Haloacetic Acids Found as Water Disinfection By-products (Selected)

Also known as HAAs

Introduction

Disinfection of the public water supply is an important aspect of public health in the prevention of disease transmission in the United States and worldwide (Calderon 2000). Haloacetic acids are formed as by-products during the disinfection of water, as the result of reactions between chlorine-based disinfection agents (chlorine, chloramine, and chlorine dioxide) and organic molecules in the source water (such as humic acid).

Humans are exposed to haloacetic acids in disinfected water, and exposure is to mixtures of disinfection by-products, including haloacetic acids and other types of by-products. Only one epidemiological study was identified that evaluated the relationship between human cancer risk and estimated exposures to several individual haloacetic acids and to a mixture of five regulated haloacetic acids (monochloroacetic, dichloroacetic, trichloroacetic, monobromoacetic, and dibromoacetic acids) (Jones et al. 2017). This study did not find an association between exposure to haloacetic acids in drinking water and the incidence of kidney cancer. Several epidemiological studies of exposure to chlorinated water or to other water disinfection by-products (such as trihalomethanes) as proxies for mixtures of by-products found an association with increased risk of urinary-bladder cancer (reviewed by IARC 2013, Villanueva *et al.* 2017). Although these studies did not investigate exposure specifically to haloacetic acids, they provided some information on the potential cancer risk of human exposure to water disinfection by-products, and they supported the relevance to humans of the cancer studies of haloacetic acids at higher doses in experimental animals.

Currently, public exposure to disinfection by-products in chlorinated water is limited through regulation of specific water disinfection by-products or classes of by-products. The existing epidemiological studies cannot separate the effects of different types of water disinfection by-products. However, toxicological studies of specific by-products, including haloacetic acids, are available to help inform public health decisions. Trihalomethanes and haloacetic acids are the largest groups of water disinfection by-products by weight, making up about 50% to 75% of total halogenated disinfection by-products and about 25% to 50% of total organic halides in drinking water (Krasner *et al.* 2006, 2016). Two trihalomethanes — chloroform and bromodichloromethane — are listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. The U.S. Environmental Protection Agency (EPA) regulates the mixture of five haloacetic acids mentioned above, two of which (dichloroacetic acid and dibromoacetic acid) are included in this listing.

NTP evaluated 13 haloacetic acids identified in chlorinated drinking water, six of which are individually listed as *reasonably anticipated to be a human carcinogen* in the Report on Carcinogens:

- bromochloroacetic acid
- bromodichloroacetic acid
- chlorodibromoacetic acid
- dibromoacetic acid
- dichloroacetic acid
- tribromoacetic acid

The available data (NTP 2018) were inadequate to evaluate haloacetic acids either as a class or as subclasses, such as those based on the number of halogen substitutions (one, two, or three) or the halogen atom(s) substituted (chlorine, bromine, or iodine) or to support listing of any of the other seven haloacetic acids identified in drinking water (monochloroacetic acid, monobromoacetic acid, monoiodoacetic acid, diiodoacetic acid, bromoiodoacetic acid, chloroiodoacetic acid, or trichloroacetic acid).

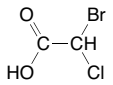
The profiles for the six listed haloacetic acids follow this introduction. The listings for bromochloroacetic acid, bromodichloroacetic acid, dibromoacetic acid, and dichloroacetic acid are based on cancer studies in experimental animals, and the listings for chlorodibromoacetic acid and tribromoacetic acid are based on other relevant data, including data on mechanisms of carcinogenesis. Most of the supporting mechanistic and other relevant information and the data on properties, use, production, exposure, and U.S. regulations to limit exposure are applicable to all six listed haloacetic acids. Therefore, the carcinogenicity data from cancer studies in experimental animals and in humans are discussed separately for each chemical, followed by combined discussions of absorption and metabolism, mechanisms of carcinogenesis, properties, use, formation and removal of disinfection by-products, exposure, regulations, and guidelines for all six listed haloacetic acids.

Bromochloroacetic Acid

CAS No. 5589-96-8

Reasonably anticipated to be a human carcinogen

First listed in the *Fifteenth Report on Carcinogens* (2021)



Carcinogenicity

Bromochloroacetic acid is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence from mechanistic studies that demonstrate the biological plausibility of its carcinogenicity in humans.

Cancer Studies in Experimental Animals

Administration of bromochloroacetic acid in the drinking water caused liver tumors in mice of both sexes and tumors at several other tissue sites in rats of both sexes. The studies were considered to have high utility for evaluating carcinogenicity because they tested sufficient numbers of experimental animals for near-lifetime exposures using adequate study designs, dosing, and pathology methods. Bromochloroacetic acid significantly increased the incidences of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in male and female mice and caused significant dose-related increases in the incidence of another type of malignant liver tumor (hepatoblastoma) in male mice. Significantly increased incidences were observed in malignant mesothelioma of the abdominal-pelvic peritoneum in male rats and in multiple fibroadenomas of the mammary gland in female rats. In addition, very rare adenomas of the large intestine were reported in rats of both sexes; the incidences were significantly increased in males and showed significant dose-related trends in both sexes. Fibroadenoma of the mammary gland and adenoma of the large intestine can progress to malignancy (NTP 2009).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to bromochloroacetic acid. A cohort study of post-menopausal

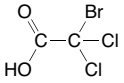
women found no association between estimated exposure to bromochloroacetic acid in drinking water and the risk of kidney cancer (Jones *et al.* 2017).

Bromodichloroacetic Acid

CAS No. 71133-14-7

Reasonably anticipated to be a human carcinogen

First listed in the *Fifteenth Report on Carcinogens* (2021)



Carcinogenicity

Bromodichloroacetic acid is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence fom mechanistic studies that demonstrate the biological plausibility of its carcinogenicity in humans.

Cancer Studies in Experimental Animals

Administration of bromodichloroacetic acid in the drinking water caused tumors at several different tissue sites in mice and rats. The studies were considered to have high utility for evaluating carcinogencity because they tested sufficient numbers of experimental animals for near-lifetime exposures using adequate study designs, dosing, and pathology methods. Significant dose-related increases in malignant liver tumors (hepatocellular carcinoma and hepatoblastoma) were observed in mice of both sexes, and increased incidences of benign liver tumors (hepatocellular adenoma) were observed in female mice. In male mice, increased incidences of benign tumors and combined benign and malignant tumors of the Harderian gland (an accessory tear gland) were observed, with dose-related trends in incidence. Tumors with significantly increased incidences in male rats included malignant mesothelioma of the abdominal-pelvic peritoneum and several types of skin tumors, including fibroma (a benign tumor) and the combined incidence of several types of malignant tumors or benign tumors that can progress to malignancy (squamous-cell papilloma, keratoacanthoma, sebaceous-gland adenoma, basal-cell adenoma, basal-cell carcinoma, or squamous-cell carcinoma). Female rats developed multiple fibroadenomas and carcinoma of the mammary gland, which increased in incidence with increasing dose of bromodichloroacetic acid (NTP 2015).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to bromodichloroacetic acid.

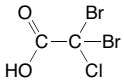
Chlorodibromoacetic Acid

CAS No. 5278-95-5

Reasonably anticipated to be a human carcinogen

First listed in the *Fifteenth Report on Carcinogens* (2021)

Also known as dibromochloroacetic acid



Carcinogenicity

Chlorodibromoacetic acid is *reasonably anticipated to be a human carcinogen* based on (1) metabolism studies providing convincing evidence that chlorodibromoacetic acid is metabolized to bromochloroacetic acid, (2) sufficient evidence for the carcinogenicity of bromochloroacetic acid from studies in experimental animals, and (3) supporting evidence from mechanistic studies that demonstrate the biological plausibility of its carcinogenicity in humans. No cancer studies in humans or experimental animals exposed to chlorodibromoacetic acid were identified.

Findings from a toxicokinetics study of rats orally exposed to chlorodibromoacetic acid suggest that it is highly metabolized *in vivo;* however, this study modeled rates of metabolism and excretion without identifying specific metabolites (Schultz *et al.* 1999). *In vitro* studies found that all metabolism of chlorodibromoacetic acid resulted from loss of a bromide ion to form bromochloroacetic acid, indicating that bromochloroacetic acid is the only metabolite (Saghir *et al.* 2011). These studies used rat and human microsomes (enzymes extracted from liver cells as small particles) exposed to chlorodibromoacetic acid under conditions that mimic those *in vivo* (e.g., at oxygen levels similar to those measured in liver tissue).

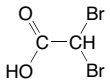
In the case of bromochloroacetic acid, administration in the drinking water caused liver and Harderian-gland tumors in mice and malignant mesothelioma, mammary-gland tumors, and skin tumors in rats (NTP 2009 and as described above). Mechanistic studies show that chlorodibromoacetic acid (like bromochloroacetic acid) causes mutations in bacteria and oxidative stress and DNA damage in cultured mammalian cells. These effects are characteristic of other human carcinogens, supporting the biological plausibility of the carcinogenicity of chlorodibromoacetic acid in humans. Therefore, it is reasonably anticipated that chronic oral exposure of humans to chlorodibromoacetic acid could cause cancer.

Dibromoacetic Acid

CAS No. 631-64-1

Reasonably anticipated to be a human carcinogen

First listed in the *Fifteenth Report on Carcinogens* (2021)



Carcinogenicity

Dibromoacetic acid is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence from mechanistic studies that demonstrate the biological plausibility of its carcinogenicity in humans.

Cancer Studies in Experimental Animals

Administration of dibromoacetic acid in the drinking water caused tumors at several different tissue sites in mice and rats. The studies were considered to have high utility for evaluating carcinogenicity because they tested sufficient numbers of experimental animals for near-lifetime exposures using adequate study designs, dosing, and pathology methods. Dibromoacetic acid caused significant dose-related increases in the incidences of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in male and female mice and another type of malignant liver tumor (hepatoblastoma) in male mice. In addition, significant increases were observed in the combined incidence of benign and malignant lung tumors (alveolar/

bronchiolar adenoma and carcinoma) in male mice. In rats, significant dose-related increases were observed in the incidence of malignant mesothelioma of the abdominal-pelvic peritoneum (the lining of the abdominal cavity) in males and in mononuclear-cell leukemia in females (NTP 2007). Although the background rates of mononuclear-cell leukemia in rats are high and variable, the incidence of these neoplasms in the mid- and high-dose exposure groups exceeded the background rates (historical controls), which increases confidence that dibromoacetic acid caused this type of leukemia.

Cancer Studies in Humans

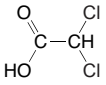
No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to dibromoacetic acid. A cohort study of post-menopausal women found no association between the risk of kidney cancer and estimated exposure via drinking water to a mixture of haloacetic acids that contained dibromoacetic acid (Jones *et al.* 2017).

Dichloroacetic Acid

CAS No. 79-43-6

Reasonably anticipated to be a human carcinogen

First listed in the *Fifteenth Report on Carcinogens* (2021)



Carcinogenicity

Dichloroacetic acid is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence from mechanistic studies that demonstrate the biological plausibility of its carcinogenicity in humans.

Cancer Studies in Experimental Animals

Administration of dichloroacetic acid in the drinking water caused liver tumors in rats and mice. All of the studies were considered to have moderate to high utility for evaluating carcinogenicity, and the findings could not be explained by potential biases. In mice of both sexes, significant increases in benign and malignant liver tumors (hepatocellular adenoma and carcinoma) were observed in several studies (Herren-Freund *et al.* 1987, DeAngelo *et al.* 1991, 1999, Daniel *et al.* 1992, Pereira 1996). In a stop-exposure study, male and female mice were exposed at weaning (four weeks of age) to dichloroacetic acid in drinking water for 10 weeks, followed by no further exposure to this chemical for 80 weeks. Significant increases in benign and malignant liver tumors were reported for both sexes, and tumor incidences approached levels found with near-lifetime exposures (Wood *et al.* 2015). Dichloroacetic acid also significantly increased the incidence of hepatocellular carcinoma and combined hepatocellular adenoma and carcinoma in male rats in two drinking-water studies (DeAngelo *et al.* 1996). (Female rats were not tested for carcinogenicity in these studies.)

Cancer Studies in Humans

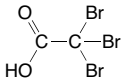
The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to dichloroacetic acid. A cohort study of post-menopausal women found no association between estimated exposure to dichloroacetic acid in drinking water and the risk of kidney cancer (Jones *et al.* 2017).

Tribromoacetic Acid

CAS No. 75-96-7

Reasonably anticipated to be a human carcinogen

First listed in the *Fifteenth Report on Carcinogens* (2021)



Carcinogenicity

Tribromoacetic acid is *reasonably anticipated to be a human carcinogen* based on (1) metabolism studies providing convincing evidence that tribromoacetic acid is metabolized to dibromoacetic acid, (2) sufficient evidence for the carcinogenicity of dibromoacetic acid from studies in experimental animals, and (3) supporting evidence from mechanistic studies that demonstrate the biological plausibility of its carcinogenicity in humans. No cancer studies in humans or experimental animals exposed to tribromoacetic acid were identified.

Findings from a toxicokinetics study of rats orally exposed to tribromoacetic acid suggest that it is highly metabolized *in vivo*; however, this study modeled rates of metabolism and excretion without identifying specific metabolites (Schultz *et al.* 1999). An *in vitro* study found that half of the total metabolism of tribromoacetic acid resulted from the loss of a bromide ion to form dibromoacetic acid (Saghir *et al.* 2011), indicating that dibromoacetic acid is the major metabolite. These studies used rat and human microsomes exposed to tribromoacetic acid under conditions that mimic those *in vivo* (e.g., at oxygen levels similar to those measured in liver tissue).

Administration of dibromoacetic acid in the drinking water caused liver and lung tumors in mice and malignant mesothelioma and mononuclear-cell leukemia in rats (NTP 2007 and as described above). Mechanistic studies showed that tribromoacetic acid (like dibromoacetic acid) causes mutations in bacteria and oxidative stress and DNA damage in cultured mammalian cells. These effects are characteristic of other human carcinogens, supporting the biological plausibility of the carcinogenicity of tribromoacetic acid in humans. Therefore, it is reasonably anticipated that chronic oral exposure of humans to tribromoacetic acid could cause cancer.

Selected Haloacetic Acids

Carcinogenicity: Mechanistic and Other Relevant Data

The mechanisms by which these haloacetic acids cause cancer in experimental animals are not known and most likely involve several modes of action. Although many of the haloacetic acids cause similar effects *in vitro* and *in vivo*, the available mechanistic and other relevant data are insufficient to enable evaluation of the carcinogenicity of haloacetic acids as a class or subclass (NTP 2018, Section 7).

Absorption and Metabolism

Ingested haloacetic acids are rapidly absorbed from the gastrointestinal tract and are found in the blood and tissues at approximately equal concentrations. Metabolism of dihaloacetic and trihaloacetic acids is complex, but the limited data available suggest that metabolism of a trihaloacetic acid to dihaloacetic acid is similar in rodents and humans (Stacpoole *et al.* 1998, Merdink *et al.* 2000, Saghir and Schultz 2005, Saghir *et al.* 2011). Dihaloacetic acids are metabolized to a greater extent than trihaloacetic acids, and their metabolism re-

sults in formation of the metabolites glyoxylate, glycolate, oxylate, glycine, and carbon dioxide.

The three trihaloacetic acids discussed here (bromodichloroacetic acid, chlorodibromoacetic acid, and tribromoacetic acid) are metabolized by liver enzymes (cytochrome P450) to remove one of the halogens, forming a dihaloacetic acid (dichloroacetic, bromochloroacetic, or dibromoacetic acid). An important effect of this metabolism relevant to potential mechanism(s) of carcinogenesis is the formation of a highly reactive free radical as part of the process. The chemical nature of bromine makes it the halogen most likely to be removed in this conversion (Saghir *et al.* 2011).

Studies on Mechanisms of Carcinogenesis

Haloacetic acids have a weak positive charge (i.e., are weak electrophiles) and are attracted to macromolecules (proteins, lipids, DNA, or RNA) with a weak negative charge (i.e., weak nucleophiles), such as thiol or amino groups on proteins; stronger electrophiles can also bind with oxygen in DNA and RNA. The body of data suggests that these listed haloacetic acids may induce cancer through reactions with macromolecules leading to oxidative stress, mutagenic and genotoxic effects, inhibition of enzymes leading to oxidative stress, and/or regulation of genes involved in carcinogenicity.

Most of the available mechanistic data on the haloacetic acids are from *in vitro* studies measuring oxidative stress, genotoxicity, and toxicity. In general, *in vitro* studies indicate that dihaloacetic acids are more genotoxic, cytotoxic, and mutagenic than trihaloacetic acids, and that substitution of bromine for one of the hydrogen atoms on the alpha carbon (as shown in the figure in Properties, below) has a more potent effect on these properties than substitution of chlorine (Kargalioglu *et al.* 2002, Plewa *et al.* 2004, Stalter *et al.* 2016). All of the listed haloacetic acids cause oxidative stress (assessed in various types of *in vitro* assays), which leads to the generation of reactive oxygen species that can damage DNA and cause mutations. In addition, exposure of experimental animals to some dihaloacetic and trihaloacetic acids (dichloroacetic, dibromoacetic, bromochloroacetic, and bromodichloroacetic acids, the only ones tested) caused oxidative stress (as evidenced by formation of 8-hydroxydeoxyguanosine DNA adducts and lipid peroxidation); the strongest response was to the brominated haloacetic acids (Larson and Bull 1992, Austin *et al.* 1996). The types of pathways that generate oxidative stress may vary across the haloacetic acids, and several pathways may be involved (Cemeli *et al.* 2006, Celik *et al.* 2009, Pals *et al.* 2011, Ondricek *et al.* 2012, Dad *et al.* 2013, El Arem *et al.* 2014a,b,c, Stalter *et al.* 2016).

Overall, the data suggest that haloacetic acids do not bind to DNA, and most likely cause genotoxicity through oxidative stress. Both the dihaloacetic acids (dichloroacetic, dibromoacetic, and bromochloroacetic acids) and trihaloacetic acids (tribromoacetic, bromodichloroacetic, and chlorodibromoacetic acids) listed here caused mutations in bacteria (NTP 2018, Section 6). Evidence for other types of genotoxicity is limited, because only a few haloacetic acids (mostly the dihaloacetic acids) were tested for each type of damage, and the findings for each end point were not always consistent across different haloacetic acids. The strongest evidence is that bromine-containing haloacetic acids (dibromoacetic, tribromoacetic, and bromochloroacetic acids) damage DNA (e.g., cause DNA strand breaks) and that dibromoacetic acid and dichloroacetic acid damage chromosomes (as indicated by micronucleus formation) and cause gene mutations *in vitro* (NTP 2018, Section 6).

Studies provide some insight into one of the mechanisms leading to oxidative stress. Dichloroacetic acid has been shown to affect energy metabolism within the cell by inhibiting a mitochondrial enzyme complex (pyruvate dehydrogenase complex), thus enhancing oxidative metabolism and potentially increasing the formation of reactive oxygen species and DNA damage and mutations, if not correctly repaired (Pals *et al.* 2011). This mechanism could potentially operate with other haloacetic acids as well. Another mechanism by which some haloacetic acids (dichloroacetic, dibromoacetic, and bromochloroacetic acids) can cause oxidative stress is via the inhibition of an enzyme involved in dihaloacetic acid metabolism (glutathione S-transferase zeta), which results in reduced metabolism and clearance of dihaloacetic acids, induction of oxidative stress, and activation of stress-response pathways (Anderson *et al.* 1999, Gonzalez-Leon *et al.* 1999).

Other studies suggest that dichloroacetic acid and dibromoacetic acid might cause cancer by regulating genes related to carcinogenicity (e.g., *c-myc*, *c-jun*, or *IGF-II*, which can promote cell growth, division, or death). Dichloroacetic acid induced hypomethylation (loss of methyl groups in DNA nucleotides) in the promoter region of the *c-myc* gene in liver, kidney, and urinary-bladder tissues in mice; enhanced cellular proliferation in mouse liver (Ge *et al.* 2001); and promoted liver tumors (Tao *et al.* 2000) and kidney tumors (Pereira *et al.* 2001) in mice.

Properties

Haloacetic acids are nonvolatile water-soluble chemicals (i.e., they do not readily evaporate). They vary in the number and type of halogen (fluorine, chlorine, bromine, or iodine) substitutions at the alpha carbon of acetic acid (as shown in the figure below). The selected haloacetic acids listed here have either two or three halogen substitutions of either chlorine or bromine. The physicochemical characteristics of each haloacetic acid depend on the numbers of chlorine and bromine atoms in the molecule.

Dihaloacetic acids **Trihaloacetic acids**

α = alpha carbon; X = halogen atom (chlorine or bromine).

At physiological pH, these haloacetic acids are in ionized form (i.e., they lose a hydrogen ion and have a negative charge). The negative log of the acid dissociation constant (pK_a, shown in the table on the next page) is a measure of the strength of an acid in solution, which increases as pK_a decreases. Therefore, trihaloacetic acids, which have lower pK_a values, are stronger acids than dihaloacetic acids. The pK_a and two other physicochemical properties are likely to be related to the toxicity of haloacetic acids, because they describe the ability of the molecules to enter cells and their potential reactivity with other molecules within a cell. Uncharged molecules enter cells much more readily than charged ones, so the potential for ionization as measured by pK_a helps predict that movement. In addition, the relative solubility of the molecule in lipids (fatty substances) compared with water also determines how readily that molecule will cross the lipid-rich cell membranes; chemists define this as the "octanol-water partition coefficient" ($\log K_{ow}$), with octanol representing the lipids. Both pK_a and $\log K_{ow}$ also affect the potential reactivity of a molecule, along with the energy of the lowest unoccupied molecular orbital (E_{LUMO}) where an electron could exist, which is a measure of its ability to exchange electrons with other molecules. The toxic potency of a haloacetic acid correlates with its reactivity in accepting electrons from other molecules, and is higher for brominated than chlorinated haloacetic acids (Plewa *et al.* 2004, Pals *et al.* 2011). A haloacetic acid molecule's reactivity increases as the energy required to break the

Haloacetic acid	Molecular weight[a]	Water solubility (g/100 mL)[a,b]	Vapor pressure (mm Hg)[a,b]	Log K_{ow}[a]	Dissociation constant (pK_a)[c]	E_{LUMO} (eV)[c,d]
Bromochloroacetic acid	173.4	25	0.14	0.61	1.40	7.78
Bromodichloroacetic acid	207.8	0.49	0.036	1.53	0.05	6.65
Chlorodibromoacetic acid	252.3	0.24	0.0052	1.62	0.04	6.42
Dibromoacetic acid	217.8	211	0.023	0.70	1.39	7.51
Dichloroacetic acid	128.9	100 at 20°C	0.179	0.92	1.41	8.44
Tribromoacetic acid	296.7	20	0.00028	1.71	0.03	6.12

Sources: [a]PubChem 2020a,b,c,d,e,f. [c]Stalter et al. 2016.
[b]Reported at 25°C (298.15°K) except as indicated. [d]Deprotonated (acetate form).

bonds with the alpha carbon and its E_{LUMO} value decrease. Physical and chemical properties of the six listed haloacetic acids are shown in the table on the next page.

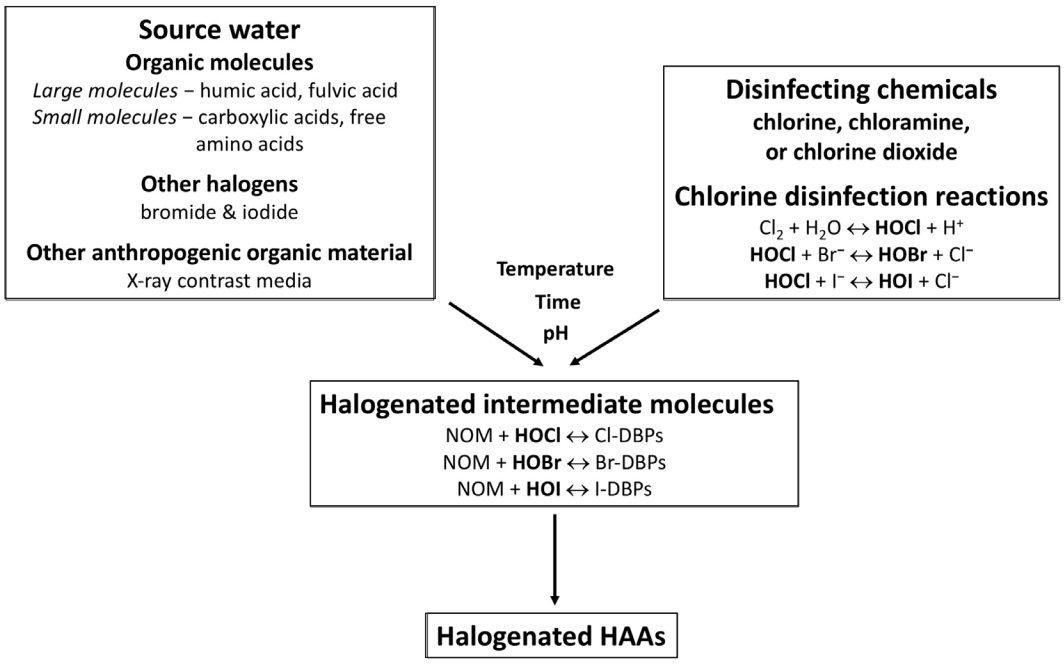
Use

Although the focus of this profile is exposure to haloacetic acids found in drinking water, some of these haloacetic acids are also used for commercial purposes. Dichloroacetic acid is used as a chemical manufacturing intermediate (e.g., in the production of glyoxylic acid), a laboratory reagent in polyethylene terephthalate production, a skin cauterizing agent, a medical disinfectant (e.g., a substitute for formalin), and treatment for congenital lactic acidosis, and it has been proposed as a targeted cancer therapeutic agent (IARC 2014). Tribromoacetic acid has been used in organic synthesis (PubChem 2020f), and dibromoacetic acid and bromochloroacetic acid have been reported to be used in research (IARC 2013).

Formation and Removal of Disinfection By-products

The purpose of water disinfection is to remove contaminants and disease-causing agents from drinking water (CDC 2015). The most common steps in conventional water treatment are coagulation and flocculation, sedimentation, filtration, disinfection, and storage (CDC 2015, EPA 2016a). Water disinfection is regulated by EPA through Surface Water Treatment Rules, which established maximum contaminant level goals for viruses, bacteria (such as *Legionella*), and other microorganisms (such as the protozoans *Giardia lamblia* and *Cryptosporidium*). EPA regulates five of the most common haloacetic acids (HAA5) in the public water supply: monochloroacetic acid, dichloroacetic acid, monobromoacetic acid, dibromoacetic acid, and trichloroacetic acid. In order to support national drinking water standards, EPA has more recently required monitoring of nine common haloacetic acids (HAA9): monochloroacetic acid, dichloroacetic acid, monobromoacetic acid, dibromoacetic acid, trichloroacetic acid, bromochloroacetic acid, chlorodibromoacetic acid, bromodichloroacetic acid, and tribromoacetic acid.

The presence of haloacetic acids in disinfected drinking water in the United States is well established, and knowledge of the chemical and physical processes that lead to their formation is important to help control their levels as required by law and to protect public health. The factors that determine the types and amounts of disinfection by-products formed during water treatment include (1) the presence of organic matter and inorganic matter in the source water, which varies daily and seasonally in concentration, (2) the disinfecting chemicals used, (3) how long the organic matter is exposed to the disinfecting chemicals, (4) the temperature at which the disinfection process takes place, and (5) the pH of the water during the disinfection process. (The relationships among these factors are summarized in the diagram below.) The organic molecules in source



Major factors affecting the formation of halogenated disinfection by-products

Organic molecules in source water plus naturally occurring or anthropogenic bromide and iodide react with various chlorine-containing disinfecting chemicals to form halogenated intermediate molecules and ultimately the halogenated HAAs.

HOCl = hypochlorous acid; HOBr = hypobromous acid; HOI = hypoiodous acid; NOM = natural organic matter; DBPs = disinfection by-products.

water are often large, complex molecules, from which intermediate molecules are formed as a result of exposure to disinfecting chemicals. Further reaction between these intermediate molecules and disinfecting chemicals during disinfection and storage result in the formation of halogenated by-products, including haloacetic acids (NTP 2018, Section 2).

Three general approaches are used for remediation of haloacetic acid disinfection by-products: (1) removal of precursors before disinfection, (2) optimization or modification of disinfection practices (e.g., altering disinfectant type, dose, or application point in the water treatment process), and (3) removal of disinfection by-products after formation. Before treatment, alum coagulation combined with the use of ion-exchange resins can remove up to 80% of precursors, activated charcoal filtration can remove up to 91%, and membrane nanofiltration can remove up to 99%. Disinfection practices can be modified through the use of ozone and ultraviolet irradiation, which do not leave residual chlorine in the water, or by using a non-chlorinated pre-oxidation chemical. Haloacetic acids can be removed after their formation through biologically active granular activated charcoal filtration.

Exposure

Disinfection of water has achieved tremendous public health benefits in the United States and worldwide through reduction in exposure of individuals to disease-causing microorganisms. Over 250 million people in the United States potentially are exposed to chlorinated drinking water, indicating that a significant number of people in the United States are exposed to haloacetic acids found as water disinfection by-products. Humans are exposed to haloacetic acids though drinking of tap water, consumption of beverages and food that have come in contact with treated water, and ingestion, dermal, and inhalation exposure to disinfected water in swimming pools and spas (both occupational and recreational). In addition, people can be occupationally exposed to dichloroacetic acid at workplaces where it is used as a chemical intermediate or through its use as a medical disinfectant.

Occurrence of Haloacetic Acids in Treated Water

The listed haloacetic acids that have been detected at the highest levels are dichloroacetic acid, bromochloroacetic acid, and bromodichloroacetic acid. The concentration ranges at which they have been detected are shown in the table below.

Listed haloacetic acid	Concentration range (µg/L)[a]	Reference
Bromochloroacetic acid	< LOD–18	IARC 2013, PubChem 2020a
Bromodichloroacetic acid	5.28–12.2	PubChem 2020b
Chlorodibromoacetic acid	< LOD–5.37	PubChem 2020d
Dibromoacetic acid	2.1 (0.63–12)[b]	EPA 2016b
Dichloroacetic acid	10.4 (1.3–32)[b]	EPA 2016b
Tribromoacetic acid	0–~10	McGuire *et al.* 2002

[a]LOD = limit of detection (not specified). [b]Median (5th percentile–95th percentile).

According to national occurrence data from the American Water Works Association for HAA5 in U.S. water disinfection systems serving populations greater than 100,000 people from 1997 to 2014, 95th percentile HAA5 concentrations generally have been decreasing since 2000 and have been at or below the EPA maximum contaminant level (MCL) of 60 µg/L since 2004 (Seidel *et al.* 2017). However, there is evidence that smaller facilities might have had more difficulty meeting this regulatory limit; EPA data indicate that from 1997 to 2004, at least 5% of smaller systems (serving fewer than 10,000 people) exceeded the HAA5 MCL. Data on HAA5 for U.S. water facilities serving communities of all sizes in 2011 indicate a median concentration of 20.1 µg/L, with the 5th percentile at 2.0 µg/L and the 95th percentile at 59.0 µg/L.

Overall Potential Exposure to Haloacetic Acids

Average daily exposure to mixtures of haloacetic acids from consumption of chlorinated tap water in the United States can be estimated as about 69 µg (5% to 95% = 6.9 to 204 µg) for men and 55 µg (5% to 95% = 5.5 to 162.2 µg) for women, based on median levels of mixtures of haloacetic acids in U.S. water facilities (2011 levels for facilities of all sizes). Daily consumption of water from all foods and liquids by adults over the age of 20 has been estimated by the Centers for Disease Control and Prevention (Rosinger and Herrick 2016) to be 3.46 L for men and 2.75 L for women, with plain tap water accounting for about one third of the total.

Sources of Exposure Other Than Drinking Water

In addition to ingesting haloacetic acids by drinking plain tap water, humans can be exposed to them in other beverages prepared with chlorinated water, such as tea, coffee, fruit drinks, and soft drinks, or by eating food that has come in contact with treated water, such as by being rinsed or washed before or after cooking or cooked in chlorinated water. Low levels of haloacetic acids may also be present in natural foods. The median amounts of haloacetic acids in food range from less than 1 µg/kg in milk to over 10 µg/kg in soft drinks, prepared salads, and minimally processed vegetables, such as fruits or vegetables washed with chlorine-based chemicals in water (Cardador and Gallego 2016). The levels of haloacetic acids in canned vegetables, fruit juices, and cheese fall between these levels. The Institute of Medicine has estimated that 20% of total water consumption is derived from foods; in addition to the 33% from tap water, the remaining 47% would derive from beverages such as tea, coffee, soft drinks, and fruit drinks (Institute of Medicine 2005).

The disinfection of water in swimming pools and spas often results in higher levels of haloacetic acids than in disinfected tap water, because of the use of a higher chlorine residual (level of chlorine remaining after initial treatment) and higher temperatures than in typical water distribution systems (Parinet *et al.* 2012, Chowdhury *et al.* 2014). Dichloroacetic acid is the most abundant haloacetic acid detected in swimming pools (Teo *et al.* 2015); in U.S. swimming pools disinfected with chlorine, its concentration has been reported to range from 52 to 6,800 µg/L (Kanan 2010, Teo *et al.* 2015). Brominated haloacetic acids (including dibromoacetic, bromodichloroacetic, and chlorodibromoacetic acid) occur at the highest concentrations in seawater swimming pools treated with chlorine bleach as disinfectant; levels of mixtures of haloacetic acids (HAA9) ranged from 417 to 2,233 µg/L in seawater pools tested (Parinet *et al.* 2012). Dermal exposure (accounting for about 1% of total exposure to haloacetic acids from swimming pools and spas) and inhalation exposure (accounting for about 5% of the exposure) are not considered major routes of exposure, as haloacetic acids are neither volatile nor appreciably absorbed through the skin (Xu *et al.* 2002, Regli *et al.* 2015). About 94% of exposure to haloacetic acids from swimming pools is through ingestion of pool water (Cardador and Gallego 2011), and haloacetic acids have been detected in the urine of swimming pool attendants and swimmers. Urinary dichloroacetic acid levels for indoor swimming pool attendants were positively correlated with length of exposure (increasing from 313 ng/L at 2 hours to 450 ng/L at 4 hours) and were higher than those for outdoor pool attendants (51 ng/L at 2 hours) (Cardador and Gallego 2011).

Regulations

Department of Transportation (DOT)

Dichloroacetic acid is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Safe Drinking Water Act

Maximum contaminant level (MCL) for HAA5 = 60 μg/L.

Food and Drug Administration (FDA)

Maximum permissible level of HAA5 in bottled water = 60 μg/L.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 ppm for dichloroacetic acid.
Dichloroacetic acid is listed as a confirmed animal carcinogen with unknown relevance to humans.
Potential for dermal absorption for dichloroacetic acid.

Environmental Protection Agency (EPA)

Integrated Risk Information System (IRIS) oral reference dose (RfD) = 4×10^{-3} mg/kg b.w. per day for dichloroacetic acid.
IRIS oral cancer slope factor = 5×10^{-2} per mg/kg b.w. per day for dichloroacetic acid.
IRIS drinking water unit risk = 1.4×10^{-6} per μg/L for dichloroacetic acid.

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