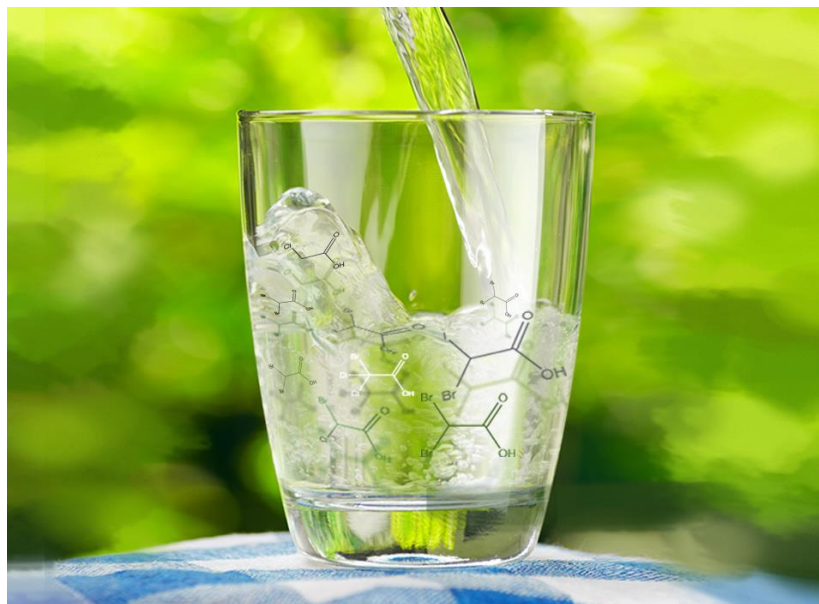


Overall Cancer Evaluation



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Outline

- Human cancer studies
 - VOTE on level of evidence
- Animal cancer results
 - VOTE on level of evidence
- Metabolism and other relevant data
- Apply RoC listing criteria
 - VOTE on preliminary listing recommendations



Inadequate evidence to evaluate

- One cohort study evaluated the association between exposure to HAAs and kidney cancer risk (Jones *et al.* 2017).
 - HAA5 (MCA, MBA, DBA, DCA, TCA), TCA, BCA, DCA.
 - No increased risks were observed.
- Exposure to HAAs occurs as a mixture.
 - Several case-control studies found that exposure to chlorinated water (or surrogates, *e.g.*, THMs) was associated with an increased risk of urinary bladder cancer (reviewed by IARC).
 - One study showed that the association varied by genetic polymorphisms in *CYP* and *GST* genes (Cantor *et al.* 2010).
 - These studies cannot distinguish between HAA exposure and other disinfection by-products.

A background image showing a hand pouring water from a chrome faucet into a clear glass. The water is bubbling as it falls into the glass. The scene is set against a white tiled wall.

Questions?



Reviewer Questions

- Level of evidence from human cancer studies (Sections 5, 8)
 - Comment on whether the information from studies in humans (Section 5) is clear, technically correct, and objectively presented.
 - Provide your preliminary vote on whether the scientific information presented from the human cancer study for haloacetic acids found as water disinfection by-products supports the NTP's level of evidence conclusion that the ***available data from epidemiological studies are inadequate*** to evaluate the relationship between human cancer risk and exposure specifically to haloacetic acids (either as a class or individual haloacetic acids).
 - **VOTE**



Drinking water exposure to haloacetic acids causes cancer in experimental animals*

Neoplasm or tissue	DCA				DBA				BCA				TCA				BDCA			
	Rats		Mice		Rats		Mice		Rats		Mice		Rats		Mice		Rats		Mice	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Liver	x		x	x			x	x			x	x			x	x			x	x
Mononuclear-cell leukemia						x														
Malignant mesothelioma					x				x								x			
Mammary gland										x								x		
Lung							x													
Skin																	x			
Harderian gland																			x	
Large intestine									x	x										


*Monochloroacetic acid (MCA) exposure did not produce tumors in experimental animals.



Level of Evidence of Animal Cancer Studies - VOTE

Water disinfection by- product	NTP's Level of Evidence	Rationale
Bromochloroacetic acid	Sufficient	Tumors in two species (R, M); multiple sites in one species (R)*.
Bromodichloroacetic acid	Sufficient	Tumors in two species (R, M)* at multiple sites.
Dibromoacetic acid	Sufficient	Tumors in two species (R, M)* at multiple sites.
Chloroacetic acid	Not sufficient	No tumors reported.
Dichloroacetic acid	Sufficient	Tumors in two species (R, M) at one site (liver).
Trichloroacetic acid	Not sufficient	Tumors in one species (M)* at one tumor site (liver).

*Mechanistic evidence of oxidative stress and DNA damage; R = rat; M = mouse

The background of the slide is a photograph of a hand holding a clear glass under a chrome faucet, filling it with water. The water is bubbling, suggesting it might be filtered or aerated. The background is a light-colored tiled wall.

NTP's Conclusions and Preliminary Listing Recommendations



Summary of NTP's Preliminary Conclusions

- A significant number of people living in the United States are or have been exposed to haloacetic acids found as water disinfection by-products.
- Data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure to individual haloacetic acids.
- There is sufficient evidence of carcinogenicity for four haloacetic acids from cancer studies in experimental animals.
- There is other relevant information (metabolism and properties) that support the evidence of carcinogenicity for two additional haloacetic acids-tribromoacetic acid and chlorodibromoacetic acid.



Chlorodibromoacetic Acid (CDBA)

- Convincing evidence that CDBA is metabolized to BCA.
 - Evidence of metabolism to BCA with rat or human liver microsomes under liver oxygen tension conditions (Saghir *et al.* 2011).
 - Oral exposure in rats results in non-renal clearance at 62.6% of total clearance, suggesting metabolism (Schultz *et al.* 1999).
- Sufficient evidence for the carcinogenicity of BCA.
 - Tumors in two species and at multiple sites in one species.
- Supporting mechanistic evidence demonstrating biological plausibility for humans.
 - Oxidative stress.
 - DNA damage.



Tribromoacetic Acid (TBA)

- Convincing evidence that TBA is metabolized to DBA.
 - Evidence of metabolism to DBA with rat liver microsomes under liver oxygen tension conditions (Saghir *et al.* 2011).
 - Oral exposure in rats results in non-renal clearance at 77.2% of total clearance, suggesting metabolism (Schultz *et al.* 1999).
- Sufficient evidence for the carcinogenicity of DBA.
 - Tumors in two species at multiple sites.
- Supporting mechanistic evidence demonstrating biological plausibility for humans.
 - Oxidative stress.
 - DNA damage.



Preliminary Listing Recommendation - VOTE

Water disinfection by-product	NTP's Listing Recommendation	Rationale
Dichloroacetic acid	RAHC	Sufficient evidence in experimental animals and supporting mechanistic data.
Dibromoacetic acid	RAHC	
Bromochloroacetic acid	RAHC	
Bromodichloroacetic acid	RAHC	
Chlorodibromoacetic acid	RAHC	Metabolism of each to a rodent carcinogen and supporting mechanistic data.
Tribromoacetic acid	RAHC	

RAHC = Reasonably Anticipated to be a Human Carcinogen