpoint	Mono-HAAs	Di-HAAs	Tri-HAAs
Properties (reactivity)	Electrophilicity (E_{LUMO}), pKa		
Metabolism & Toxicokinetics	Comparative data		
Mechanistic data	Comparative data: potency		
Animal cancer data	Br-HAAs more cancer sites than Cl-HAAs TD_{50} and BMDLs for quantitative assessment		

- 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

Evaluate Published QSARs

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_{LUMO}
  - pKa relates to bioavailability/transport
  - E_{LUMO} relates to intrinsic activity/covalent interaction with macromolecules

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Could we develop a similar QSAR model to predict carcinogenicity?

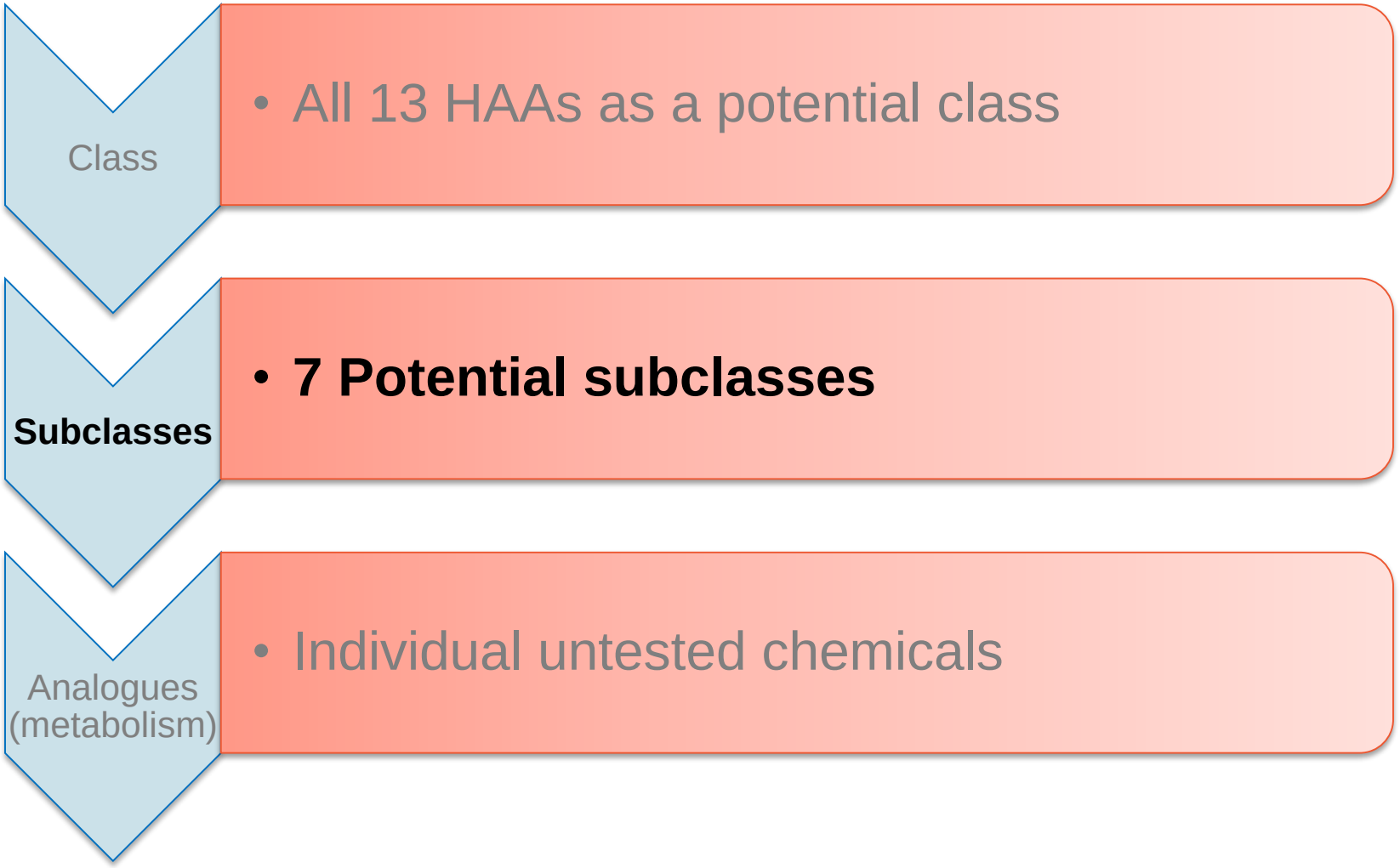
Evaluate QSAR Modeling for Carcinogenicity

QSAR approach failed to predict animal 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



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)?

Conduct Read-Across Analysis for Subclasses

Data were insufficient to support read across for subclasses

Subclass	Members*	Confidence as a potential category for read across
Mono-HAAs	MCA, MBA, MIA	No
Di-HAAs	DCA, DBA, BCA, DIA, CIA, BIA	Low
Tri-HAAs	TCA, BDCA, CDBA, TBA	Low
Cl-HAAs	MCA, DCA, BCA, CIA, TCA	No
Br-HAAs	BA, DBA, BCA, BIA, TBA, BDCA, CDBA	Low/moderate
I-HAAs	IA, DIA, CIA, BIA	No
Br-Di-/Tri-HAAs	DBA, BCA, BIA, BDCA, CDBA, TBA	Moderate

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

Brominated-Di/Tri-HAAs Subclass

Example evaluation

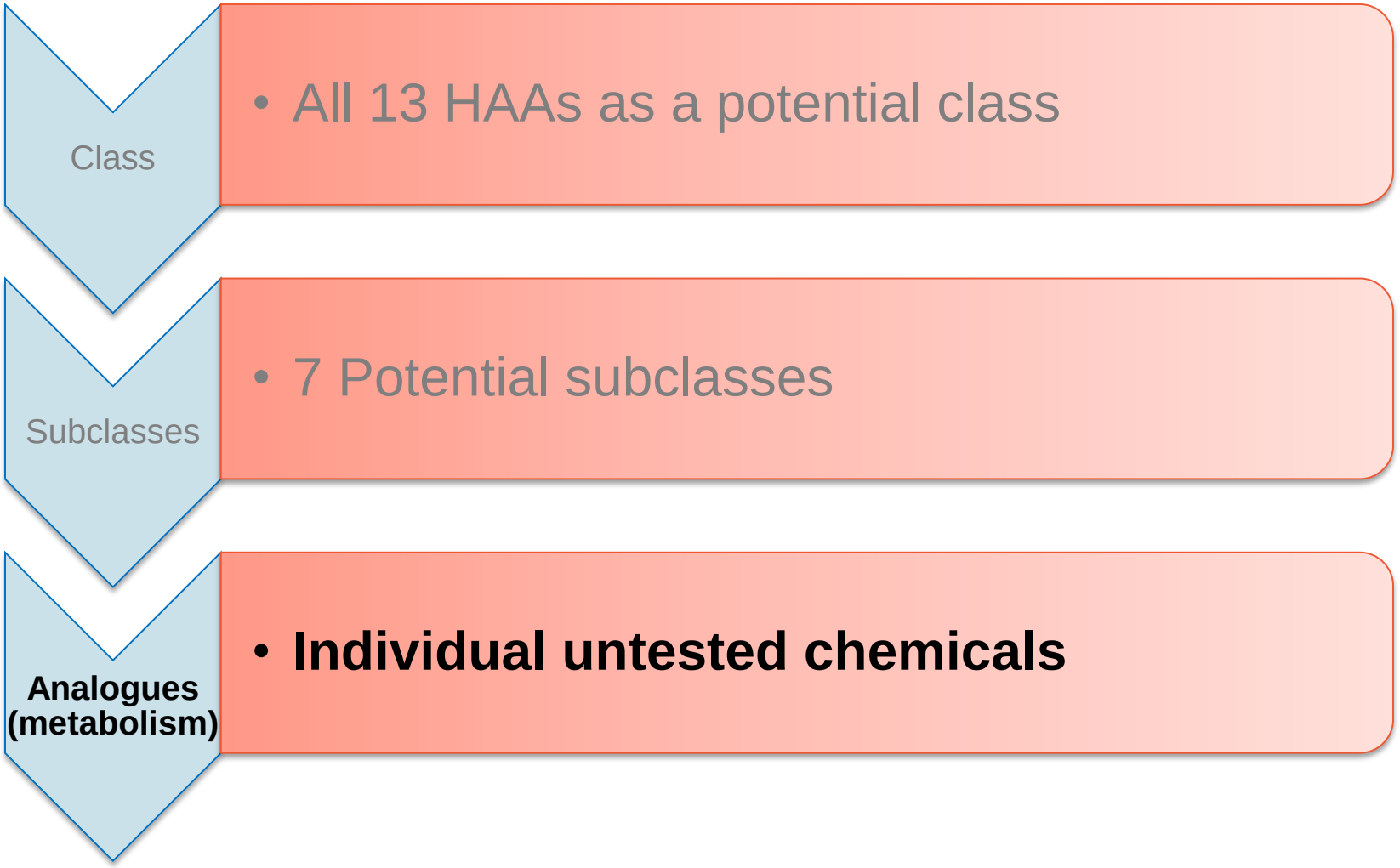
Subclass	Members*	Confidence as a potential category for read across
Br-Di-/Tri-HAAs	DBA, BCA, BIA, BDCA, CDBA, TBA	Moderate

- 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.

Evaluate Individual Untested Chemicals

Outline



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

No. of Bromines	Parent	Relative extent of metabolism	Metabolite
0	TCA		DCA
1	BDCA		DCA
2	CDBA		BCA
3	TBA		DBA

All Tested Br-HAAs are Rodent Carcinogens

Species/ Tumor type	Tested chemicals			Untested chemicals	
	BCA	DBA	BDCA	CDBA	TBA
Rats	✓	✓	✓		
MCL	–	✓	–		
Mesothelioma	✓	✓	✓		
Mammary	✓	–	✓		
Skin	–	–	✓		
Mice	✓	✓	✓		
Liver	✓	✓	✓		
Lung	–	✓	–		
Harderian gland	–	–	✓		

✔ = tumor site, – = not a tumor site

CDBA and TBA are metabolized to rodent carcinogens

Species/ Tumor type	Tested chemicals			Untested chemicals	
	BCA	DBA	BDCA	CDBA	TBA
Rats	✓	✓	✓		
MCL	–	✓	–		
Mesothelioma	✓	✓	✓		
Mammary	✓	–	✓		
Skin	–	–	✓		
Mice	✓	✓	✓		
Liver	✓	✓	✓		
Lung	–	✓	–		
Harderian gland	–	–	✓		

✔ = tumor site, – = not a tumor site

Other Supporting Data

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

Species/ Tumor type	Tested chemicals			Untested chemicals	
	BCA	DBA	BDCA	CDBA	TBA
Rats	✓	✓	✓		
MCL	–	✓	–		
Mesothelioma	✓	✓	✓		
Mammary	✓	–	✓		
Skin	–	–	✓		
Mice	✓	✓	✓		
Liver	✓	✓	✓		
Lung	–	✓	–		
Harderian gland	–	–	✓		

✔ = tumor site, – = not a tumor site

Prediction

CDBA and TBA are predicted to be rodent carcinogens

Species/ Tumor type	Tested chemicals			Untested chemicals	
	BCA	DBA	BDCA	CDBA	TBA
Rats	✓	✓	✓	Predicted	Predicted
MCL	–	✓	–		
Mesothelioma	✓	✓	✓	Likely site	Likely site
Mammary	✓	–	✓		
Skin	–	–	✓		
Mice	✓	✓	✓	Predicted	Predicted
Liver	✓	✓	✓	Very likely site	Very likely site
Lung	–	✓	–		
Harderian gland	–	–	✓		

✔ = tumor site, – = not a tumor site

Other Supporting Data

- 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**

HAAs as a Class or Subclass(es)

Questions?

HAAs as a Class or Subclass(es)

Reviewer 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.