

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

Studies in Experimental Animals



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National Institute of Environmental Health Sciences July 24, 2017





Outline

Overview of studies in experimental animals

Study quality assessment

Cancer assessment

- Liver tumors
- Tumors at other sites
- Summary



Six haloacetic acids had chronic cancer data available

Mono-haloacetic acids





- 19 publications met inclusion criteria.
 - Reported on the presence or absence of neoplastic and related lesions.
 - Had a concurrent or historical control group.
 - Chronic studies with a duration of 12 months or greater or were studies with transgenic animals or co-carcinogen studies, e.g., initiation-promotion (i-p) studies.



Signaling Questions

Study design/population

Exposure conditions

Outcome assessment and measurement

Confounding

Analysis and reporting

Overall study utility: High (+++) Moderate (++) Low (+) Inadequate (0)

Responses for questions:

- Minimal concern
- Some concern
- Major concern
- Critical concern
- No information



- Study quality assessment
 - Follows <u>RoC Protocol;</u> details in <u>RoC Handbook</u>.
 - Consensus results of two independent reviewers reported in Appendix C of monograph.
- Initiation-promotion studies and transgenic studies; provided supportive information.
 - Dichloroacetic acid and trichloroacetic acid are complete carcinogens (Herren-Freund 1987), as well as cancer promoters (Pereira *et al.* 1997).
 - Dichloroacetic acid used as a positive to test TG.AC and p53 (+/-) transgenic mouse models, found to be inadequate models (NTP 2007b).
- Chronic carcinogenicity studies most informative.



Chronic Carcinogenicity Studies

Haloacetic acids	Species	Exposure route	Reference	Utility*
Monohaloacetic acids Monochloroacetic acid	Mouse	Gavage Gavage Drinking water	*High = +++, NTP 1992 NTP 1992 DeAngelo <i>et al.</i> 1997	Moderate = ++, Low + +++ ++ +++
Dichloroacetic acids Dichloroacetic acid	Mouse ♂♀ Mouse ♂ Mouse ♀ Rat ♂	Drinking water Drinking water Drinking water Drinking water	Wood <i>et al</i> 2015 DeAngelo <i>et al.</i> 1991, 1999 Bull <i>et al.</i> 1990 Daniel <i>et al.</i> 1992 Pereira <i>et al.</i> 1996 Richmond <i>et al.</i> 1995 DeAngelo <i>et al.</i> 1996	++ +++, ++ + ++ ++ ++ ++
Dibromoacetic acid	Mouse ♂♀ Rat ♂♀	Drinking water Drinking water	NTP 2007 NTP 2007	+++ +++
Bromochloroacetic acid	Mouse ♂♀ Rat ♂♀	Drinking water Drinking water	NTP 2009 NTP 2009	+++ +++
Trichloroacetic acids Trichloroacetic acid	Mouse ୁ Mouse ହ Mouse	Drinking water Drinking water Intraperitoneal Inj. Drinking water	Herren-Freund <i>et al.</i> 1987 Bull <i>et al.</i> 1990 DeAngelo <i>et al.</i> 2008 Pereira <i>et al.</i> 1996 Von Tungeln <i>et al.</i> 2002 DeAngelo <i>et al.</i> 1997	++ + +++ ++ ++ ++
Bromodichloroacetic acid	Mouse	Drinking water Drinking water	NTP 2015 NTP 2015	+++ +++



HALOACETIC ACID	R	AT	MOU	JSE
	Male	Female	Male	Female
Monochloroacetic acid	-	-	-	-
Dichloroacetic acid	HCC	NT	HCC	HCC
Trichloroacetic acid	-	NT	HCC	HCC
Dibromoacetic acid	-	-	HCC, HBI	HCC
Bromochloroacetic acid	-	-	HCC, HBI	HCC
Bromodichloroacetic acid	-	-	HCC, HBI	HCC, HBI

HCC = hepatocellular carcinoma; HBI = hepatoblastoma (carcinoma variant); NT = not tested; - = no liver tumors





B. Chlorine-containing HAAs in male mice



Individual comparisons: **P* < 0.05 ****P* < 0.001. Trend test *P*-value < 0.001; *P* < 0.01 for TCA Sources: NTP 2007a, 2009, 2015; DeAngelo *et al.*, 1999, 2008



Drinking water exposure to brominated HAAs caused increased tumor incidence at sites in addition to liver

Haloacetic acid	Tissue site or neoplasia	Specie	s, sex
Dibromoacetic acid	Malignant mesothelioma	Rat	ð
	Mononuclear cell leukemia	Rat	Ŷ
	Lung	Mouse	3
Bromochloroacetic	Malignant mesothelioma	Rat	3
acid	Mammary gland	Rat	P
	Large intestine	Rat	3 9
Bromodichloroacetic	Malignant mesothelioma	Rat	3
acid	Skin	Rat	ð
	Mammary gland	Rat	Ŷ
	Harderian gland	Mouse	3



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	Mononuclear cell leukemia	Rat	Ŷ
	Lung	Mouse	3
Bromochloroacetic	Malignant mesothelioma	Rat	3
acid	Mammary gland	Rat	9
	Large intestine	Rat	3 9
Bromodichloroacetic	Malignant mesothelioma	Rat	ð
acid	Skin	Rat	3
	Mammary gland	Rat	P
	Harderian gland	Mouse	ð



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	Lung	Mouse	δ
Bromochloroacetic	Malignant mesothelioma	Rat	3
acid	Mammary gland	Rat	P
	Large intestine	Rat	3 9
Bromodichloroacetic	Malignant mesothelioma	Rat	5
acid	Skin	Rat	5
	Mammary gland	Rat	Ŷ
	Harderian gland	Mouse	S



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

	DÇA			DBA			ВСА				ТСА				BDCA						
	Ra	ats	Mi	се	Rats		Mice		Ra	Rats		Mice		Rats		Mice		Rats		Mice	
tissue	М	F	М	F	М	F	Μ	F	Μ	F	Μ	F	Μ	F	М	F	М	F	Μ	F	
Liver	х		x	Х			x	x			х	Х			x	Х			Х	x	
Mononuclear-cell leukemia						x															
Malignant mesothelioma					x				x								x				
Mammary gland										x								x			
Lung							x														
Skin																	х				
Harderian gland																			х		
Large intestine									x	X											

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



Defer vote on carcinogenicity in experimental animals

Evidence from studies of individual haloacetic acids in experimental animals

Mechanistic and other relevant data and evaluation of haloacetic acids as a class or subclass(es)

Vote on preliminary level of evidence conclusion and NTP listing recommendation for the haloacetic acids



Studies in Experimental Animals

Questions?



Reviewer Questions

- Comment on whether the scientific information from cancer studies in experimental animals for each of the haloacetic acids found as water disinfection by-products is clear, technically correct, and objectively presented.
 - Identify any information that should be added or deleted.
- Comment on whether the approach and assessment of the utility of the animal carcinogenicity studies (study quality and sensitivity, ie, the ability to detect a true effect or hazard) for informing the cancer evaluation is systematic, transparent, objective, and clearly presented (Appendix C, Sections 4.2).
- Comment on and provide any scientific criticisms of NTP's cancer assessment of the experimental animal studies of exposure to the haloacetic acids found as water disinfection by-products and on how findings from the scientific evidence across studies were synthesized (Section 4.4).