Bromine as a drinking-water disinfectant

World Health Organization

Alternative drinking-water disinfectants: bromine

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List of abbreviations and terms used in the document

ADI	acceptable daily intake
Br^-	bromide
Br_2	elemental bromine
BrCl	bromine monochloride
bw	body weight
DBP	disinfection by-product
DMH	dimethylhydantoin
GDWQ	Guidelines for Drinking-water Quality
HAA	haloacetic acid
$HOBr^-$	hypobromous acid
HOCl	hypochlorous acid
HWT	household water treatment
IARC	International Agency for Research on Cancer
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LRV	$\log_{10}$ reduction value
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NTP	National Toxicology Program
OBr^-	hypobromite
OCl^-	hypochlorite
POU	point-of-use
PPM	parts per million
THM	trihalomethane

UK	United Kingdom
USA	United States of America
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

1. Introduction

Disinfection of water has greatly contributed to reducing risks to public health from microbiologically-contaminated drinking-water.

Numerous disinfection techniques have been developed over the centuries that are used in a wide range of applications, ranging from large and small public drinking-water plants to point-of-entry and point-of-use (POU) treatment devices.[1] Although chlorine has been used for more than 100 years, and several other disinfectants have been studied extensively, in many cases questions remain with respect to the optimization of biocidal effectiveness under a range of conditions (i.e. efficacy), the chemistry of the formation and toxicological significance of disinfection by-products (DBPs), interactions with other water components, and the biocidal effectiveness and toxicology of disinfectant residuals. Chemical disinfectants can react with natural organic matter or break down to produce unwanted by-products. Many newer products and applications are being developed and marketed for use, particularly in developing countries, however, the same unanswered questions exist about these, including their efficacy and potential for DBP formation.

Elemental bromine (Br_2), bromine monochloride (BrCl), hypobromous acid ($HOBr^-$) and bromodimethylhydantoin are used in swimming pools and marketed as a replacement for chlorine, with one advantage being that there are no asthma-related problems for individuals in contact with the disinfected water (e.g. swimmers and/or lifeguards).[2] Bromine in various chemical forms is also used in water fountains and cooling towers. In general, the use of bromine in potable water disinfection is very limited and is impeded by costs, concerns about brominated DBPs, as well as a lack of knowledge on its efficacy in certain areas. However, some applications do exist, as bromine is used to disinfect potable water in non-residential settings, for example, aboard ships and on oil and gas drilling/production platforms. Due to the safety risks of handling liquid bromine (i.e. burns to hands and eyes, release of toxic vapour), it is combined, for example, with dimethylhydantoin (DMH) to form bromodimethylhydantoin and other polymeric brominated hydantoins for disinfection applications. Bromodimethylhydantoin is provided as tablets or cartridges which dissolve slowly to release hypobromous acid. Hypobromous acid can also be generated on site by reaction between sodium bromide and chlorine. In addition, bromine is also combined with chlorine, both of which are hazardous and corrosive, to produce bromine monochloride, which is also classified as hazardous and corrosive.[3] Polymeric brominated hydantoins provide an immobilized controlled source of bromine release. For example, an immobilized bromine flow-through product is currently used in POU water treatment products (see section 2.2.3).

The emphasis of this literature review is to evaluate the available evidence on the biocidal efficacy and toxicity of bromine (Br_2, and other forms) as a water disinfectant. Information included in this review was obtained using a targeted literature search strategy, with inclusion dates up to November 2013 and further "ad hoc" searches were carried out up to the closing date for public review (16 December 2016). Further details of the search strategy are included in Appendix 1.

[1] Point-of-use devices treat only the water intended for direct consumption (drinking and cooking), typically at a single tap or limited number of taps, while POE treatment devices are typically installed to treat all water entering a single home, business, school, or facility.

[2] Although there is some literature relating to health effects associated with dermal exposure of regular swimmers to bromine in swimming pools, this is beyond the scope of this document.

[3] See: http://echa.europa.eu/en/substance-information/-/substanceinfo/100.034.169

2. Disinfectant characteristics and efficacy

2.1 Chemistry basics

Bromine, chlorine, iodine, and fluorine belong to the halogen group of elements. All of the halogens share the common property of being oxidants with seven electrons in their outer shell. As oxidizing agents, halogens accept an electron to become the analogous halide ion. Different halogens vary in their oxidation potential. The halogen with the strongest oxidative power is fluorine, followed by chlorine, bromine, and iodine. Their reactivities are directly correlated with their electronegativities, which are as follows (based on the Pauling nomenclature of electronegativity values):[4]

fluorine (3.98) > chlorine (3.16) > bromine (2.96) > iodine (2.66).

The reactivities of the given halogens therefore decrease from left to right. Nevertheless, the usefulness of a particular halogen as a disinfectant is determined not only by its reactivity, but also by its manageability, selectivity, chemical stability, and other factors including the potential to form by-products. At ambient temperature, bromine is a brownish-red corrosive liquid. It is the only non-metallic element that is liquid under Standard Ambient Temperature and Pressure (SATP[5]), and evaporates easily under conditions slightly above SATP as a red vapour with a strong irritating odour resembling that of chlorine.

2.1.1 Water solubility, taste and odour

Bromine is more soluble in water than iodine, but less so than chlorine. Water solubility is reported to be 3.55 g/100 mL (West, 1984).

Free halogen residuals usually produce tastes and odours in potable water. Bryan et al. (1973) compared taste threshold determinations of chlorine, iodine and bromine residuals in water. The threshold taste values for chlorine residuals varied with pH: 0.075 mg/L at pH 5.0; 0.156 mg/L at pH 7.0; and 0.450 mg/L at pH 9.0. In contrast, threshold taste values for iodine and bromine did not vary appreciably with pH, ranging from 0.147 to 0.204 mg/L for iodine and 0.168 to 0.226 mg/L for bromine. Chlorine has a high vapour pressure (5100 mm Hg at 20 °C) and readily volatilizes, especially in the presence of sunlight or higher temperatures; iodine has a low vapour pressure (1 mm Hg at 38.7 °C) resulting in little loss by volatilization. Bromine has a vapour pressure between chlorine and iodine of 175 mm Hg at 20 °C with an odour threshold of 0.05 to 3.5 mg/L (IPCS, 1999).

2.1.2 Chemical speciation of bromine in water and corresponding disinfection powers

Elemental bromine (Br_2) disproportionates rapidly in water to give bromide (Br^-) and hypobromous acid (HOBr), which is in equilibrium with hypobromite (OBr^-) in a pH-dependent manner (Table 1).

$$Br_2 + 2H_2O \leftrightarrow HOBr + H_3O^+ + Br^-$$

$$HOBr + 2H_2O \leftrightarrow OBr^- + H_3O^+$$

Bromide can be further oxidized to form bromate (BrO_3^-) via a complex series of oxidation/reduction disproportionation oscillation processes. Bromate is typically associated with use of ozone in water

[4] The Pauling scale is a dimensionless relative quantity that describes the electronegativity of an atom in the periodic table.

[5] SATP: 298.15 K (25 °C) 0.987 atm.

treatment, but there are situations where it can be formed in chlorinated water systems. Bromate can also be present as a by-product in hypochlorite from the electrolytic production of chlorine.

The different chemical species vary in their disinfection power. In analogy to hypochlorous acid (HOCl) and hypochlorite (OCl^-), hypobromous acid and hypobromite compounds display antimicrobial activity, with hypobromous acid being the more effective disinfectant. The most effective pH range for bromine to operate as a disinfectant is therefore between pH 6.0 and 8.5, when hypobromous acid predominates (Table 1). As hypobromous acid does not dissociate at alkaline pH as much as hypochlorous acid does, the disinfection efficacy of bromine is not as pH sensitive as chlorine (most effective pH range between 6.0 and 7.5; Table 1). In addition, bromine and hypobromous acid react with ammonia and amines to produce bromoamines that are more effective biocides than the corresponding chloramines (World Health Organization [WHO], 2004a). Thus, bromine has the potential to be a much more effective disinfectant than chlorine in sewage treatment and in other waters containing ammonia and other reduced forms of nitrogen.

Table 1: pH-dependent speciation of bromine and chlorine in water (Russel, 2006)

pH	Bromine		Chlorine	
	% bromine as $HOBr^-$	% bromine as OBr^-	% chlorine as HOCl	% chlorine as OCl^-
6.0	100	0	90.0	10.0
6.5	99.4	0.6	80.0	20.0
7.0	98.0	2.0	70.0	30.0
7.5	94.0	6.0	37.5	62.5
8.0	83.0	17.0	25.0	75.0
8.5	57.0	43.0	12.5	87.5

2.2 Disinfection efficacy of bromine

2.2.1 Microbiocidal efficacy of bromine

In the following section and in Table 2, results from selected studies on the efficacy of bromine are summarized.

Bromine is primarily used as an alternative disinfectant for swimming pools, spas and cooling tower water, but not for municipal drinking-water, partly due to cost and partly to concerns about the formation of brominated DBPs.

However, the disinfection of drinking-water with bromine has been recognized and allowed by the USEPA since 1976, although not for use as a municipal drinking-water disinfectant.[6] The use of

[6] In 2010, USEPA issued a Final Registration Review Decision for bromine (Case 4015) stating that the use of bromine to treat potable water does not trigger the need for a drinking-water assessment. In addition, the USEPA stated that "Bromine is registered for use to treat/disinfect potable water (examples of potable water system treatment sites include, but are not restricted to, aboard ships and on oil and gas drilling/production platforms)."

bromine to inactivate bacteria, viruses and protozoa has been reported in a number of laboratory-scale disinfection studies (Kim, 2014). Early studies on the germicidal action of bromine were reported by Tanner and Pitner (1939). The authors determined the concentration of free bromine (in the form of hypobromous acid) required to reduce aerobic spore-forming bacteria, mould spores, yeasts and non-spore forming bacteria to below detection limits within a set contact time (30 seconds) at room temperature; for aerobic spore-forming bacteria, the effect of neutral (pH 6.8–7.2) and low (pH 3.5–4.0) pH was also investigated (Table 2). The authors reported the resistance of the organisms to bromine to be in the following order (decreasing resistance):

bacterial spores > mould spores > yeasts and non-spore-forming bacteria.

For each aerobic spore-forming bacterium tested, bromine was 3–4 times more effective at the lower pH (Table 2).

Goodenough (1964) demonstrated the use of bromine as a disinfectant for swimming pool water. A residual of 0.8 mg/L greatly reduced (but did not eliminate) total bacterial counts; bactericidal activity was also shown to increase with decreasing pH within the range pH 7.8–7.0. Initial studies by Lindley (1966) on bromine efficacy against *Escherichia coli* and f2 coliphage, which were expanded on by Krusé et al. (1970), showed that free bromine at a level of 4 mg/L was able to bring about a 5 $\log_{10}$ reduction of *E. coli* and a 3.7 $\log_{10}$ reduction of f2 coliphage within 10 minutes at pH 7.0 and 0 ºC. Williams et al. (1988) showed that a water-soluble organic N-bromo oxazolidinone was 50 times more effective against *Staphylococcus aureus* than the N-chloro analog. A later study also highlighted the effectiveness of bromine against *Pseudomonas aeruginosa* at higher temperatures (38 ºC) (Clark and Smith, 1992).

Sharp et al. (1975) assessed the inactivation of reovirus by bromine (in the form of hypobromous acid) and reported a plateau of resistance after rapid inactivation of reovirus within the first three minutes (3 $\log_{10}$ reduction) using 0.75 mg/L bromine. As treatment continued, the disinfection rate decreased and finally did not result in further inactivation. Such resistance was not observed when subjecting reovirus suspensions to light centrifugation; this was probably due to the removal of aggregates (Sharp et al., 1975). Indeed, the negative impact of aggregates on the disinfection rate was confirmed in a follow-up study by the same authors, who reported first-order inactivation kinetics at a rate of 10^3 units/second for bromine (in the form of hypobromous acid) against reovirus (pH 7.2, 3.3 µM bromine; Sharp et al., 1976). Whereas this disinfection rate was measured with suspensions of single virus particles, disinfection efficacy decreased in the presence of small virus aggregates. It was suggested that aggregates strongly influenced viral resistance to bromine, as is the case with many disinfectants.

Further studies on the effects of virus particle aggregation on the effectiveness of bromine (in the form of hypobromous acid) disinfection kinetics have been reported by Floyd et al. (1976), using monodispersed poliovirus type 1 at pH 7.0 and a temperature range of 2 to 20 ºC. Greater inactivation was seen with increasing concentration of bromine (0.6–22 µM) and increasing temperature, with $\log_{10}$ reduction values (LRVs) ranging between 1 to 3.8 for contact times between 6 and 16 seconds. Use of monodispersed virus particles minimized virus aggregation, which is considered to provide a protective barrier against disinfection (Scarpino et al., 1972). For comparison, Floyd et al. (1978) demonstrated the efficacy of hypobromite and molecular bromine against poliovirus, with both bromine species able to achieve LRVs between 2 to 4 within 4 seconds at 4 ºC in buffered water.

The effectiveness of bromine against cysts of the protozoan parasite *Entamoeba histolytica* has been shown to be greater than chlorine or iodine (Stringer et al., 1975). In addition, evidence on bromine

inactivation of purified *Cryptosporidium parvum* oocyst infectivity in cell cultures has been reported (Kim, 2014). However, cystocidal studies assessing the inactivation of the waterborne protozoan parasite *Giardia lamblia* by bromine have not been identified.

Both bromine and chlorine will lose free residuals under similar conditions of oxidant demand. This has been reported for the use of bromine in cooling tower waters (with bromine concentrations of 400 mg/L and pH 7.7) where residual levels below 0.5 mg/L were reached within hours and were seen to be ineffective against *Legionella pneumophila* (Thomas et al., 1999). Further examples have been reported (Johnson & Overby, 1970; Mercado-Burgos et al., 1975). Bromine may be a superior disinfectant to chlorine when organic matter or ammonium is present as it provides a longer-term release of active bromine. Bromine has been reported to be more effective than chlorine to inactivate poliovirus in reclaimed water (derived from tertiary treated wastewater) containing dissolved organic matter and ammonia (Freund et al., 2010).

Table 2: Disinfection capabilities of bromine (HOBr)

Microorganism	Dose (mg/L)[a]	Comments	Log_{10} reduction value; contact time	Reference
Proteus vulgaris	40–60	pH 3.5–4.0	CK; 30 s	Tanner & Pitner (1939)
	170	pH 6.8–7.2	CK; 30 s	
		Temperature not stated		
Bacillus megatherium	28–35	pH 3.5–4.0	CK; 30 s	Tanner & Pitner (1939)
	110	pH 6.8–7.2	CK; 30 s	
		Temperature not stated		
Bacillus species (*mesentericus*, *subtilis* (565), *subtilis* (566))	160–220	pH 3.5–4.0	CK; 30 s	Tanner & Pitner (1939)
	> 450	pH 6.8–7.2	CK; 30 s	
		Temperature not stated		
Aspergillus niger	25–28	pH not stated; room temperature	CK; 15–30 s	Tanner & Pitner (1939)
Oöspora lactis	8.0	pH not stated; room temperature	CK; 15–30 s	Tanner & Pitner (1939)
Mucor species	30	pH not stated; room temperature	CK; 15–30 s	Tanner & Pitner (1939)
Penicillium species	1.0–5.0	pH not stated; room temperature	CK; 15–30 s	Tanner & Pitner (1939)
Yeasts (*Cryptococcus, Mycoderma, Monila albicans*)	0.25–0.5	pH not stated; room temperature	CK; 15–30 s	Tanner & Pitner (1939)
Saccharomyces species	3.0	pH not stated; room temperature	CK; 15–30 s	Tanner & Pitner (1939)
Staphylococcus species (*aureus* (92), *albus* (76), sp. (80), *aureus* (77), *aureus* (79), *aureus* (89))	0.10–0.25	pH not stated; room temperature	CK; 15–30 s	Tanner & Pitner (1939)
E. coli (252, 251)	0.15	pH not stated; room temperature	CK; 15–30 s	Tanner & Pitner (1939)
E. coli	4.0	pH 7.55; 0 ºC	2.7–4.5; 5–30 min	Lindley (1966)
	4.0	pH 6.0–8.0; 0 ºC	3.2–4.7; 10 min	Krusé et al. (1970)

Microorganism	Dose (mg/L)[a]	Comments	Log_{10} reduction value; contact time	Reference
Pseudomonas aeruginosa	0.2–1.5	pH 7.5; 38 ºC	> 2; 0.5–10 min	Clark & Smith (1992)
f2 coliphage	4.0	pH 7.55; room temperature	2.3–4.5; 1–30 min	Lindley (1966)
	4.0–8.0	pH 7.5; 0 ºC	3.3–5.0; 10 min	
	4.0	pH 6.0–8.0; 0 ºC	2.5–6.5; 10 min	Krusé et al. (1970)
Eberthella typhosa	0.03–0.06	pH not stated; room temperature	CK; 15–30 s	Tanner & Pitner (1939)
Reovirus	22.5–7.0	pH 7.0; 2 ºC	2.3–3.4; 3 min–30 s	Sharp et al. (1975)
Poliovirus (type 1)	00.6–22.0 µM	pH 7.0; 2 ºC	1–3.8; 16 s	Floyd et al. (1976)
	1.9–10.0 µM	pH 7.0; 10 ºC	1–3.4; 16–12 s	
	1.9–9.5 µM	pH 7.0; 20 ºC	2.3–3.2; 8–6 s	
Other				
Entamoeba histolytica (cysts)	1.5–4.0	pH 4.0–10.0; 4–10 ºC	3; 10 min	Stringer et al. (1975)
Cryptosporidium parvum	5	pH 7.5; 25 ºC	0.8[b]; 240 min	Kim (2014)
Giardia lamblia	No studies identified			

a–dose in mg/L unless stated otherwise; b–declining rates of inactivation over time to a maximum of 0.8 log_{10}; CK–complete kill.

2.2.2 Disinfection in the presence of impurities

Bromine combines with ammonia in water to form bromamines, commonly monobromamine (NH_2Br), dibromamine ($NHBr_2$) and tribromamine (NBr_3) (Johnson & Overby, 1970; Russell, 2006; Anderson et al., 1982).

In an early study, Johannesson (1958) demonstrated the effectiveness of monobromamine against *E. coli*, with 0.28 mg/L monobromamine achieving a 3.1 $\log_{10}$ reduction in 10 minutes at pH 8.2. Sollo et al. (1975) and Johnson & Sun (1975) confirmed the efficacy of monobromamine against total coliforms and *E. coli* respectively, with Sollo et al. (1975) also reporting increased effectiveness of monobromamine at higher pH.

Floyd et al. (1978) reported inactivation of poliovirus by tribromamine with > 3 $\log_{10}$ reduction occurring within seconds to 1 minute of contact time for concentrations between 3 and 50 µM. In contrast, monobromamine achieved LRVs of 2.3 to > 3 within 1 and 8 minutes of contact time at doses between 3 and 40 µM. These results indicate that monobromamine is much more effective than monochloramine for virus inactivation for which comparable LRVs require hundreds of minutes.

Mercado-Burgos et al. (1975) showed bromamines to be effective against *Schistosoma mansoni* ova, with a concentration of 25 mg/L (as bromine) achieving complete kill within 15 minutes.

In tertiary treated sewage (alum coagulated secondary effluent) with an ammonia concentration of 33.5 mg/L, poliovirus inactivation at 3 °C was 99% (2 $\log_{10}$ reductions) in 30 minutes by a dose of 3 mg/L bromine or 10 mg/L dose of chlorine. Estimated times for 2 $\log_{10}$ reductions of bromine at doses of 2, 3 and 5 mg/L were about 10, 30 and 70 minutes, respectively, at both pH 7 and 9. Poliovirus inactivation by bromine was equally effective at pH 7 and 9, but chlorine effectiveness was lower at pH 9 than 7 (Johnson & Sun, 1975).

Sollo et al. (1975) directly compared the use of bromine and chlorine (present as bromamines and chloramines) as disinfectants of wastewater effluents. Brominated effluents had consistently lower levels of total coliforms than the chlorinated effluents. The effectiveness of bromine treatment over chlorine increased with increasing pH which is considered to be due to the predominance of the more potent dibromamine species over monobromamine species at higher pH.

A further comparison of the use of bromine and chlorine for disinfection of highly contaminated water was reported by McLennan et al. (2009). Samples were prepared by mixing 9 volumes of potable non-disinfected well water with raw sewage with final turbidities averaging 7.5 ± 2.0 nephelometric turbidity units. When passing water through POU disinfection cartridges with a contact time of 30 minutes, log reductions for bromine and chlorine were comparable for total coliforms, *E. coli*, heterotrophic plate counts, *Enterococcus*, and *Clostridium*. However, bromine was shown to be more effective than chlorine for inactivating coliphages, with LRVs of 1.9 and 1.1, respectively.

2.2.3 Point of use water purification devices using bromine

Many communities in developing countries do not have sufficient funds or infrastructure to adequately protect drinking-water from faecal contamination, systematically treat water for drinking purposes or provide safe water at the tap (Coulliette et al., 2010). One option to reduce microbial (and chemical) threats is household water treatment (HWT) or POU devices comprised of physical (e.g. biosand filter, ceramic filter) or chemical (e.g. chlorine, flocculation/coagulation) barriers. A number of alternative systems are available, including some utilizing bromine.

Halogenated N-halamine media have been developed as part of a household water purification system which is commercially available and sold throughout India and other countries. Canisters containing chlorinated DMH or brominated DMH polymers are available; an important feature of these is their ability to be regenerated by consumers. These have been tested and found to produce minimal amounts of brominated species (Bridges et al., 2009). The primary function of this disinfection technology is a contact biocide that is used as a packed bed filter when incorporated into a treatment train. These polymers have been evaluated for disinfection efficacy; the N-bromamine version was found to be more effective than the N-chloroamine (Sun et al., 1995). To test the disinfection impact of the media only, Coulliette et al. (2010) used these polymers without the other toxin removal devices (e.g. filter). The authors reported that both units were effective against MS2 bacteriophage (with a mean ± standard error reduction of 2.98 ± 0.26 $\log_{10}$ and 5.02 ± 0.19 $\log_{10}$, respectively) and microcystin toxin (with reductions of 27.5% and 88.5% to overall mean ± standard error concentrations of 1600 ± 98 ng/L and 259 ± 50 ng/L, respectively). However, the mono-brominated media was seen to be most effective (Coulliette et al., 2010). Halogenated N-halamine derivatives conjugated on polystyrene beads have been reported to show broad antimicrobial activity affected by the covalently bound oxidative bromine, not free bromine. Tested materials have exhibited strong antimicrobial activity against *E. coli* and bacteriophages MS2 of 7 and approximately 4 log reduction, respectively (Farah et al., 2015). Such devices have also been shown to be effective with water of poor quality, that is, when contaminated with sewage (Coulliette et al., 2010; Enger et al., 2016).

2.2.4 Comparison of efficacy with chlorine

The disinfection properties of bromine and chlorine have been previously compared (Keswick et al., 1978; Keswick et al., 1982; Taylor & Butler, 1982). Although the properties of bromine and chlorine differ in a number of ways, as described below, they do have many performance characteristics in common.

The commonalities of bromine and chlorine include:

- different classes of microorganisms have different susceptibilities (activity against *Giardia lamblia* is unknown); the order of resistance to both bromine and chlorine disinfection from least to most resistant is:

  bacteria < viruses < bacterial spores < helminth ova and protozoan parasites; and
- the effectiveness of bromine and chlorine is impacted by temperature, disinfectant concentration, contact time, pH and organic and inorganic content.

With regards to the advantages of bromine over chlorine:

- bromine is more effective in disinfecting bacteria, viruses and protozoan parasites at higher pH levels (pH 9 or 9.5) and in the presence of ammonia;
- bromine provides greater protection across a wider pH range; and
- bromine is more effective for poor quality water.

The disadvantages of bromine over chlorine include:

- the safety of long-term consumption of bromine and its DBPs when used as a drinking-water disinfectant is not fully established. At present brominated DBPs are generally considered more toxic than chlorinated DBPs (see section 3.6.2); it should be noted that brominated DBPs are also produced in chlorinated water in the presence of bromide.

2.2.5 World Health Organization International Scheme to Evaluate Household Water Treatment Technologies

Assessment of the microbial effectiveness of disinfectants as a household-level water treatment option should, as far as possible, model actual use conditions in the field; e.g. water of varying quality, realistic contact times and testing of all three classes of pathogens which cause diarrhoeal disease. In order to comprehensively assess effectiveness, WHO has set tiered health based performance targets for HWT products based on reductions of bacteria, viruses and protozoa (WHO, 2011). These targets are based on microbial risk models using assumed levels of reference pathogens in untreated water. Since 2014, WHO has been testing products against those performance targets through the WHO International Scheme to Evaluate Household Water Treatment Technologies.[7] Box 1 gives further information on the Scheme and its three tiers of $\log_{10}$ performance targets for bacteria, viruses and protozoans. At the time of this report, bromine products have not been tested, but may be included in future rounds.

[7] http://www.who.int/water_sanitation_health/water-quality/household/scheme-household-water-treatment/en/

Box 1. WHO International Scheme to Evaluate Household Water Treatment Technologies

The objective of the Scheme is to independently and consistently evaluate the microbiological performance of household and POU water treatment technologies. The evaluation considers both turbid and non-turbid water, and is carried out to manufacturers' instructions for daily household use.[7] The results of the evaluation are intended to assist and inform Member States and procuring UN agencies in the selection of these technologies.

The performance targets define treatment requirements in relation to source water quality for each pathogen class as detailed below.

Performance target	**Bacteria** (log_{10} reduction required)	**Viruses** (log_{10} reduction required)	**Protozoa** (log_{10} reduction required)	**Classification** (assuming correct and consistent use)
★★★	**≥ 4**	**≥ 5**	**≥ 4**	Comprehensive protection (very high pathogen removal)
★★	**≥ 2**	**≥ 3**	**≥ 2**	Comprehensive protection (high pathogen removal)
★	Meets at least 2-star (★★) criteria for two classes of pathogens			Targeted protection
–	Fails to meet WHO performance criteria			Little or no protection

The performance of HWT products is classified as 3-star (★★★); 2-star (★★); and 1-star (★), denoting descending order of performance, based on log_{10} reductions of bacteria, viruses and protozoa from drinking-water. Performance that does not meet the minimum target is given no stars. Products that meet 3-star (★★★) or 2-star (★★) performance targets are classified as providing "Comprehensive protection" against the three main classes of pathogens which cause diarrhoeal disease in humans. The use of these products is encouraged where there is no information on the specific pathogens in drinking-water (and a prudent approach is to protect against all three classes), or where piped supplies exist but are not safely managed. Products that meet the performance targets for at least 2-star (★★) for only *two* of the three classes of pathogen are given one star (★) and are classified as providing "Targeted protection". In general, the use of these products may be appropriate in situations where the burden of diarrhoeal disease is high due to known classes of pathogens, such as a cholera outbreak.

3. Safety and toxicity of bromine

The toxicity of bromine has been reviewed by a limited number of international bodies, and opinions from the expert bodies on intake are described below. In addition, a detailed assessment of toxicological literature for bromine was undertaken (to November 2013, with further ad hoc searches to the closing date for public review [16 December 2016]) and the relevant findings are included here.

The reactivity of bromine in biological systems makes it difficult to separate the effects of bromine from those of bromine compounds and metabolites that are formed on contact with moisture in mucous membranes and with tissues of the respiratory and gastrointestinal system. Due to its reactivity, bromine does not persist as an element in living tissue, but quickly forms bromide and organobromine compounds. For a full narrative of the toxicity of bromide, the reader is referred to the background document prepared by the WHO (2009)[8] to inform the WHO Guidelines for Drinking-water Quality (GDWQ). However, for ease of reference, bromide exposure and toxicity data are summarized in the sections below.

3.1 Human exposure

Bromine occurs naturally as bromide in various chemical forms in the earth's crust and seawater. Bromide concentrations in seawater are generally in the range of 65 mg/L to in excess of 80 mg/L in some confined sea areas (WHO, 2009). Bromide levels in natural waters are highly variable (10–1000 µg/L), although typically range from trace amounts to approximately 0.5 mg/L (von Gunten, 2003). Groundwaters and reservoirs located near seawater have the potential to have higher levels of bromide related to the geology; desalinated seawater also has the potential to contain bromine (from 1 mg/L to several mg/L; WHO, 2017) depending upon the source water and the type of desalination being practiced.

Bromine is a volatile liquid at room temperature and, therefore, inhalation exposure is considered the most relevant route of exposure to humans. Minimal exposure may also occur through ingestion of food, for example, seafood has relatively high levels of bromide. The typical daily dietary intake of bromide is 2–8 mg in the USA, and 8.4–9.4 mg in the Netherlands (WHO, 2009). Fumigants containing bromide, mainly methyl bromide, are used for soil disinfection as well as postharvest treatment of plant products (PHE, 2009).

3.2 Guideline values

3.2.1 WHO drinking-water quality guidelines

The WHO Guidelines for Drinking-water Quality (GDWQ) have not evaluated bromine as it quickly forms hypobromous acid and bromide in water. A drinking-water guideline value has not been proposed for bromide as it occurs in drinking-water at concentrations well below those of health concern (WHO, 2017). However, to provide guidance to Member States, should the chemical be found in drinking-water or its sources, the GDWQ includes a health-based value of 6 mg/L for adults and 2 mg/L for children. For bromate, a provisional guideline value of 10 µg/L is included based on achievable analytical quantitation limits and treatment methods.

[8] The latest version of the background document is dated 2009 and so will undergo review. However, no new studies were identified up to December 2016 to amend the findings of the document.

3.2.2 Other values

At a joint meeting of the Food and Agriculture Organization of the United Nations/WHO in 1988, an acceptable daily intake (ADI) of 0–1 mg/kg bw (body weight) was established for bromide ion, based on a no-observed-effect level (NOEL) from a human study reported by Sangster et al. (1986).

The European Agency for the Evaluation of Medicinal Products (EMEA, 1997) also utilized the study by Sangster et al. (1986) to derive an ADI of 0.4 mg/kg bw based on marginal effect within normal limits of electroencephalograms in females at 9 mg/kg bw per day, including a safety factor of 10 for population diversity (see section 3.3.3).

The United Kingdom Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT, 2000) considered dietary intake of bromine. Intake was estimated from the 1997 total diet study as 3.6 mg/person per day (equivalent to 0.06 mg/kg bw per day). The Committee noted that the upper boundary of the ADI proposed by Food and Agriculture Organization of the United Nations/WHO of 1 mg/kg bw could be taken as a tolerable daily intake. Estimated dietary intakes were therefore well below the acceptable level, allowing for significant exposure from other routes (EA, 2005).

When used as a pesticide, the USEPA has defined bromide as "exempt from the requirement of tolerance" (USEPA, 2010).

Most recently, NSF International[9] has proposed a combined bromine/bromide action level of 10 mg/L for drinking-water. The derived maximum contaminant level applies specifically to elemental bromine and inorganic bromide ion and is considered protective of human health. The maximum contaminant level does not consider potential formation of bromate or DBPs (NSF, 2011).

3.3 Human toxicity data

3.3.1 Toxicokinetics

3.3.1.1 Absorption

Following inhalation, bromine is absorbed by the lungs (as bromide) and deposition in the lungs is primarily determined by the water solubility of bromine (IPCS, 1999). Following ingestion, bromide is rapidly and completely absorbed from the intestine by passive, paracellular transport (HCN, 2005). Bromide uptake and equilibrium concentrations are interrelated with chlorine levels: as chloride intake increases, the excretion of bromide increases (WHO, 2009).

No data could be located regarding absorption of bromine vapours via the ocular or dermal routes of exposure, however it is likely to react on the surface of the body immediately on contact (PHE, 2009).

[9] This document was prepared to allow toxicological evaluation of bromine/bromide in drinking-water, as an extractant from one or more drinking-water system components or as a contaminant in a drinking-water treatment chemical, evaluated under NSF/ANSI standards.

3.3.1.2 Distribution

Absorbed bromine (as bromide and organobromine chemicals by all routes of exposure) is distributed widely into various tissues and mainly into the extracellular fluid of the body (PHE, 2009).

3.3.1.3 Metabolism

No data could be identified regarding the metabolism of bromine. However, bromine has been shown to quickly form bromide in living tissue and is partitioned in the body similarly to chloride. Its presence is related to the amount of chloride intake (HCN, 2005).

3.3.1.4 Elimination

Bromide is excreted mainly by the kidneys and in small quantities in sweat, tears, and other body excretions. The biological half-life of bromide has been reported to be between 12 and 30 days in humans, with that in rats being markedly shorter, at approximately 3 days (HCN, 2005).

3.3.2 Acute toxicity

No median lethal dose (LD_{50})[10] values for bromine or bromide have been reported for humans.

Due to its water solubility, bromine generally produces effects on the upper respiratory tract. However, inhalation of high concentrations, for example, in confined spaces, may also cause marked effects on the lower airways. Acute inhalation exposure to bromine results in symptoms of respiratory irritation including, shortage of breath, cough, choking and wheezing, bronchoconstriction, inflammation of the oesophagus, and laryngeal spasm; respiratory distress has led to hypoxaemia, metabolic acidosis and death (DEFRA, 2006). Acute inhalation of high concentrations of bromine vapour has resulted in brown colouration of the eyes, tongue, and mucous membranes of the mouth as well as catarrh (thick phlegm or mucus in an airway), salivation, coughing, feeling of suffocation, glottis cramps, hoarseness, bronchitis and bronchial asthma (USEPA, 2009). Central nervous system effects documented following overdoses of bromide-containing medicines or fumigants include ataxia, slurred speech, tremor, nausea, vomiting, lethargy, dizziness, visual disturbances, headaches, impaired memory and concentration, disorientation, and hallucinations (IPCS).[11]

Accidental (acute) ingestion of liquid bromine has been associated with haemorrhagic nephritis, with oliguria or anuria, (reduced or increased urine production respectively) developing within 1 to 2 days (concentration not stated). Associated injuries due to corrosivity and inhalation of vapour were not described (PHE, 2009).

Bromine is highly irritating to the skin in both liquid and vapour form. Acute dermal exposure to bromine results in localized blister formation, brownish discolouration of the skin and slow-healing ulcers. Appearance of injury is often delayed (Sagi et al., 1985).

Ocular effects following exposure to bromine vapour (0.5 parts per million [ppm]) include stinging and burning of the conjunctiva and lacrimation, and at higher levels (not stated) photophobia and blepharospasm (i.e. forcible closure of the eyelids) have been reported (PHE, 2009).

The irritating properties of bromine vapour act to prevent prolonged exposure at high concentrations. Exposure for 50 minutes at levels of 0.006 ppm (0.04 mg/m^3) is associated with some irritation of the

[10] The dose required to kill half the members of a test population after a specified test duration.
[11] http://www.inchem.org/documents/pims/chemical/pim080.htm

eyes; at levels of 0.2 ppm (1.3 mg/m^3), clear irritation of eyes, nose, and throat occurs; and levels of 0.5 ppm (3.3 mg/m^3) and above cannot be tolerated due to the severity of these symptoms (Rupp & Henscler, 1967).

Doses of bromide giving plasma levels of 12 mmol/L (96 mg/L) produce bromism (the chronic state of bromide intoxication), and plasma levels greater than 40 mmol/L (320 mg/L plasma) are sometimes fatal. The signs and symptoms of bromism relate to the nervous system, skin, glandular secretions and gastrointestinal tract (WHO, 2009).

3.3.3 Repeat dose toxicity

Data relating to the effects in humans following chronic exposure (by all routes) to bromine could not be identified.

The key repeat dose toxicity study in humans for bromide reported by Sangster et al. (1986) and described in the WHO background document (WHO, 2009), determined a conservative NOEL of 4 mg sodium bromide/kg bw per day based on marginal effect within normal limits of electroencephalograms in females at 9 mg/kg bw per day.

3.3.3.1 Systemic effects

No data could be located regarding systemic effects in humans following repeated exposure to bromine or bromide.

3.3.3.2 Neurotoxicity

No data could be located regarding neurotoxic effects in humans following repeated exposure to bromine or bromide.

3.3.3.3 Reproductive and developmental toxicity

No data could be located regarding reproductive and developmental effects in humans following repeated exposure to bromine or bromide.

3.3.3.4 Immunotoxicity

No data could be located regarding immunotoxic effects in humans following repeated exposure to bromine or bromide.

3.3.3.5 Genotoxicity

No data could be located regarding genotoxic effects in humans following repeated exposure to bromine or bromide.

3.3.3.6 Carcinogenicity

Bromine and bromide are not listed as carcinogens by the International Agency for Research on Cancer (IARC). No data are available to assess the carcinogenicity of bromine or bromide in humans.

3.4 Animal toxicity studies

The predominant route of exposure reported in experimental studies to date relate to the inhalation of bromine. Although not directly relevant to drinking-water, except potentially in cases of aerosol

formation, these studies are included as the main experimental evidence available. In addition, once inhaled, bromine will be rapidly converted to bromide as for oral intake.

3.4.1 Toxicokinetics

No data could be located regarding the toxicokinetics of bromine or bromide in animals.

3.4.2 Acute toxicity

The 30-minute median lethal concentration (LC_{50})[12] of bromine (vapour) in female (NMRI) mice was reported to be 174 ppm (1158 mg/m^3) with an observation period of 10 days. Generally, mortality occurred in two distinct periods, either, within the first 4 days (the majority) or between days 8 and 10. The cause of death in the animals was reported to be either bronchospasm (spasm of bronchial smooth muscle producing narrowing of the bronchi) or lung oedema (fluid accumulation in the lung) in the early deaths and peribronchitis (a form of bronchitis consisting of inflammation and thickening of the tissues around the bronchi) with abscess formation during days 8 to10 (HCN, 2005).

An LC_{50} of 240 ppm (1569 mg/m^3) has been reported in mice (strain and sex not specified) exposed to bromine vapour for 2 hours (PHE, 2009).

Exposure to 22 and 40 ppm (147 and 266 mg/m^3) bromine vapour for 3 hours caused mortality in 0 of 10 and 3 of 10 mice, respectively, while 7 of 10 and 8 of 10 animals, respectively, died within 10 days following a 6-hour exposure. Bitron & Aharonson (1978) studied the delayed mortality (observation time: 30–45 days) following a single inhalation event of bromine (in comparison with formaldehyde, sulphur dioxide, and chlorine). Mice were exposed to bromine concentrations of 240 ppm (approximately 1600 mg/m^3) for 15–270 minutes or to 750 ppm (approximately 5000 mg/m^3) for 5–30 minutes. A 100-minute LC_{50} of 240 ppm and a 9 minute LC_{50} of 750 ppm were identified.

Cats, rabbits and guinea pigs (strain and sex not specified) exposed to 23 ppm (approximately 150 mg/m^3) bromine vapour for 7 hours showed slight irritation of the respiratory tract, whilst at 180 ppm (1176 mg/m^3) CNS function disturbances were seen; a lowest-observed-adverse-effect level (LOAEL) of 23 ppm (150 mg/m^3) was identified (Bingham et al., 2001).

Bromide is considered to have very low acute toxicity. Oral LD_{50} values of 3500 mg/kg bw have been reported for the rat and 5020–7000 mg/kg bw for the mouse (WHO, 2009).

3.4.3 Repeat dose toxicity

3.4.3.1 Systemic toxicity

A limited number of experimental studies on the effects of chronic exposure to excess bromine have been reported:

- Exposure to bromine vapours at 33 and 67 mg/m^3 (5 and 10 ppm) for 8 hours/day for 3 days did not cause mortality, but body weights were decreased; this was attributed to irritation of the upper respiratory tract. A LOAEL of 33 mg/m^3 (5 ppm) was identified from this study (Schlagbauer & Henschler, 1967).
- Rats, mice and rabbits (strain and sex not specified) were exposed via inhalation to bromine vapour continually for 4 months at doses of 0.13–1.31 mg/m^3 (approximately 0.02–0.2 ppm). At the highest dose, animals developed disturbances in respiratory, nervous and endocrine

[12] The concentration required to kill half the members of a test population after a specified test duration.

functions. No adverse effects were observed at the lowest dose employed. A no-observed-adverse-effect level (NOAEL) of 0.13 mg/m^3 (0.02 ppm) could be identified from this study (Schlagbauer & Henschler, 1967).

- Rats (strain and sex not specified) were fed liquid bromine (38%) at 20 mg/kg bw per day in a 28-day oral study. Clinical signs of salivation and decreased activity were observed, with increased red blood cell count, haemoglobin and packed cell volume, increased serum glucose and increased urinary volume with protein also being reported (USEPA, 2005a).

The key repeat dose toxicity study identified for bromide, as described in the WHO background document (WHO, 2009), determined a NOAEL for sodium bromide of 300 mg/kg diet (240 mg/kg diet as bromide; 12 mg/kg bw per day) based on effects on the thyroid in male Wistar rats. An important finding of this study was the increased toxicity of sodium bromide in rats fed a low-chloride diet, with toxicity being around 10 times higher than for rats on a diet containing standard chlorine levels.

3.4.3.2 Neurotoxicity

No data could be located regarding neurotoxic effects in animals following repeated exposure to bromine or bromide.

3.4.3.3 Reproductive and developmental toxicity

Ivanov et al. (1976) reported that a 4-hour exposure to bromine vapour at 15 ppm affected spermatogenesis in male mice; further details were not reported.

In a three-generation reproduction study (two litters per generation), Wistar rats fed sodium bromide at 19 200 mg/kg bw showed complete infertility. Fertility and offspring viability were also reduced at 4800 mg/kg diet. No treatment-related effects were observed in reproductive performance, viability or body weight of the offspring in the second and third generations bred only from the groups dosed of 0, 75, 300 and 1200 mg/kg diet. Relative adrenal weight was significantly reduced in adult (F0) females at 4800 and 1200 mg/kg feed but effects on other organs did not show a clear pattern of dose-response (WHO, 2009).

No experimental studies relating to the developmental toxicity of bromine were identified.

3.4.3.4 Immunotoxicity

No data could be located regarding immunotoxic effects in animals following repeated exposure to bromine or bromide.

3.4.3.5 Genotoxicity *(in vivo)*

No data could be located regarding genotoxic effects in animals following repeated exposure to bromine or bromide. (See 3.4.4 for *in vitro* genotoxicity studies.)

3.4.3.6 Carcinogenicity

No experimental studies relating to the carcinogenicity of bromine or bromide were identified. Studies are underway to assess the role of bromide in the cancers of the thyroid and testes mesothelium from the metabolism of bromate to bromide in high dose tests (J. Cotruvo, personal communication; 1 April 2016).

3.4.4 *In vitro* toxicity studies

Liquid bromine, tested at a concentration of 38 % and a volume of 10 µg/plate, was positive in the *Salmonella typhimurium* microsome reverse mutation assay with strains TA 1537 and TA 100 in the absence of S9 and with strain TA 1537 in the presence of S9 activation. As would be expected from its reactivity, bromine was cytotoxic for all strains with and without metabolic activation at more than 3333 µg/plate (USEPA 2005a).

Sodium and ammonium bromide were studied in an Ames test with *Salmonella typhimurium* strains TA98 and TA100. At dose levels of 0.001–10 mg/plate, both with and without metabolic activation, no mutagenic effect was observed (WHO, 2009).

3.5 Vulnerable populations

No information on the possible impact of bromine or bromide on vulnerable populations was identified.

3.6 Toxicity of brominated disinfection by-products

3.6.1 Formation and occurrence of brominated disinfection by-products

When present in water, either as part of the ambient conditions or when used as a disinfectant, bromine and bromide have the ability to form brominated DBPs. The common source of brominated DBPs is chlorination of water containing bromide. The bromide is oxidized by chlorine to hypobromous acid which rapidly halogenates organic matter, producing the following brominated and mixed halogenated DBPs:

- bromoform;
- dibromoacetic acid;
- tribromoacetic acid;
- bromoacetic acid;
- bromochloroacetic acid;
- bromodichloroacetic acid
- dibromochloroacetic acid;
- dibromoacetonitrile;
- 2-bromo-2-methylpropanal;
- 2,3,5-tribromopyrrole;
- bromoacetone;
- bromoalkanes;
- bromohydrins; and
- brominated trihalomethanes (including bromodichloromethane, chlorodibromomethane, and tribromomethane (bromoform)).

Many of the DBPs listed above are generally present at very low concentrations (fractional parts per billion levels), although elevated levels are possible.

It has been suggested that one of the main DBPs of concern in high bromide-containing waters is bromate (WHO, 2005), particularly when the water is ozonated or a low-quality hypochlorite is used. Brominated trihalomethanes (THMs) may occur at concentrations exceeding those of chloroform when source waters with elevated bromide levels are chlorinated (Krasner et al., 1989) while ozonation prior to chlorination can further enhance the formation of brominated THMs (Shukairy et al., 1994). Among

the most prevalent brominated THMs are chlorodibromomethane, bromodichloromethane and tribromomethane (bromoform). In recent years, there has been a growing concern of public water systems facing higher bromide levels in their source waters from anthropogenic contamination through coal-fired power plants, conventional oil and gas extraction, textile mills, and hydraulic fracturing (McTigue et al., 2014; States et al., 2013).

Evaluation of the formation of brominated DBPs from use of bromine containing HWT and/or POU devices remains to be fully investigated.

3.6.2 Toxicological evaluations of brominated by-products

Epidemiology studies indicate increased risk of bladder cancer associated with increased THM concentrations in drinking-water, with brominated DBP species, or other co-occurring DBPs (including chlorinated DBPs) being potentially significant contributing factors (Cantor et al., 2010). This has been highlighted as a possible issue in recent literature, linked to a potential increase in bromide levels in drinking-water sources in the USA as a result of anthropological contamination (Regli et al., 2015).

Several brominated DBPs have been shown in animal studies to be more carcinogenic than their chlorinated analogs (Richardson, 2003a). Richardson (2007) has summarized the relative occurrence and genotoxicity of a wide variety of DBPs including brominated compounds.

WHO (2009) reports that bromate is mutagenic both *in vitro* and *in vivo*. The IARC has classified potassium bromate in Group 2B (possibly carcinogenic to humans) concluding that there is inadequate evidence for carcinogenicity in humans but sufficient evidence of carcinogenicity in animals. The IARC has classified dibromochloromethane and bromoform in Group 3 (not classifiable as to its carcinogenicity to humans) and dibromoacetonitrile in Group 2B. The USEPA has also classified bromate as a probable human carcinogen by the oral route based on data from male and female rats, bromoform and bromodichloromethane as likely to be carcinogenic to humans by all routes of exposure, and dibromochloromethane as having suggestive evidence of carcinogenicity (USEPA, 2005a). Health Canada also considers bromate to be carcinogenic to humans.[13] Although classified as probably carcinogenic to humans, WHO (2009) states that there is insufficient information to conclude the carcinogenic mode of action of potassium bromate. Later studies have reported that the mode of action of bromate, at levels well above those found in drinking-water, does not involve genotoxicity in rats (Bull & Cotruvo, 2013; Yamaguchi et al., 2008).

The carcinogenicity of brominated THMs were assessed in a series of older studies carried out by the National Toxicology Program (NTP) using corn oil as the vehicle (NTP, 1985; NTP, 1987; NTP, 1989a; NTP, 1989b). Due to concerns surrounding a possible corn oil vehicle effect, where available, studies utilizing drinking-water as the vehicle are described below.

Limited reports of a two-year feeding study using SPF Wistar rats administered chlorodibromomethane have been identified. The authors observed no increase in gross tumours in male rats treated with chlorodibromomethane at doses of 10, 39, or 210 mg/kg per day, or in female rats treated at doses of 17, 66, or 350 mg/kg per day (Tobe et al., 1982).

In a 2-year oral study, CBA x C57B1/6 mice were administered chlorodibromomethane in drinking-water at concentrations of 0, 0.04, 4.0 or 400 mg/L (equivalent to doses of 0.008, 0.76 or 76 mg/kg per

[13] http://www.healthycanadians.gc.ca/health-system-systeme-sante/consultations/bromate/document-eng.php

day); controls were untreated. Survival time was not related to dose in either male or female animals. No increase in tumour incidence was observed in treated animals in comparison with controls (Voronin et al., 1987).

Male Wistar rats were administered bromodichloromethane in drinking-water at concentrations of 0, 175, 350 or 700 mg/L (equivalent to 0, 6, 12 or 25 mg/kg per day) for 102 weeks. Body weights of treated groups remained similar to those of control animals. An increased incidence of inflammation in the liver was noted at the two higher doses, however the relevance of this is uncertain. There were no increased incidences of neoplasms that were attributable to bromodichloromethane (NTP, 2006).

In a 2-year study in female B6C3F1 mice, bromodichloromethane was administered in drinking-water at concentrations of 0, 175, 350, or 700 mg/L (equivalent to 0, 9, 18 or 36 mg/kg per day) Mean body weights were lower in treated groups when compared to controls from week 4 of the study. The incidence rates of hepatocellular carcinoma or adenoma (combined) or hemangiosarcoma in all organs in treated animals were not statistically significantly different from those in controls. The authors concluded that under the conditions of the assay, bromodichloromethane was not carcinogenic (NTP, 2006).

No oral study utilizing water as a vehicle for administration of bromoform could be identified and therefore the study using corn oil as the vehicle is described. Bromoform was administered for 103 weeks in corn oil by gavage for 5 days per week to groups of F344/N rats and B6C3F1 mice. Daily doses of 0, 100 or 200 mg/kg were administered to rats and female mice, and 0, 50 or 100 mg/kg to male mice. In comparison to controls, decreased body weights were noted in male rats in the high (12–28%) and low (5–14%) dose groups, with a decrease in female rats in the high dose group only (10–25%). Female mice also showed a decrease in body weight in the high (5–16%) and low (6–11%) dose groups relative to controls; body weights of male mice were not decreased. Adenomatous polyps or adenocarcinomas were noted in the large intestine (colon and rectum) of male rats at the highest dose (3 of 50) and female rats at both doses (1 of 50 and 8 of 50) in comparison to controls (0 of 50 in both sexes) but this was not considered significant. No tumours were apparent in mice at either dose of bromoform. The authors concluded that under the conditions of the study, there was clear evidence of carcinogenicity for female rats, some evidence for male rats and no evidence for male and female mice (NTP, 1989). The IARC concluded that there was limited evidence for the carcinogenicity of bromoform in animals, and inadequate evidence in humans, with an overall evaluation of Group 3 (not classifiable as to its carcinogenicity to humans).

The NTP (1989b) has also assessed the reproductive and developmental toxicity of bromoform in CD-1 mice following administration at doses of 0, 50, 100 or 200 mg/kg per day by oral gavage. Varying degrees of hepatocellular degeneration were seen in all treated animals, however no changes in reproductive parameters were noted at levels below significant hepatotoxicity.

Prevalent brominated acetic acids include monobromoacetic acid, dibromoacetic acid and bromochloroacetic acid. These DBPs have been covered in a background document from the WHO (WHO, 2004b) to support the GDWQ. In brief, the following toxicities were identified for these brominated acetic acids:

- Monobromoacetic acid has an oral LD_{50} in rats of 177 mg/kg bw, (Linder et al., 1994), with observed clinical symptoms of excess drinking-water intake, hypomobility, laboured breathing and diarrhoea following acute exposure. Chronic studies were not identified. Monobromoacetic acid

was mutagenic in *Salmonella typhimurium* (NTP, 2000a) and positive with microsomal activation in the Ames fluctuation test using *S. typhimurium* strain TA100 (Giller et al., 1997). Monobromoacetic acid produced DNA strand breaks in L-1210 mouse leukaemia cells (Stratton et al., 1981).

- Dibromacetic acid has a reported oral LD_{50} in rats of 1737 mg/kg bw, with observed clinical symptoms of excess drinking-water intake, hypomobility, laboured breathing, diarrhoea and ataxia following acute exposure. Spermatotoxicity was also apparent on histopathological examination (Linder et al., 1994). Sub-chronic and chronic exposure studies have identified liver toxicity, immunotoxicity, and spermatotoxicity. Dibromoacetic acid was mutagenic in *S. typhimurium* (NTP, 2000b) and in the Ames fluctuation test with *S. typhimurium* tester strain TA100, with and without metabolic activation (Giller et al., 1997). Dibromoacetic acid is associated with DNA repair in the SOS chromotest, with and without metabolic activation (Giller et al., 1997) and DNA damage (Austin et al., 1996).
- Chronic exposure to bromochloroacetic acid has been associated with induced liver toxicity and reproductive changes (decreased implants and decreased number of live fetuses per litter). Bromochloroacetic acid was mutagenic in *S. typhimurium* in the standard Ames assay (NTP, 2009). DNA damage has been reported (Austin et al., 1996).

In USEPA's health criteria document for brominated acetic acids (USEPA, 2005a); monobromoacetic acid, bromochloroacetic acid, and dibromoacetic acid were all identified as "not classifiable as to human carcinogenicity" under the 1986 Carcinogen Risk Assessment Guidelines, and "inadequate for an assessment of human carcinogenic potential" under the 1999 Draft Guidelines for Carcinogen Risk Assessment. The IARC has classified bromochloroacetic acid and dibromoacetic acid as Group 2B (possibly carcinogenic to humans).

Genotoxicity and cytotoxicity studies of brominated and chlorinated haloacetic acids (HAAs) have been described by Plewa et al. (2008). Brominated HAAs were found to be more cytotoxic than their chlorine analogs, with a rank order of:

bromoacetic acid = dibromoacetic acid > chloroacetic acid > tribromoacetic acid > dichloroacetic acid > trichloroacetic acid.

Brominated HAAs were also more genotoxic than their chlorine analogs, with a rank order of:

bromoacetic acid = chloroacetic acid > dibromoacetic acid > tribromoacetic acid.

3.7 Summary of the safety and toxicity of bromine

Due to its reactivity, bromine, as with chlorine does not persist as an element in living tissue, but quickly forms bromide and brominated organic chemicals, making the study of the toxicokinetics difficult. This is reflected in the very limited toxicokinetic data available for bromine from human and animal studies. Many reports have utilized data from toxicity studies for sodium bromide in place of bromine. Bromide and chloride are always present in body fluids in animals in steady state at levels dependent upon intake, and both are excreted readily. Increased chloride intake will increase the excretion of bromide.

Symptoms of acute bromine toxicity via the inhalation route include respiratory irritation/distress and central nervous system effects (all dependant on concentration). Bromine is highly irritating to the skin

in both liquid and vapour form, with appearance of injury in the form of often delayed blister formation. Ocular irritation following exposure to bromine vapour is reported. Although rare, ingestion of liquid bromine is associated with haemorrhagic nephritis, with oliguria or anuria, developing within 1 to 2 days. Where comparisons can be made, the findings from human studies are supported by those from animal studies. The acute toxicity of bromide is considered to be very low.

Sub-chronic and chronic bromine toxicity studies in humans were not identified from available literature. Animal studies are also very limited but suggest chronic exposure to bromine may have adverse effects on reproduction. Repeat dose oral toxicity studies with bromide in rats indicate adverse effects on the thyroid, with toxicity being enhanced by a low chloride diet. Reproductive and developmental toxicity of sodium bromide were also noted in a three-generation study in rats.

Bromine and bromide are not classifiable as human carcinogens. Bromine has shown positive results in reverse mutation assays with and without metabolic activation. Bromide has not shown evidence of mutagenicity in similar assays.

Among the most prevalent brominated THMs are chlorodibromomethane, bromodichloromethane and tribromomethane (bromoform). These are not carcinogenic when tested by the NTP protocol (WHO, 2017). There are large toxicological data gaps across all DBPs, however where available, brominated DBPs have been shown in general to be more genotoxic than the chlorinated analogs.

Prevalent brominated acetic acids include monobromoacetic acid, dibromoacetic acid and bromochloroacetic acid.

Brominated HAAs have been found to be more cytotoxic and genotoxic than their chlorine analogs (see Section 3.6.2 for the rank order).

The potential for formation of brominated DBPs from the use of bromine as an alternative disinfectant is unknown, although more brominated DBPs would be formed based upon dose levels compared to chlorine.

4. Environmental considerations

Environmental considerations are largely beyond the scope of this report however, as noted in Table 3, the impact of release of bromine into the environment to "non-target" organisms should be considered.

Table 3: Environmental toxicity of bromine to "non-target" species[14]

Group of organisms	Common name (scientific name)	Median lethal dose (LD_{50})	Acute toxicity rating
Fish (freshwater)	Bluegill sunfish (*Lepomis macrochirus*)	0.52 mg/L (24 h)	Highly toxic
	Rainbow trout (*Oncorhynchus mykiss*)	0.31 mg/L (24 h)	Highly toxic
Invertebrates	Water flea (*Daphnia magnamagna*)	1.5 mg/L (24 h)	Moderately toxic
	Water flea (*Daphnia magnamagna*)	1 mg/L (48 h)	Moderately toxic

[14] Source: Kegley SE, Hill BR, Orme S, Choi AH, PAN Pesticide Database, Pesticide Action Network, North America (Oakland, CA, 2016), http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PC35462; visited September 2017.

5. Discussion and conclusions

The decision on whether bromine can serve as a disinfectant for drinking-water and wastewater treatment is likely to be a balance between the dose required to achieve efficacy (see section 2.2), its advantages over other disinfectants, particularly chlorine (see section 2.2.4), aesthetic impacts, preventing potential adverse health effects (see section 3) from chronic exposure, and cost. Any potential risk of adverse effects should be considered in context of the benefit of water disinfection which should always take precedence.

Disinfection with bromine and the comparison of its efficacy with chlorine appears greatly understudied. Compared to the wealth of literature available for chlorine, a very limited number of studies have investigated the effect of alternative halogens including bromine. Bromine has demonstrated effectiveness in removing several pathogens in laboratory settings, but has not been tested against many protozoan parasites including *Giardia*.

Bromine disinfection is superior to chlorine for microbiological inactivation when applied to low-quality water containing ammonia and other nitrogenous components (McLennan et al., 2009). This may give support for the use of bromine as a potential alternative to chlorine in disaster relief scenarios, however, further investigations would be required. Also, these potential benefits should be balanced with the significant issues surrounding the ease and safety of bromine generation and its subsequent use for water purification purposes. Practical handling of free bromine is a safety issue; it is usually combined with DMH, an organic carrier. Other chemical forms of bromine are currently used for disinfection of non-drinking-waters including swimming pools and cooling towers.

At the household level, there are a number of additional considerations beyond efficacy, for determining whether any water treatment product, including bromine, will protect against adverse health effects. Achieving health gains from household water treatment requires products to be used correctly and consistently, and thus, clear product information and use instructions are important. In addition, user preferences, supply chains and availability, and cost are important factors to consider. Products such as bromine which require a reliable supply chain can be problematic in resource-scare settings where such systems are not in place.

Toxicity studies in humans or animals for bromine *per se* via ingestion are very limited; this is mostly due to the corrosiveness and high reactivity of bromine; it quickly forms bromide in living tissues. Human studies with sodium bromide have allowed derivation of an ADI for bromide of 0.4 mg/kg bw based on the most sensitive toxicological endpoint relating to changes within electroencephalograms. However, a drinking-water guideline value has not been proposed for bromide in the WHO GDWQ as it occurs in drinking-water at concentrations well below those of health concern. However, the GDWQ includes a health-based value of 6 mg/L for adults and 2 mg/L for children (WHO, 2017). For bromate, a provisional guideline value of 10 µg/L is recommended as a pragmatic value based on difficulties in removing bromate once it is formed.

The greatest potential concern to humans from using bromine as a drinking-water disinfectant may stem from the generation of brominated DBPs. The formation of brominated DBPs during water disinfection with chlorine has been well studied. There are toxicity data in some of these studies that indicate that brominated DBPs may be more toxic in some respects than their chlorinated analogs. Currently the potential for formation of brominated DBPs from the use of bromine as an alternative drinking-water disinfectant in HWT and POU devices has not been comprehensively addressed, although some devices have been shown to produce minimal amounts of brominated products (Bridges et al., 2009).

In summary, the current evidence is sufficient to indicate that:

- In a similar way to chlorine, as a drinking-water disinfectant, bromine can be most effective against bacteria, effective to a somewhat lesser extent against viruses, and least effective against some protozoan parasites; however, the evidence base is more limited in comparison to chlorine;
- Bromine appears to be effective against cysts of the protozoan parasite *Entamoeba histolytica,* and there is some evidence of limited effectiveness against oocysts of *Cryptosporidium parvum*; studies on the efficacy of bromine against *Giardia* cysts were not available; and
- Somewhat similar to chlorine and iodine, disinfection efficacy is impacted by the temperature, bromine concentration, contact time, pH and organic and inorganic content; however, bromine is much less affected by pH and ammonia.

In general, the use of bromine in wastewater disinfection is promising and warrants further study, and reasons for particular consideration have been outlined above. However, active bromine would not be recommended for use as a primary disinfectant at the current time due to the concerns with the formation and potential toxicity of organobromine and organobromine DBPs and the availability of widely used, well-characterized disinfectants. Although the evidence base indicates that it may be a superior disinfectant to chlorine in several respects, there is a need for additional data on the range of microorganisms against which it is effective and under what conditions.

POU devices that provide contact disinfection may be appropriate under targeted circumstances (such as when pathogenic bacteria and viruses are the organisms of concern) or when combined with another barrier that is effective against protozoa, provided that there is little release of bromine into the finished water to minimize DBP formation. The use of POU devices should be appropriately approved or certified to ensure efficacy and safety.

6. References

Anderson AC, Reimers RS, DeKernion P (1982). A brief review of the current status of alternatives to chlorine disinfection of water. Am Public Health. 72(11):1290–93.

Austin EW, Parrish JM, Kinder DH, Bull RJ (1996). Lipid peroxidation and formation of 8-hydroxydeoxyguanosine from acute doses of halogenated acetic acids. Fundam Appl Toxicol. 31:77–82.

Bingham E, Cohrssen B, Powell CH (2001). Patty's Toxicology. 5th ed. Vol. 1–9. New York (NY) [cited by PHE (2009)].

Bitron MD, Aharonson EF (1978). Delayed mortality of mice following inhalation of acute doses of CH_2O, SO_2, Cl_2 and Br_2. Am Ind Hyg Assoc J. 39:129–38.

Bridges M, Reckhow D, Liu B, Cotruvo J (2009). Analysis and comparisons of disinfection by-products from brominated hydantoinylated cross-linked polystyrene to traditional chlorination. In: Proceedings. Water Environment Federation Disinfection Conference, Atlanta GA, 2 October 2009: (1):440.

Bryan PE, Kuzminski LN, Sawyer FM et al. (1973). Taste thresholds of halogens in water. J Am Water Works Assoc. 65:363–68.

Bull RJ, Cotruvo JA (2013). Nongenotoxic mechanisms involved in bromate-induced cancer in rats. J Am Water Works Assoc. 105(12):E709–20.

Cantor KP, Villanueva CM, Silverman DT, Figueroa JD, Real FX, Garcia-Closas R et al. (2010). Polymorphisms in *GSTT1, GSTZ1*, and *CYP2E1*, disinfection by-products, and risk of bladder cancer in Spain. Environ. Health Perspect. 118:1545–5.

Clark C, Smith P (1992). The survival of *Pseudomonas aeruginosa* during bromination in a model whirlpool spa. Lett Appl Microbiol. 14(1):10–12 [cited by Kim J, Sobsey M (2013)].

Clasen TF, Parra GG, Boisson S et al. (2005). Household-based ceramic water filters for the prevention of diarrhea: a randomized, controlled trial of a pilot program in Columbia. Am J Trop Med Hyg. 73:790–95 [cited by Coulliette et al. (2010)].

Clasen TF, Brown J, Collin SM (2006). Preventing diarrhea with household ceramic water filters: assessment of a pilot project in Bolivia. Int J Environ Health Res. 16:231–239 [cited by Coulliette et al. (2010)].

COT (2000). Committee on Toxicity of Chemicals in Food Consumer Products and the Environment, Statement on the 1997 total diet study - fluorine, bromine and iodine, in COT statement 2000/05; pp. 26–28.

Coulliette AD, Peterson LA, Mosberg JAW et al. (2010). Evaluation of a new disinfection approach: Efficacy of chlorine and bromine halogenated contact disinfection for reduction of viruses and microcystin toxin. Am J Trop Med Hyg. 82(2):279–88.

DEFRA (2006). Bromine. Expert panel on air quality standards. United Kingdom Department for Food, Environment and Rural Affairs [cited by PHE (2009)].

Enger KS, Leak E, Aw TG et al. (2016). Antibacterial and antiviral effectiveness of two household water treatment devices that use monobrominated hydantoinylated polystyrene. J Water Health. 14(6):950–60.

EA (2005). A review of the toxicity and environmental behaviour of bromine in air. United Kingdom Environment Agency (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/290734/scho0105bimu-e-e.pdfa, accessed February 2015).

EMEA (1997). Bromide, sodium salt. Summary report. London, European Agency for the Evaluation of Medicinal Products, Committee for Veterinary Medicinal Products, March (EMEA/MRL/182/97-Final (http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500011113.pdf, accessed November 2017).

Farah S, Aviv O, Laout N, Ratner S, Domb AJ (2015). Antimicrobial N-brominated hydantoin and uracil grafted polystyrene beads. J Control Release. 216:18–29.

Floyd R, Johnson JD, Sharp DG (1976). Inactivation by bromine of single poliovirus particles in water. Appl Environ Microbiol. 31:298–303.

Floyd R, Sharp D, Johnson J (1978). Inactivation of single poliovirus particles in water by hypobromite ion, molecular bromine, dibromamine and tribromamine. Environ Sci Technol. 12(9):1031–35.

Freund A, Johnson JD, Sobsey M (2010). Comparative inactivation of poliovirus in reclaimed water by bromine and chlorine. In: Proceedings. International Water Association Biennial Meeting, Montreal QC, January 2010.

Giller SF, Le Curieux F, Erb F, Marzin D (1997). Comparative genotoxicity of halogenated acetic acids found in drinking water. Mutagenesis. 12(5):321–28.

Goodenough RD (1964). Variables on the bactericidal activity of bromine in water. Swimming Pool Age [cited by Kim J, Sobsey M (2013)].

HCN (2005). Health-based reassessment of administrative occupational exposure limits; Bromine. Health Council of the Netherlands (http://www.gr.nl/en/publications/gezonde-arbeidsomstandigheden/health-based-reassessment-of-administrative-occupatio-123, accessed February 2015).

IARC (1999). Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances. Lyon, International Agency for Research on Cancer; pp. 481–496 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 73).

IPCS (1999). Bromine. Poisons Information Monograph. PIM 080. Geneva, World Health Organization, International Programme on Chemical Safety [cited by PHE (2009)].

Ivanov NG, Klyachkina AM, Germanova AL (1976). Experimental materials on hygienic regulation of bromine and hydrogen bromide in the air of the working zone. Gig Tr Prof Zabol *20*(3):36–39 (in Russian) [cited by USEPA (2005)].

Johannesson JK (1958). Anomalous bactericidal action of bromamine. Nature. 181:1799–1800 [cited by Kim J, Sobsey M (2013)].

Johnson J, Overby R (1970). Bromine and bromamine disinfection chemistry. In: Proceedings. National Specialty Conference on Disinfection, Amherst. American Society of Civil Engineers; pp. 37–60 [cited by Kim J, Sobsey M (2013)].

Johnson JD, Sun W (1975). Bromine Disinfection of Wastewater. In: Johnson J, ed. Disinfection: Water and Wastewater. Ann Arbor: Ann Arbor Science Publishers, Inc.; 179–91 [cited by Kim J, Sobsey M (2013)].

Keswick BH, Fujioka RS, Burbank NC et al. (1978). Comparative disinfection efficiency of bromine chloride and chlorine for poliovirus. J Am Water Works Assoc. 70(10):573–77.

Keswick BH, Fujioka RS, Loh PC et al. (1982). Comparative Disinfection by Bromine Chloride and Chlorine of Viruses and Bacteria in Wastewater. J Water Pollut Control Fed. 52(10): 2581–88.

Kim J (2014). Critical review of studies on bromine disinfection of water and wastewater: Literature review. The University of North Carolina at Chapel Hill, Department of Environmental Sciences and Engineering (https://cdr.lib.unc.edu/search/uuid:35ed8d6a-85a0-4569-ae0b-b72a18157c1b, accessed February 2016).

Krasner SW, McGuire MJ, Jacangelo JG et al. (1989). The occurrence of disinfection by-products in US drinking water. J Am Water Works Assoc. 81:41–53.

Krusé CW, Hsu Y-C, Griffiths AC et al. (1970). Halogen action on bacteria, viruses, and protozoa. In: Proceedings. National Specialty Conference on Disinfection, Amherst: American Society of Civil Engineers. pp. 113–36 [cited by Kim J (2014)].

Linder RE et al. (1994). Acute spermatogenic effects of bromoacetic acids. Fundam Appl Toxicol. 22:422–30.

Lindley AC (1966). The activity of bromine against f2 bacteriophage and its host *Escherichia coli* K-12 under various aqueous conditions [thesis]. Baltimore: Johns Hopkins University, School of Hygiene and Public Health [cited by Kim J (2014)].

McTigue NE, Cornwell DA, Graf K, Brown R (2014). Occurrence and consequences of increased bromide in drinking water sources. J Am Water Works Assoc. 106 (11):E492–E508.

Mercado-Burgos N, Hoehn RC, Holliman RB (1975). Effect of halogens and ozone on *Schistosoma* ova. J Water Pollut Control Fed. 47(10): 2411–19.

McLennan SD, LA Peterson, JB Rose (2009). Comparison of point-of-use technologies for emergency disinfection of sewage-contaminated drinking water. Appl Environ Microbiol. 75(22):7283–86.

NSF (2011). Bromine/bromide (CAS# 7726-95-6/24959-67-9) - Oral risk assessment document (http://www.techstreet.com/standards/nsf-bromine-bromide-2011?product_id=1848270, accessed February 2015).

NTP (1985). NTP Technical report on the toxicology and carcinogenesis studies of chlorodibromomethane (CAS NO. 124-48-1) in F344/N rats and B6C3F1 mice (gavage studies) (http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr282.pdf, accessed February 2015).

NTP (1987). NTP Technical report on the toxicology and carcinogenesis studies of bromodichloromethane (CAS NO. 75-27-4) in F344/N rats and B6C3F1 mice (gavage studies) (http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr321.pdf, accessed February 2015).

NTP (1989a). NTP Toxicology and carcinogenesis studies of tribromomethane (bromoform) (CASRN 75-25-2) in F344/N rats and B6C3Fi mice (gavage studies). Technical Report Series No. 350. Research Triangle Park (NC): National Toxicology Program (http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr350.pdf, accessed February 2015).

NTP (1989b). Bromoform. Reproduction and fertility assessment in Swiss CD-1 mice when administered by gavage. Research Triangle Park (NC): National Toxicology Program.

NTP (2000a). Water disinfection byproducts (bromoacetic acid). Research Triangle Park (NC): National Toxicology Program (http://ntpserver.niehs.nih.gov/htdocs/Results_Status/Resstatb/M920034.html, accessed February 2015).

NTP (2000b). Water disinfection byproducts (dibromoacetic acid). Research Triangle Park (NC): National Toxicology Program (http://ntpserver.niehs.nih.gov/htdocs/Results_Status/Resstatw/M960093.html, accessed February 2015).

NTP (2006). Toxicology and carcinogenicity studies of bromodichloromethane (CASRN 75-27-4) in male F344/N rats and female B6C3F1 mice (Drinking water studies). Technical Report Series No. 532. Research Triangle Park (NC): National Toxicology Program (https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr532.pdf, accessed February 2015).

NTP (2009). Studies of bromochloroacetic acid (CAS No. 5589-96-8) in F344/N rats and B6C3F1 mice (drinking water studies). Research Triangle Park (NC): National Toxicology Program.

NTP (2013). Draft OHAT approach for systematic review and evidence integration for literature-based health assessments-February 2013. Research Triangle Park (NC): National Toxicology Program (https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf, accessed April 2015).

PHE (2009). Bromine: Toxicological overview. Public Health England (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/337537/Bromine_Toxicological_Overview_phe_v1.pdf, accessed February 2015).

Plewa MJ, Muekkner M, Richardson, S (2008). Occurrence, synthesis, and mammalian cell cytotoxicity and genotoxicity of haloacetamides: An emerging class of nitrogenous drinking water disinfection byproducts. Environ Sci Technol. 42: 955–61.

Regli S, Chen J, Messner M, Elovit M, Letkiewicz F, Pegram R et al. (2015). Estimating potential increased bladder cancer risk due to increased bromide concentrations in sources of disinfected drinking waters. Environ Sci Technol. 49(22):13094–102.

Richardson SD (2011). In: Disinfection by-products: Formation and occurrence in drinking water. In Encyclopedia of Environmental Health; Nriagu, JO, ed. Elsevier: Burlington; Vol. 1; pp. 110−136.

Richardson SD, Plewa M J, Wagner ED, Schoeny R, DeMarini DM (2007). Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: A review and roadmap for research. Mutat Res. 636:178−242.

Richardson S (2003a). Disinfection by-products and other emerging contaminants in drinking water. Trends Analyt Chem. 22(10): 666–84.

Richardson SD, Thruston AD Jr, Rav-Acha C et al. (2003b). Tribromopyrrole, brominated acids, and other disinfection byproducts produced by disinfection of drinking water rich in bromide. Environ Sci Technol. 37(17): 3782−93.

Rupp H, Henschler D (1967). Wirkungen geringer chlor- und bromkonzentrationen auf den menschen. Int Arch Gewerbepathol Gewerbehyg. 23:79−90 [cited by HCN, 2005].

Russel DL (2006). Practical wastewater treatment. Hoboken (NJ): John Wiley & Sons.

Sagi A, Baruchin AM, Ben-Yakar Y, Kon M, Eyal A, Mahler D et al. (1985). Burns caused by bromine and some of its compounds. Burns 11:343−50.

Sangster B, Blom JL, Baas C, Loeber JG, Rauws A (1986). Onderzoek naar de invloed van natriumbromide bij menselijke vrijwilligers: III. Bilthoven, Rijksinstituut voor de volksgezondheid en milieuhygiene (RIVM), October (Report No. 348301001) [cited by WHO, 2009].

Scarpino P, Berg G, Chang S, Dahling D, Lucas M (1972). A comparative study of the inactivation of viruses in water by chlorine. Water Res. 6(8):959–65 [cited by Kim J, 2014].

Schlagbauer M, Henschler D (1967). Toxizität von chlor und brom bei einmaliger und wiederholter inhalation. Int Arch Gewerbepathol Gewerbehyg. 23:91–8 [cited by HCN, 2005].

Sharp DG, Floyd R, Johnson JD (1976). Initial fast reaction of bromine on reovirus in turbulent flowing water. Appl Environ Microbiol. 31(2):173–81.

Sharp DG, Floyd R, Johnson JD (1975). Nature of the surviving plaque forming units of reovirus in water containing bromine. Appl Microbiol. 29(1):94–101.

Shukairy HM, Miltner RJ, Summers RS (1994). Bromide's effect on DBP formation, speciation and control: Part I, Ozonation. J Am Water Works Assoc. 86(6):72–87.

Sollo F, Mueller H, Larson T, Johnson J (1975). Bromine disinfection of wastewater effluents. In: Johnson J, ed. Disinfection: Water and Wastewater. Ann Arbor: Ann Arbor Science Publishers, Inc.; 163–77 [cited by Kim J (2014)].

States S, Cyprych, G, Stoner M, Wydra F, Kuchta J, Monnell, J et al. (2013). Marcellus shale drilling and brominated THMs in Pittsburgh, Pa., drinking water. J Am Water Works Assoc. 105:E432–48.

Stauber CE, Ortiz GM, Loomis DP, Sobsey MD (2009). A randomized controlled trial of the concrete biosand filter and its impact on diarrheal disease in Bonao, Dominican Republic. Am J Trop Med Hyg. 80:286–93 [cited by Coulliette et al 2010].

Stratton CE, Ross WE, Chapman S (1981). Cytotoxicity and deoxyribonucleic acid damage associated with bromoacetate. Biochem Pharmacol. 30:1497–1500.

Stringer R, Cramer W, Krusé C (1975). Comparison of bromine, chlorine and iodine as disinfectants for amoebic cysts. In: Johnson J, ed. Disinfection: Water and Wastewater. Ann Arbor: Ann Arbor Science Publishers, Inc.; pp. 193–209 [cited by Kim J (2014)].

Sun G, Allen LC, Luckie EP, Wheatley WB, Worley SD (1995). Disinfection of water by N-halamine biocidal polymers. Ind Eng Chem Res. 34(11):4106–09.

Tanner F, Pitner G (1939). Germicidal action of bromine. Proceedings of the Society for Experimental Biology and Medicine. 143–45 [cited by Kim J (2014)].

Taylor GR, Butler M (1982). A comparison of the virucidal properties of chlorine, chlorine dioxide, bromine chloride and iodine. J Hyg. 89(2):321–328.

Thomas WM, Eccles J, Fricker C (1999). Laboratory observations of biocide efficiency against *Legionella* in model cooling tower systems. ASHRAE Trans 105(SE-99-3); pp. 607–26.

Tobe M, Suzuki Y, Aida K et al. (1982). Studies on the chronic oral toxicity of tribromomethane, dibromochloromethane and bromodichloromethane. Unpublished intra-agency report to the National Institute of Hygienic Sciences. Tokyo Medical and Dental University, Tokyo, Japan; 8–43 [cited by USEPA IRIS, http://www.epa.gov/iris/subst/0222.htm#carc].

USEPA (2010). Bromine Final Registration Review Decision. Case 4015. EPA-HQ-OPP-2009-0167. February. Washington (DC): United States Environmental Protection Agency. Office of Prevention, Pesticides, and Toxic Substances.

USEPA (2005a). Bromine/Bromide. EPA-HQ-OPP-2006-0143-0005. Washington (DC): United States Environmental Protection Agency. Office of Prevention, Pesticides and Toxic Substances (http://www.epa.gov/pesticides/reregistration/bromine/, accessed February 2015).

USEPA (2005b). Drinking water criteria document for brominated trihalomethanes. EPA-822-R-05-011. November 2005. Washington (DC): United States Environmental Protection Agency. Office of Science and Technology (https://nepis.epa.gov/Exe/ZyPDF.cgi/P1006GVD.PDF?Dockey=P1006GVD.PDF, November 2017).

USEPA (2005c). Economic analysis for the final stage 2 Disinfectants and disinfection byproducts rule. EPA-815-R-05-010. December 2005. Washington (DC): United States Environmental Protection Agency.

USEPA (2005d). Drinking water criteria document for brominated acetic acids. EPA-822-R-05-007. November 2005. Washington (DC): United States Environment Protection Agency. Office of Science and Technology.

USEPA (2006). National primary drinking water regulations: Stage 2 Disinfectants and disinfection byproducts rule. Washington (DC): United States Environmental Protection Agency. Office of Science and Technology. Fed Regist. 71:387–493.

USEPA (2009). Bromine summary document: Registration review preliminary work plan. Washington (DC): United States Environmental Protection Agency.

USEPA (2010). Bromine final registration review decision. Case 4015. EPA-HQ-OPP-2009-0167. Washington (DC): United States Environmental Protection Agency.

von Gunten U (2003). Ozonation of drinking water: Part II. Disinfection and by-product formation in presence of bromide, iodide or chlorine. Water Res. 37:1469–87.

Voronin VM, Donchenko AI, Korolev AA (1987). Experimental study of the carcinogenicity of dichlorobromomethane, and dibromochloromethane formed during chlorination of water (Russ.). Gig Sanit. 1:19–21 [cited by USEPA IRIS: https://www.epa.gov/iris#carc, accessed February 2015).

West RC, editor (1984). Handbook of Chemistry and Physics. Boca Raton (FL): CRC Press.

Westerhoff P, Chao P, Mash M (2004). Reactivity of natural organic matter with aqueous chlorine and bromine. Water Res. 38:1502–13.

WHO (2004a). Disinfectants and disinfectant by-products. Environmental Health Criteria 216. Geneva: World Health Organization (http://www.who.int/ipcs/publications/ehc/ehc_216/en/, accessed February 2015).

WHO (2004b). Brominated acetic acids in drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality. Geneva: World Health Organization (http://www.who.int/water_sanitation_health/dwq/chemicals/brominatedaceticacids.pdf, accessed February 2015).

WHO (2005). Bromate in drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality. Geneva: World Health Organization (http://www.who.int/water_sanitation_health/dwq/chemicals/bromate260505.pdf, accessed February 2015).

WHO (2009). Bromide in drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality. Geneva: World Health Organization (http://www.who.int/water_sanitation_health/dwq/chemicals/Fourth_Edition_Bromide_Final_January_2010.pdf, accessed February 2015).

WHO (2011). Evaluating household water treatment technologies: Health based targets and microbiological performance standards. Geneva: World Health Organization (http://www.who.int/water_sanitation_health/publications/2011/household_water/en/, accessed February 2015).

WHO (2017). Guidelines for drinking-water quality: Fourth edition. Geneva: World Health Organization (http://www.who.int/water_sanitation_health/publications/drinking-water-quality-guidelines-4-including-1st-addendum/en/, accessed September 2017).

Williams DE, Elder ED, Worley SD (1988). Is free halogen necessary for disinfection? Appl Environ Microbiol. 54(10):2583–85.

Yamaguchi T, Wei M, Hagihara N, Omori M, Wanibuchi H, Fukushima S (2008). Lack of mutagenic and toxic effects of low dose potassium bromate on kidneys in the big blue rat. Mutat Res. 652(1):1–11.

Appendix A: Methodology

Two initial literature searches were conducted in November 2013 as follows:

i) to update toxicity assessment; and
ii) to update efficacy assessment.

The search strategy and terms are outlined in Box 1 and 2 respectively, below.

Box 1- Search strategy for updating toxicity assessment for bromine

((KEY(human OR animal) OR TITLE-ABS-KEY({in vitro} OR {in vivo})) AND DOCTYPE(ar OR re) AND PUBYEAR > 2004) AND ((TITLE-ABS-KEY(toxicokinetic OR irritation OR sensitisation) OR TITLE-ABS-KEY(genotoxicity OR mutagenicity OR carcinogenicity) OR TITLE-ABS-KEY({Acute toxicity} OR {Repeat dose toxicity} OR {Chronic toxicity}) OR TITLE-ABS-KEY({Reproductive toxicity} OR {Developmental toxicity})) AND DOCTYPE(ar OR re) AND PUBYEAR > 2004) AND (((CASREGNUMBER(7726-95-6) AND DOCTYPE(ar OR re) AND PUBYEAR > 2004))

Box 2- Search strategy for updating efficacy assessment for bromine

(TITLE-ABS-KEY(bromine) AND TITLE-ABS-KEY({drinking water} OR {potable water}) AND TITLE-ABS-KEY(disinfection OR microorganism OR bacteria OR virus OR protozoa OR antimicrobial OR bactericidal OR bacteriostatic)) AND PUBYEAR > 2004.

Searches were carried out using Scopus and Web of Knowledge databases. Titles and abstracts of journal articles identified from the initial literature searches included 24 papers relating to bromine toxicity and 195 papers relating to bromine efficacy, which were reviewed to inform on their potential relevance to the project. For those titles selected, which were included in the document, papers were obtained in full for review to extract key data. Additional searches were carried out up to the closing date for public review (16 December 2016), particularly for identification of "grey" literature and earlier studies.

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