Iodine as a drinking-water disinfectant

Alternative drinking-water disinfectants: iodine

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List of abbreviations and terms used in the document

AI	adequate intake
bw	body weight
Ct	product of disinfectant concentration and contact time
DBP	disinfection by-product
GI	gastrointestinal
HAV	hepatitis A virus
HOCl	hypochlorous acid
HIO	hypoiodous acid
HWT	household water treatment
I_2	elemental iodine
IO_3^-	iodate
I^-	iodide
NOAEL	no-observed-adverse-effect level
NTU	nephelometric turbidity units
OI^-	hypoiodite
PBI	protein bound iodine
POU	point-of-use
PPM	parts per million
T4	thyroxine
T3	triiodothyronine
THM	trihalomethane
TRH	thyrotropin releasing hormone
TSH	thyroid stimulating hormone

UL	tolerable upper intake limit
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.

Over the centuries numerous water disinfection techniques have been developed that are used in a wide range of applications ranging from large and small public drinking-water treatment plants to point-of-entry and point-of-use (POU) treatment devices.[1] Chlorine has been used for more than 100 years and several other disinfectants have been studied extensively, but in many cases, questions remain with respect to 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 constituents, and the effectiveness and toxicology of disinfectant residuals. Most chemical disinfectants can react with natural organic matter or breakdown to produce unwanted by-products. Many newer products and applications are being developed and marketed for use, particularly in developing countries, and even more unanswered questions exist about some of those products, including efficacy and DBP formation.

Iodine is an essential nutrient. In addition, it has been used generally as an antiseptic for skin wounds, as a disinfecting agent in hospitals and laboratories, and in the production of pharmaceuticals. In terms of the disinfection of drinking-water, iodine is commonly used in the form of tablets or solutions during emergencies and by travellers (Ongerth et al., 1989; Backer & Hollowell, 2000). At regular intervals, there is renewed interest in the use of iodine as an alternative disinfectant to chlorine (and other disinfectants) for drinking-water.

Iodine-based disinfection of water has a long history: iodine in concentrations between 2.5–7 mg/L (equivalent to parts per million [ppm]) has been used for potable water treatment since the early 1900s, especially for military operations (Hitchens, 1922; Vergnoux, 1915). Tablet formulations have been used since the 1940s to ensure the microbiological safety of drinking-water for military personnel deployed in the field (Chang & Morris, 1953). Also, in more recent times, iodine (and bromine) has become attractive for particular applications. Elemental iodine is used, for example, as a drinking-water disinfectant aboard space vessels at a residual concentration of approximately 2 ppm (Atwater et al., 1996). The more general use of iodine is impeded, however, by the potential for excess iodine intake, cost and the possibility of the formation of toxic DBPs.

The emphasis of this literature review is to evaluate available evidence on the efficacy and toxicity of iodine as a water disinfectant. Information included in this review was initially 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). Additional 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 point-of-entry treatment devices are typically installed to treat all water entering a single home, business, school, or facility.

2. Disinfection characteristics and efficacy

2.1 Chemistry basics

Iodine, chlorine, bromine and fluorine belong to the halogen group of elements in the periodic table. 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 and 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):[2]

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

The reactivities of the given halogens therefore decreases 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 selectivity, chemical stability and other factors including the potential to form by-products. Fluorine, the most reactive of all elements of the periodic table, is so unstable that it reacts with surrounding water molecules in a violent reaction forming hydrogen fluoride and oxygen. The reactivity of other halogens is more selective, making them more suitable for practical applications. Among the three halogens used for disinfection purposes (chlorine, iodine and bromine), iodine has the highest atomic weight and is the only one to exist as a solid at room temperature.

2.1.1 Water solubility, taste and odour

Elemental iodine is less soluble in water than chlorine or bromine. Water solubility depends on pH and temperature and is reported to be 0.03 mg/L at 20 ºC, 0.78 mg/L at 50 ºC and 4.45 mg/L at 100 ºC (West, 1984). A saturated aqueous solution of iodine can be produced by passing water through a column of crystalline iodine. The iodine concentration achieved will be approximately 200 mg/L at 10 ºC and 400 mg/L at 30 ºC (Chang, 1968). This concentrated solution can be diluted to achieve the desired concentration of iodine.

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 did not vary appreciably with pH, ranging from 0.147 to 0.204 mg/L. In contrast to chlorine, which has a high vapour pressure and readily volatilizes, especially in the presence of sunlight or higher temperatures, iodine has a low vapour pressure resulting in little loss by volatilization (Black et al., 1970).

2.1.2 Chemical speciation of iodine in water and corresponding disinfection powers

Once elemental iodine (I_2) is added to water, it hydrolyses in a pH-dependent manner to form hypoiodous acid (HIO) and iodide (I^-). The overall stoichiometry of iodine hydrolysis between pH 2 and 7 is given below; for a more detailed description of iodine hydrolysis, the reader is referred to Lengyel et al. (1993):

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

$$I_2 + H_2O \leftrightarrow HIO + I^- + H^+$$

Similar to hypochlorous acid (HOCl), hypoiodous acid can deprotonate to form hypoiodite (OI^-) according to the following general reaction:

$$HIO \leftrightarrow H^+ + OI^-$$

The different chemical species of iodine vary in their disinfection power. The active disinfectants are elemental iodine and hypoiodous acid (Backer & Hollowell, 2000). Other species including iodide, iodate (IO_3^-) and hypoiodite have mild or little antimicrobial activity (Chang, 1958). Comparing the two disinfection-active chemical species, the oxidizing power of hypoiodous acid is nearly twice that of elemental iodine (West, 1984). A comparison of oxidizing potentials with the equivalent chlorine species is shown in Table 1.

Table 1: Comparison of oxidizing potentials of iodine and chlorine species (West, 1984)

Chemical species	Oxidizing potential (in volts)
I_2	0.535
HIO	0.987
Cl_2	1.358
HOCl	1.482

Cl_2–chlorine

The disinfection efficacy of the different chemical species depends not only on oxidizing potential, but also on penetration power. Elemental iodine has higher penetrating power than hypoiodous acid (White, 1992).

A comprehensive study of disinfection efficacy was performed by Chang & Morris (1953). Iodine concentrations in the range 5–10 ppm were found to be effective against different types of microorganisms within 10 min at room temperature. Organisms tested included enteric bacteria, amoebic cysts, cercariae, leptospira and viruses. Overall, different classes of microorganisms have different susceptibilities to iodine: vegetative bacteria tend to be most sensitive, whereas viruses have an intermediate sensitivity and protozoa tend to be more resistant (Backer & Hollowell, 2000). Moreover, elemental iodine and hypoiodous acid contribute to different extents to the disinfection efficacy against different microbes. Chemical speciation is highly pH dependent (addressed in the next section). Disinfection sometimes follows first-order kinetics with the primary determinants of effectiveness being disinfectant concentration and time of exposure of the microorganism (expressed as Ct in mg·min/L i.e. the product of disinfectant concentration (C in mg/L) and contact time (t in min). Departures from first-

order kinetics can occur due to such phenomena as declines in iodine concentration over time, microbial aggregation and microbial protection by other particles.

2.1.2.1 Effect of pH

Both the hydrolysis and the subsequent equilibrium between elemental iodine and hypoiodous acid are pH-dependent, but the effect is not as pronounced as with chlorine. Table 2 shows the proportions of elemental iodine, hypoiodous acid and hypoiodite for a pH range between pH 5 and 9, in comparison with the chlorine equivalents.

Table 2: Effect of pH on the speciation of iodine and chlorine (0.5% titratable iodine)

pH	Iodine			Chorine		
	I_2 (%)	HIO (%)	OI^- (%)	Cl_2 (%)	HOCl (%)	OCl^- (%)
5	99	1	0	0.5	99.5	0
6	90	10	0	0	99.5	0.5
7	52	48	0	0	96.5	3.5
8	12	88	0.005	0	21.5	78.5
9	-	-	-	0	1	99

Cl_2–chlorine; OCl^-–hypochlorite
Adapted from Chang (1958), Black et al. (1970) and Ellis & van Vree (1989).

Higher pH results in a progressive decline in elemental iodine with a shift in the equilibrium toward hypoiodous acid. As the active disinfectants are elemental iodine and hypoiodous acid, to use iodine most effectively as a disinfectant, the pH should be near neutral to mildly alkaline (pH 7–7.5) to allow adequate levels of both elemental iodine and hypoiodous acid (Table 2). At ≥ pH 8.0, hypoiodous acid was reported to be unstable and to slowly decompose into iodate and iodide (Ellis & van Vree, 1989). However, in the absence of a stronger oxidant such as chlorine, iodate formation does not occur readily (Black et al., 1970). More detailed information about speciation and its pH dependence is available in Gottardi (1999). Overall, the disinfection effectiveness of iodine is not as heavily influenced by pH as chlorine is. Hypochlorite formation increases at values > pH 7. Strong evidence has been provided that hypochlorite has less disinfection power that can be influenced by concentrations of anions, such as sodium and potassium (Chang & Morris, 1953; Keirn & Putnam, 1968; Haas et al., 1986; Jensen et al., 1980).

The progressive decline of free iodine residual and increasing proportion of hypoiodous acid with increasing pH also has fundamental consequences for the disinfection power of iodine. Different effects occur along this gradient and different iodine species have different disinfection efficacies for different groups of microbes (Ellis et al., 1993). In generalized terms, elemental iodine is primarily effective against bacterial spores and protozoan cysts, whereas hypoiodous acid is known to be an effective

bactericide and virucide (Ellis et al., 1993). For example, Chang (1966) reported elemental iodine to be 2–3 times more effective against *Entamoeba histolytica* cysts than hypoiodous acid, whereas hypoiodous acid was found to be approximately 40 times more effective than elemental iodine against viruses. Hypoiodous acid also had greater germicidal activity against vegetative bacteria than elemental iodine (e.g. hypoiodous acid was found 3–4 times more effective than elemental iodine against *Escherichia coli*).

The effect of pH on speciation of iodine and the resulting effect on disinfection efficacy is exemplified in a study by Taylor & Butler (1982). The authors reported that iodine was more effective against poliovirus at pH 9 than at lower pH values, probably due to the fact that at this pH most iodine will exist in the form of hypoiodous acid, which has greater virucidal activity than elemental iodine (Chang, 1966). The virucidal efficacy of hypoiodous acid and elemental iodine was reported to be respectively 4–5 times and 200 times less than hypochlorous acid (Clarke et al., 1964).

As the prevalent iodine species varies with pH, the most suitable pH range for the disinfection of different microbial groups will also vary. Overall trends in disinfection power of the various iodine species for different groups of microorganisms are summarised in Table 3 below.

Table 3: Trends in disinfection power for different iodine species when applied to different microbial groups and pH range where the most effective disinfectant prevails (Taylor and Butler, 1982)

Microbial group	Disinfection effectiveness of different iodine species	Suitable pH range for disinfection
Bacteria (vegetative)	HIO > I_2	pH 5–8
Bacteria (spores)	I_2 > HIO	pH 5–7
Viruses	HIO > I_2	pH 8–9
Protozoa[a]	I_2 > HIO	pH 5–7

Information about suitable pH is based on abundance of the most effective iodine species for a certain microbial group. Overall, vegetative bacteria are most susceptible.

[a] elemental iodine is effective against *Giardia* cysts but not effective against *Cryptosporidium* oocysts.

While these tendencies hold true for microorganisms suspended in clean water, disinfection efficacies can be altered in the presence of turbidity and in poor quality water. The underlying reason is that although hypoiodous acid is more reactive and has a higher oxidation potential, it has less penetrating power than elemental iodine. If microorganisms are sheltered in particles, as found in turbid and poor quality water, the enhanced penetrating power becomes more important than overall reactivity (Ellis et al., 1993). Even if microorganisms are not attached to particles, the higher oxidation potential of hypoiodous acid (prevalent at pH 8–9) might lead to preferential reaction with oxidizable organic matter (e.g. in the case of turbid water with elevated total organic content) leaving less residual available for disinfection (Ellis et al., 1993). More information on the effects of turbidity can be found in Section 2.2.2. Karalekas et al.

(1970) reported the effect of 1 ppm iodine on 6 different bacterial species. A noticeable reduction of the germicidal effect was reported when increasing the pH from 5 to 9 (while noticing little difference between pH 5 and 7). A slight decline in disinfection efficacy against *E. coli* and faecal streptococci was also observed by Ellis & van Vree (1989) when increasing the pH from pH 7 to 8.5. The reduced efficacy of iodine at higher pH was explained by Ellis et al. (1993) by the progressive decline of free iodine residual. In studies on the effects of water quality and pH on inactivation of hepatitis A virus (HAV), poliovirus 1 and echovirus 1 by 8 and 16 mg/L doses of iodine, HAV was inactivated more efficiently by iodine than were the other two test viruses, and the order of virus inactivation was:

HAV > echovirus 1 > poliovirus 1 (Sobsey et al, 1991).

Virus inactivation was generally more effective at higher pH, in cleaner water, at higher temperature and at higher iodine dose.

The partitioning into different chemical species with different disinfection power is not only dependent on pH, but also the initial concentration of titratable iodine (Chang, 1966). The lower the iodine concentration, the higher the relative percentage of hypoiodous acid at a given pH.

2.1.2.2 Effect of temperature

For iodine, the pH effect on disinfection efficacy is more noticeable at lower temperatures (Ellis et al., 1993). In general, higher doses of iodine are required at lower temperatures to achieve the same degree of disinfection (Chambers et al., 1952). As with chlorine, the reason can be found in the lower reactivity of the disinfectant at lower temperature as the reaction rate is negatively correlated with the temperature via the reaction constant. At low temperatures near the freezing point, a higher contact time is therefore required to compensate for the loss in reactivity. Chang & Morris (1953) reported a doubling of required contact time when decreasing the temperature from 25 °C to near freezing temperature (2–3 °C). Temperature dependence of disinfection efficacy is however not fully understood as different effects might counter-act each other. Ellis et al. (1993) found better germicidal performance at 5 °C than at 20 °C, whereas an increase to 35 °C further reduced the effectiveness. This contradicts previous findings but was explained by an increase in the oxidation potential at higher temperatures leading to faster inactivation and less residual. The authors concluded that higher temperatures favour increased hydrolysis leading to higher concentrations of hypoiodous acid which, in turn, has a higher oxidation potential than elemental iodine.

2.2 Efficacy of iodine

2.2.1 Bactericidal efficacy of iodine

Chang & Morris (1953) investigated the bactericidal effects of a number of Ct combinations of iodine on different bacterial pathogens. Tests conducted with *E. coli* showed that iodine concentrations of ≥ 0.05 ppm consistently reduced the culturability of 10^4 bacteria cells/mL to less than 1 cell/mL within 10 min (25 °C, pH 8.1–8.5). Other results obtained when exposing 10^6 *E. coli* cells/mL to different iodine concentrations are shown in Table 4 below.

Table 4: Bactericidal efficacy of iodine (adapted from Chang & Morris, 1953)

Iodine concentration (in ppm)		Viable cells/100 mL (log_{10} reduction)			
Initial	30 min	5 min	10 min	20 min	30 min
1.0	0	1600 (2.80)	540 (3.27)	240 (3.62)	130 (3.89)
2.0	1.2	4.6 (5.34)	1.0 (6.00)	1.0 (6.00)	2.2 (5.66)
3.0	1.6	4.6 (5.34)	4.6 (5.34)	4.6 (5.34)	< 1 (6.00)
4.0	2.6	24 (4.62)	6.9 (5.16)	2.5 (5.60)	1.0 (6.00)
5.0	3.3	< 1 (6.00)	< 1 (6.00)	< 1 (6.00)	< 1 (6.00)

Bactericidal efficacy of different iodine concentrations to reduce viability of *E. coli* spiked into tap water at an initial concentration of 10^6 cells/mL. A standard iodine dose of between 7 to 9 ppm was used to meet the iodine demand in the tap water and to obtain a bactericidal residual of 1 to 5 ppm. The experiment was performed at 25 °C and a pH between pH 8.1 to 8.5.

Adapted with permission from: Chang S, Morris J (1953). Elemental iodine as a disinfectant for drinking water. Ind Eng Chem. 45: 1009–12. Copyright (1953) American Chemical Society.

Chang & Morris (1953) reported stronger inactivation than seen with *E. coli* for other enteric bacteria including, *Salmonella typhimurium*, *Shigella dysenteriae* and *Vibrio cholera*, with initial iodine concentrations of 7–8 ppm and pH 4.5–8.1. The authors reported that there was no effect of pH on bactericidal efficacy of iodine in the range pH 4.5–8.1. Similar (but declining) results were obtained with values up to pH 10, which is in sharp contrast to the strong pH dependence of chlorine.

2.2.2 Disinfection in the presence of turbidity

There is limited information discussing the effects of turbidity on the disinfection capability of iodine. When testing the effect of ammonium and urea on the efficacy of iodine disinfection, concentrations up to 5 ppm were not found to have any measurable effect on the inactivation of *E. coli* (Chang & Morris, 1953). The same held true when adding different clays in concentrations of up to 500 ppm. It is generally accepted that iodine shows less reactivity with organic nitrogenous impurities compared to chlorine (Punyani et al., 2006) but does react to produce iodamines. The organic colour of water (due to the presence of natural organic substances) is associated with iodine demand and reduced efficacy. At organic colour concentrations > 70 ppm, a doubling of the dose was found to be required for disinfection. A study by Ellis & van Vree (1989) found that when supplementing water with sediments from a natural stream, the stepwise increase in turbidity up to a maximum of 1000 nephelometric turbidity units (NTU) reduced the germicidal effectiveness of iodine.

In general, the disinfection capability of iodine, as with all disinfectants is reduced with increasing turbidity as microorganisms can be protected from the iodine by adsorption to, or enmeshment in, solid particles in water. In addition, there may be an increasing disinfectant demand due to reactions between organic particles and the disinfectant. Sobsey et al. (1991) reported that the inactivation of HAV by iodine at doses of 8 and 16 mg/L was less effective in “dirty water” (i.e. 10 mg/L of a 1:1 mixture of humic and fulvic acids and 5 NTU of bentonite clay turbidity). Ellis et al. (1993) applied iodine to water supplemented with stream sediments to achieve three different turbidity ranges (5–7, 50–54 and 93–97

NTU). Water was additionally adjusted to values of pH 6, 7.5, and 9 and different temperatures (5, 20, and 35 ºC). Under all conditions tested, a dose of 3 mg/L iodine with a contact time of 30 min was found sufficient to inactivate *E. coli*. When supplementing water with digested sludge (up to the highest turbidity range) or raw sludge (5–7 NTU), doses of 8 or 10 mg/L iodine were necessary to achieve inactivation for the same contact time. The authors argued that the nature of the turbidity was more important than its density. It was hypothesized that the higher organic and nitrogen content of the sludge compared to the stream sediments was responsible. When comparing disinfection efficacy with chlorine at 1.0 mg/L, chlorine was reported to be slightly more effective for water containing stream sediments (e.g. at 20 ˚C and pH 7.5 the percentage inactivation of *E. coli* ranged from 99.52–100% for chlorine at turbidities between 94–5 NTU, with the corresponding values for iodine ranging between 98.58–99.97%). However, iodine was found more efficient in cases where sludge was added, particularly at the higher temperature and pH values (e.g. at 20 ˚C and pH 7.5, percentage inactivation of *E. coli* ranged from 21.7–38.74% for chlorine at turbidities between 97–5 NTU, with the corresponding values for iodine ranging between 42.40–50.70% [Ellis et al., 1993]).

2.2.3 Iodine-based disinfection products

Iodine-based disinfection products available today can be divided into two categories; iodine solutions and iodine resins. A summary of the disinfection capabilities of each is given in Table 5.

2.2.3.1 Iodine solutions

Iodine solutions are made by adding iodine (e.g. tincture of iodine, a 2% iodine solution), or by adding a tablet containing iodine, a carrier, and stabilizing agents to enhance dissolvability (e.g. tetraglycine hydroperiodide, sodium acid pyrophosphate and talc) to the water to be disinfected. The United States Army has utilised iodine as a drinking-water disinfectant since 1952, issuing iodine-based tablets to American soldiers. The United States Army continues to provide iodine-based tablets in addition to other emergency field drinking-water products. Today, there are several commercial off the shelf individual water purification devices that use iodine for disinfection.

For non-drinking-water disinfectant applications, iodine has been compared with chlorine and bromine as alternative disinfectants for swimming pools. Although not directly related to the use of iodine as a drinking-water disinfectant, these studies provide useful evidence of the efficacy of iodine for water disinfection and the tolerance of individuals to residual concentrations of iodine. Typical of the now dated studies, Black et al. (1959) investigated the effectiveness of iodine solutions for disinfecting public and domestic swimming pools in Florida, USA. The solutions were added in the form of potassium iodide over three weeks (twice weekly) at a dose equivalent to 1–2 ppm of iodine. The crystalline potassium iodide was either spread over the surface of the pool together with a small amount of chlorine to release free iodine, or uniformly distributed through a recirculation system. Iodine was found to be fully effective in meeting bacteriological standards. The amount of iodine required for public pools with high bathing activity was reported to be only slightly higher than required for pools with low bathing load (domestic pools), suggesting that the iodine residual appeared to be less sensitive to bathing load than the chlorine residual. The authors considered that this was due to iodine not reacting with ammonium, as does chlorine. However, the reason is more likely to be due to the direction of the equilibrium between iodine and ammonium. The study concluded that a daily dosage of 1 or 2 ppm of iodine would suffice to disinfect domestic or public pools. This translates into a residual concentration of approximately 0.2 ppm (Black et al., 1959).

Available evidence indicates that iodine solutions can be effective disinfectants against bacteria and, to a lesser extent, viruses. Recommended dosages range from between 4 and 16 mg/L with contact times ranging from 20–35 min, resulting in Ct values of 80–560 mg·min/L to achieve a 6 $\log_{10}$ reduction/inactivation of bacteria and a 4 $\log_{10}$ reduction/inactivation of viruses. Iodine is least effective against protozoa and in particular, ineffective against *Cryptosporidium parvum* oocysts, where the doses and contact times required are impractical for drinking-water disinfection (Gerba et al., 1997).

2.2.3.2 Resins

Iodine resins are solid-phase iodine disinfectants through which water is passed, with disinfection occurring through direct contact of the microorganisms and the iodine sorbed onto the resin as exchangeable ions. Iodine resins are generally considered demand-release disinfectants as iodine is released to the microorganism after coming into contact with the resin, and generally produce a dilute iodine residual. As is the case with iodine solutions, available data on iodine resins indicates they are effective disinfectants against bacteria, viruses, and some protozoa (Punyani et al., 2006; Vasudevan & Tandon, 2010). However, the resins have not, to date, been proven effective against *Cryptosporidium* oocysts.

Resin-based iodine release systems comprise (1) organic iodide compounds, (2) iodophors (iodine in combination with non-ionic surfactants) and (3) iodine incorporated resins (Punyani et al., 2006). Iodine resins used in individual water purification devices are generally combined with other treatment processes, such as filtration, to remove iodine residuals and iodine-resistant microorganisms. Modern applications of resins have resulted in an increase in their use. Devices used by National Aeronautics and Space Administration for space flights are prominent examples. Controlled release of iodine on board the International Space Station Alpha is achieved through a flow-through device (referred to as Microbial Check Valve) containing an iodinated polymer (Atwater et al., 1996; Gibbons et al., 1990). The iodine residual concentration released into the water stream flow is a maximum of approximately 2 mg/L. The released dissolved iodine undergoes a series of hydrolytic reactions resulting in the formation of iodide, triiodide, hypoiodous acid and hypoiodide, with different biocidal capabilities associated to each inorganic species (Punyani et al., 2006; Venkobachar & Jain, 1983). Another resin employed by National Aeronautics and Space Administration consists of the iodine-polyvinyl pyrrolidone (iodine-PVP) complex which releases iodine and iodide at concentrations of 2–3 mg/L and 1.5 mg/L, respectively (Punyani et al., 2006). Again, the dissolved iodine speciates into a variety of different inorganic compounds. Greatest biocidal activity can be attributed to iodine and hypoiodous acid (Gazda et al., 2004; Gottardi, 1991).

A number of other resins have been developed with some promising results. Considering the potential health impact of released aqueous iodine, Punyani et al. (2006) proposed the development of resins that do not release iodine, but inactivate microorganisms during flow through by contact. Whereas resins loaded with iodate did not exhibit a germicidal effect, polyiodide resins were reported to be efficient for drinking-water disinfection (Vasudevan & Tandon, 2010).

Table 5: Disinfection capabilities of iodine solutions and resins[a]

Parameter	Iodine solutions	Iodine resins
General	Cysts most resistant. Achieving *Giardia* cyst inactivation will ensure adequate bacteria and virus inactivation.	Cysts most resistant. Achieving *Giardia* cyst inactivation will ensure adequate bacteria and virus inactivation.
Bacteria	4 $\log_{10}$ reduction at Ct values < 10 mg·min/L.[b]	Triiodide and pentaiodide resins can potentially provide a 6 $\log_{10}$ reduction under most natural water quality conditions.
Viruses	2 $\log_{10}$ reduction at Ct values of 15–75 mg·min/L.[c] 4 $\log_{10}$ reduction for HAV, poliovirus 1 and echovirus 1 by doses of 8 and 6 mg/L in 60 min or less, depending on water quality, pH and temperature.	Triiodide and pentaiodide resins can potentially provide a 4 $\log_{10}$ virus reduction under most natural water quality conditions.
Giardia cysts	3 $\log_{10}$ reduction at Ct values of 45–241 mg·min/L at > 20 °C. Provide additional contact time and higher Ct values at < 20 °C to achieve 3 log inactivation.	3 $\log_{10}$ reduction at 25 °C and 4°C using pentaiodide resin compared with 0.2–0.4 log reduction with triiodide resin. Additional contact time after passing through resin needed compared to iodine solutions.
Cryptosporidium oocysts	Not effective at practical Ct values.[d]	Not effective at practical Ct values.[d]
Effect of temperature	Major effect. Increase contact time and/or dose at colder temperatures. Ct values up to 720 mg·min/L recommended for *Giardia* cyst inactivation in colder waters (< 5 °C).	Major effect.[e] Increase contact time after passing through pentaiodide resin at colder temperatures. Allow up to 40 min additional contact time for *Giardia* cysts inactivation in colder waters (< 5 °C).
Effect of pH	Minor effect. Generally effective over typical pH levels for natural waters.	Minor effect. Generally effective over pH range typical for natural waters.
Effect of Turbidity	Affects disinfection capability. Provide additional contact time and/or increase iodine dose in more turbid waters.	Affects disinfection capability. Heavy organic matter loading can significantly reduce disinfection capability.

Source: Adapted from Technical Information Paper #-31-005-0211 (2011).

[a] Testing was carried out using iodinated resins only, with no filter applied, as would normally be found in individual water purification devices. Whilst bacteria and viruses are not physically filtered by the resin, due to electrostatic interactions, *Giardia* cysts and *Cryptosporidium* oocysts are filtered by the resin bed. However, subsequent use of the resin leads to release or flushing of cysts and oocysts, which could remain viable.

[b] Assuming a contact time of 20 min, a 0.5 mg/L iodine residual would be necessary to provide 4 $\log_{10}$ reduction of *E. coli* at near neutral pH at any temperature encountered in natural waters (20 min x 0.5 mg/L = 10 mg·min/L).

[c] 2 $\log_{10}$ reduction at near neutral to alkaline pH levels (pH 6–10) and various water temperatures (5–30 °C) at Ct values of 15–75 mg·min/L with the higher Ct values occurring at lower pH levels and colder water temperatures.

[d] Gerba et al. (1997).

[e] Temperature dependence of disinfection efficacy is not fully understood as different effects might counter-act each other. Current "best-practice" is given.

The residual iodine concentration with iodine resins is much less than concentrations from the recommended doses of tablet or liquid forms of iodine (Table 6).

Table 6: Residual iodine in demand-free water using recommended doses of available product

Iodine products	Recommended dose per litre of water[a]	Residual concentration of iodine
Iodine tablets (tetraglycine hydroperiodide)	1–2 tablets	8–16 mg/L
Iodine solution (tincture; 2%)	0.25–0.5 mL	4–8 mg/L
Providone-iodine solution (10%)	0.35–0.70 mL	4–8 mg/L
Saturated iodine crystals in water	13–26 mL	4–8 mg/L
Pentaiodide resin (room temp)	-	1–2 ppm[b]
Triiodide resin (room temp)	-	0.2 ppm
Triiodide resin at 42 °C	-	1 ppm
Triiodide resin at 71 °C	-	6–10 ppm
Triiodide resin and granular activated carbon	-	0.01 ppm

Modified from Backer & Hollowell (2000).

[a] Lower dose in clear, warm water (> 15 °C), higher dose in very cold or cloudy water. Disinfection activity is a function of iodine, contact time and water temperature.

[b] mg/L equivalent to ppm.

2.2.4 Comparison of efficacy with chlorine

The properties of iodine and chlorine differ in several important ways. Although speciation of iodine is pH dependent, a notable property of iodine is that it provides protection across a wider pH range than chlorine (Black et al., 1965; Ellis et al., 1993). Compared with chlorine, iodine has also greater chemical stability and shows less reactivity with organic nitrogenous contaminants, leaving a higher free residual; the reduced reactivity with organic contaminants leads to a reduction in iodine demand (Backer & Hollowell, 2000). On the negative side, less is known about iodine in regard to disinfection performance on some important pathogens in waters of different quality and above all on potential negative health impacts. In addition, the lower reactivity of iodine compared to chlorine requires the use of higher doses. A comparison with chlorine is given below:

Commonalities with chlorine:

- Different classes of microorganisms have different susceptibilities (e.g. neither are effective against *Cryptosporidium* oocysts); and
- Effectiveness is impacted by temperature, concentration, contact time, pH and organic content.

Advantages of iodine over chlorine:

- Provides protection across a wider pH range;
- Greater chemical stability;
- Less disinfection demand through reduced reactivity with organic nitrogenous impurities;
- Germicidal action of iodine occurs over a wider range of water quality conditions than chlorine; and
- Works better for water of poor quality.

Disadvantages of iodine compared to chlorine (these relate mainly to potential health concerns, as discussed fully in Section 3):

- The safety of long-term consumption of iodine when used as a drinking-water disinfectant is not established;
- Excess iodine intake is not safe for people with thyroid disease; and
- Higher concentrations are required as compared to chlorine to achieve comparable disinfection efficacy.

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

Existing evidence pertaining to the effectiveness of disinfectants against all three classes of pathogens which cause diarrhoeal disease, may not reflect actual use conditions in the field (e.g. water of varying quality, shorter contact times). In order to comprehensively assess effectiveness, WHO has set tiered health-based $\log_{10}$ reduction performance targets for household water treatment (HWT) products for the removal and/or inactivation of bacteria, viruses and protozoa (WHO, 2011). These performance targets are based on microbial risk models using assumed levels of reference pathogens in untreated water. Since 2014, WHO has been evaluating products against those performance targets through the WHO International Scheme to Evaluate Household Water Treatment Technologies.[3] Box 1 gives further information on the Scheme. At the time of this report, iodine has not been tested but may be included in future rounds.

[3] 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.[3] 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 iodine

The health effects of iodine have been reviewed by a number of international bodies:

- European Food Safety Authority (EFSA, 2014);
- Council for Responsible Nutrition (CRN, 2013);
- USEPA, 2006;
- Agency for Toxic Substances and Disease Registry (ATSDR, 2004);
- World Health Organisation /Food and Agriculture Organisation (WHO/FAO, 2004);
- World Health Organisation (WHO, 2003);
- Expert Group on Vitamins and Minerals (EVM, 2003);
- European Commission Scientific Committee on Food (EC, 2002);
- Institute of Medicine (IOM, 2001); and
- Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1988).

In this section, opinions from expert bodies on intake of iodine, as detailed above, are described. In addition, a detailed assessment of recent[4] toxicological literature for iodine was undertaken and the relevant findings are included here.

3.1 Human exposure

Iodine is an essential dietary element for mammals. It is required for the synthesis and function of the thyroid hormones thyroxin (T4) and triiodothyronine (T3), as well as being the precursor of iodotyrosines. Through these hormones, iodine has an important role in energy-yielding metabolism and on the expression of genes that impact many physiological functions, from embryogenesis to growth and development, neurological and cognitive functions (EFSA, 2014).

The only natural sources of iodine for humans and animals are the iodides in food and water. The use of iodine and iodophors for sanitizing purposes has been reported to result in significant amounts of iodine entering the food chain (Phillips, 1997). The iodine content of foods is highly variable both between food categories as well as within each category. Marine products such as shellfish and molluscs, and eggs and milk are the richest sources of dietary iodine (Phillips, 1997). In Japan, iodine intake exceeds that of most other countries, primarily due to substantial seaweed consumption. Zava & Zava (2011) utilized information from a number of sources including dietary records, food surveys, urine iodine analysis (both spot and 24-hour samples) and seaweed iodine content, to estimate daily Japanese iodine intake. The authors estimated that the Japanese iodine intake averages 1000–3000 µg/day (1–3 mg/day). The iodine content of drinking-water is also highly variable. In Denmark, tap water concentrations of iodine from a number of locations were reported to contain between < 1.0–139 µg/L (median 2.6 µg/L) (Pedersen et al., 1993). Drinking-water in the USA has a reported mean concentration of total iodine of 4 µg/L, with a maximum concentration of 18 µg/L (Andersen et al., 2008). Chronic excessive iodine intake has been linked to development of goitre (enlarged thyroid gland) (Zhao et al., 2000), early onset of sub-clinical thyroid disorders, hyperthyroidism (excessive production and/or secretion of thyroid hormones) and hypothyroidism (diminished production of thyroid hormones), an increased incidence of autoimmune

[4] To November 2013, with further ad hoc searches were carried out up to the closing date for public review (16 December 2016).

thyroiditis (inflammation of the thyroid gland) and increased risk of thyroid cancer (Laurberg et al., 1998; Teng et al., 2006).

In contrast, iodine deficiency remains a major public health concern in many countries, including some European countries (WHO/UNICEF/ICCIDD, 2007; Zimmermann & Andersson, 2011; Andersson et al., 2012). Chronic deficiency has been linked with compensatory thyroid hyperplasia with goitre, with an associated increase in risk of thyroid cancer. In an attempt to counteract the deficiency, iodine fortification of salt is recommended by WHO and has been implemented in approximately 120 countries worldwide (WHO/UNICEF/ICCIDD, 2007). Of these, 40 are European countries:[5] it is mandatory in 13 countries, voluntary in 16 and not regulated in the remaining countries. The amount of iodine added varies from 10–75 mg/kg salt with a majority of values in the range 15–30 mg/kg.

3.2 Guideline values

3.2.1. WHO Guidelines for Drinking-water Quality

The WHO Guidelines for Drinking-water Quality (WHO, 2017) did not formally establish a guideline value for iodine. Iodine was last reviewed by WHO for the Guidelines for Drinking-water Quality in 1993, when it was concluded that available data suggested that derivation of a guideline value for iodine on the basis of information on the effects of iodide was inappropriate and there were few relevant data on the effects of iodine. Also, because iodine is not recommended for long-term disinfection, lifetime exposure to iodine concentrations such as might occur from drinking-water disinfection is unlikely (WHO, 2003).

3.2.2 Other values

In 1988, the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1988) set a Provisional Maximum Tolerable Daily Intake for iodine of 1 mg/day (17 µg/kg body weight [bw] per day) from all sources. This upper limit was reaffirmed by WHO in 1994 (WHO, 1994). This was based on the tolerance of high doses of iodine in healthy iodine-replete adults and did not include neonates and young infants. In light of the recognition that excess iodine could lead to hypothyroidism, hyperthyroidism and thyroid autoimmunity in vulnerable individuals, in 2004 the WHO/FAO recommended the following nutrient intakes for iodine (WHO/FAO, 2004):

- Infants and children 0–59 months: 90 µg/day
- Children 6–12 years: 120 µg/day
- Adolescents and adults, from 13 years of age through adulthood: 150 µg/day
- Pregnant women: 200 µg/day
- Lactating women: 200 µg/day

In 2001, the Food and Nutrition Board at the United States National Institute of Medicine recommended the following dietary intakes for iodine (IOM, 2001):

- Infants
    - 0–6 months: 110 µg/day

[5] List of countries available from: http://www.who.int/nutrition/publications/VMNIS_Iodine_deficiency_in_Europe.pdf

  - 7–12 months: 130 µg/day
- Children
  - 1–3 years: 90 µg/day
  - 4–8 years: 90 µg/day
  - 9–13 years: 120 µg/day
- Adolescents and Adults
  - Males age 14 and older: 150 µg/day
  - Females age 14 and older: 150 µg/day
- Pregnant women: 220 µg/day
- Lactating women: 290 µg/day

The same group derived tolerable upper intake levels of between 200 and 1100 µg/day (children between 1–3 years and all adults respectively) from all sources. Recommendations for adults were based on changes in serum thyrotropin concentrations in response to varying levels of ingested iodine in adults, with children's levels obtained by extrapolation from adult levels with adjustment on the basis on body weight (IOM, 2001).

In 2002, the European Commission Scientific Committee on Food (EC, 2002) provided a Tolerable Upper Intake Limit (UL) for iodine of 600 µg/day for adults (including pregnant and lactating women). This value was based on dose-response studies of short duration (two weeks) in small numbers of subjects (n=10–32). An increased response of thyroid stimulating hormone (TSH) to thyrotropin-releasing hormone (TRH) at intakes of 1700–1800 µg/day was reported by Gardner et al. (1988) and Paul et al. (1988) but changes were not associated with any adverse clinical outcome. In a five-year study, Stockton & Thomas (1978) also reported an absence of clinical thyroid pathology following similar intakes. An uncertainty factor of 3 was applied to the highest intake assessed in these studies (1800 µg/day) to derive the UL for adults. For children, an adjustment based on body weight was applied to the adult value. The report concluded that dietary intakes are unlikely to exceed 500 µg/day, since the 97.5 percentile intake in European men is 434 µg/day.

The UK's Expert Group on Vitamins and Minerals (EVM, 2003) set a guidance level for iodine intake, concluding that neither human nor animal data were sufficient to set a UL value. Following assessment of the findings from several clinical studies of supplemental iodine, the author's concluded that 500 µg/day of supplemental iodine "would not be expected to have any significant adverse effects in adults." This led to recommendation of guidance levels of 500 µg/day for supplemental iodine and 930 µg/day for total intake from all sources (EVM, 2003).

The Council for Responsible Nutrition (CRN, 2013) recommended an upper limit for iodine intake of 500 µg/day based on the absence of adverse effects in healthy adults following daily oral intake of iodine supplements of 500 µg. In 2014, the European Food Safety Authority published Adequate Intake (AI) levels for iodine in different age groups (including pregnant and breast-feeding women), based in part on a large epidemiological study in European school-aged children (EFSA, 2014). The study showed that goitre prevalence is lowest for a urinary iodine concentration <100 µg/L, associated with iodine intakes of 150 µg/day in adults.

From this, the following AI levels were recommended:

- Infants (< 1 year of age): 70 µg/day
- Children
    - Aged between 1–3, 4–6 and 7–10 years: 90 µg/day
    - Aged between 11–14 years: 120 µg/day
    - Aged between 15–17 years: 130 µg/day
- Adults: 150 µg/day
- Pregnant or breast-feeding women: 200 µg/day

For individuals from countries with long-standing iodine deficiency disorder, the Expert Committee on Human Nutrition of the Agence Française de Sécurité Sanitaire des Aliments has suggested a provisional maximal tolerable daily intake of 500 µg/day to avoid the occurrence of hyperthyroidism (AFSSA, 2001).

3.3 Human toxicity data

3.3.1 Toxicokinetics

3.3.1.1 Absorption

Iodine is readily absorbed through inhalation and ingestion, with dermal absorption being extremely low (< 1% of applied dose). Human volunteers exposed to radioactive elemental iodine vapour by inhalation showed clearance with a half-life of 10 minutes, with the majority of iodine being removed by mucociliary clearance to the gastrointestinal (GI) tract (Black & Hounam, 1968; Morgan et al., 1968). Iodine ingested in the form of water-soluble salts shows 100% absorption from the GI tract (Fischer et al., 1965). Absorption of iodine from the GI tract has been shown to be similar in adults, adolescents, children and older infants, however, uptake in newborns is reported to be between 2–20% lower (Ogborn et al., 1960; Morrison et al., 1963).

Iodine ingested in forms other than iodide is reduced to iodide in the gut prior to absorption by the small intestine (Fisher et al., 1965; Fish et al., 1987; Hays, 2001) with an efficacy of 92% (IOM, 2001; Jahreis et al., 2001; Aquaron et al., 2002). Iodide absorption is reduced in the presence of humic acids in drinking-water (Gaitan, 1990), and of thiocyanates, isothiocyanates, nitrates, fluorides, calcium, magnesium and iron in food and water (Ubom, 1991).

3.3.1.2 Distribution

In human volunteers exposed to radiolabelled iodine via ingestion, between 20–30% of the dose was distributed to the thyroid within 10 hours, with between 30–60% being excreted in urine (Morgan et al., 1967a, b). Of total body iodine typically 70–90% is concentrated in the thyroid gland. Maternal exposure to iodine results in exposure of the fetus to thyroid hormones, with accumulation of iodine in the fetal thyroid gland commencing at around 70–80 days gestation (Evans et al., 1967; Book & Goldman, 1975).

3.3.1.3 Metabolism

As noted above, iodine undergoes rapid conversion to iodide which is then transported by the sodium iodide symporter to the thyroid and utilised for the production of T4 and T3 hormones (Morgan et al.,

1967a, b; Black & Hounam, 1968). Competition with sodium iodide symporter transport of iodine occurs from exposure to numerous anions including perchlorate, chlorate, nitrate and thiocyanate.

3.3.1.4 Elimination

Around 97% of iodine is excreted in the urine as iodide, with faecal elimination of between 1–2% (Larsen et al., 1998; Hays, 2001). Absorbed iodine can also be excreted in breast milk, saliva, sweat, tears and exhaled air (Cavalieri, 1997). The elimination half-life of absorbed iodine is considerably variable between individuals, and has been estimated as 31 days for healthy adult males (Van Dilla & Fulwyler, 1963; Hays, 2001).

3.3.2 Acute toxicity

Several biological mechanisms protect against acute iodine toxicity; these include reduced iodine uptake and preferential production of the more heavily iodinated thyroid hormones. Not all exposed subjects will react to excess iodine. Clinical features of acute iodine toxicity that have been produced following accidental or deliberate ingestion, or medical procedures such as wound irrigation, include GI disturbance (vomiting and diarrhoea), metabolic acidosis, seizure, stupor, delirium and collapse. Sensitivity reactions, such as iodide mumps, iododerma and iodide fever may also occur following treatment with iodine-containing drugs, or the use of radiographic contrast media (EVM, 2003).

Deaths (usually within 48 hours) in humans have occurred for iodine ingested in tinctures at doses ranging from 1200–9500 mg (17–120 mg/kg). Acute oral toxicity is primarily due to irritation of the GI tract, marked fluid loss and shock occurring in severe cases (ATSDR, 2004).

3.3.3 Repeat dose toxicity

A large number of human experimental, clinical, and epidemiological studies on the effects of repeat doses of excess iodine on human health has been reported.

3.3.3.1 Systemic effects

Both sub-acute (≤ 30 days) and sub-chronic (30–90 days) exposure studies for iodine intake have been reported:

Men who drank iodized water providing iodine doses of 0.17–0.27 mg/kg bw per day for 26 weeks reported no adverse effects (Morgan & Karpen, 1953).

The ingestion of about 3 mg iodine/day for 6 months during daily mouth-rinsing with an iodine-containing mouthwash had no effect on thyroid function (Ader et al., 1988).

A study on the effects of doses of 250, 500 or 1500 µg iodide/day for 14 days on thyroid function was carried out in 9 euthyroid men (normal thyroid function; mean age 34 years) and 23 euthyroid women (mean age 32 years) with 5 age-matched controls (Paul et al., 1988). The parameters examined were protein bound iodine (PBI) of the thyroid total serum iodine, T4, T3, TSH, integrated 1-hour serum TSH response to an intravenous dose of 500 µg TRH, and 24-hour urinary iodine excretion. The dietary intake of iodine was estimated from the urinary iodine excretion to be approximately 200 µg/person/day making the total ingested doses approximately 450, 700 and 1700 µg iodide/day. The estimated dose of 1700

µg/day was associated with an increase in total serum iodine without affecting the PBI, a significant decrease in serum T4 and T3 levels and an increase in TSH levels. Administered doses of 700 and 450 µg/day did not significantly affect the measured parameters. Only 1700 µg/day increased the TSH response to TRH (in women more than in men). The TSH response to TRH was also increased, though not significantly, in the individuals receiving 700 µg iodide/day. No biochemical effects were detected with 450 µg of iodide/day. However, this study used only small groups, extended over only 2 weeks and the dietary iodine intake was not determined analytically but was estimated.

In another study, 10 males (mean age 27 years) were treated for 2 weeks with either 500, 1500 or 4500 µg iodide/day (Gardner et al., 1988). The dietary intake was estimated from urine iodine excretion to have been approximately 300 µg/person/day making the total ingested doses approximately 800, 1800 or 4800 µg iodide/day. Serum levels of T4, T3, TSH, PBI, and total iodide, the TSH response to intravenous TRH and 24-hour urinary excretion of iodide were measured before treatment and again on day 15. Serum T4 levels decreased significantly after ingestion of 1800 µg and 4800 µg/day but did not change with 800 µg/day. Serum T3 levels did not change following administration of any of the doses. Serum TSH levels remained unchanged in those receiving 800 µg/day but increased in those receiving 1800 µg and 4800 µg/day. The TSH response to TRH was significantly enhanced with all iodide doses administered. No adverse effects were reported and no significant symptoms of thyroid dysfunction were noted. Again, only small groups of males were studied, exposure was rather short and the actual dietary intake of iodine was not determined analytically but estimated.

Chow et al. (1991) assessed the effect of supplementing normal dietary intakes of iodide to give a total iodide intake of approximately 750 µg iodide/day, or a placebo for a period of 28 days. Volunteers were groups of women aged 25–54 years. They were either thyroid antibody positive (subclinical Hashimoto's thyroiditis) (n=20), antibody negative (n=30), aged 60–75 years and from an area with adequate dietary iodine supply (n=29) or from an area that was previously iodine deficient (n=35). In all iodine-supplemented groups, mild biochemical hypothyroidism was present, evidenced by decreases in T4 levels and increases in TSH levels. None of the groups on supplemental iodide showed any incidence of hyperthyroidism. Following iodide supplementation TSH levels increased above the normal level of 5 milli-international units (mU)/L in 3 of the 60–75 year-old subjects, while the raised TSH levels increased even further in 2 antibody-positive subjects.

Chronic (> 6 months) exposure through ingestion of iodine at levels > 0.03 mg/kg bw is considered to be associated with adverse health effects (ATSDR, 2004). The introduction of iodized bread in The Netherlands raised the daily intake by 120–160 µg iodine resulting in an increase in the incidence of hyperthyroidism (Van Leeuwen, 1954). The consumption of winter milk[6] in the UK raised the iodine intake of women to 236 µg/day and of men to 306 µg/day and was also associated with a peak incidence of hyperthyroidism (Nelson & Phillips, 1985). In 32 young Swiss adults with simple goitre (and urinary iodine excretion of 32 µg/day) administered 200 µg iodine/day, only one case of transient hyperthyroidism appeared which showed a serum T4 of 14 µg/100 mL, a serum T3 of 293 ng/100 mL, suppressed TSH, tachycardia and weight loss (Baltisberger et al., 1995).

[6] Seasonal differences in the iodine content of milk are apparent and vary directly in relation to farming practices.

Peace Corps volunteers in Niger, West Africa using iodine-resin water purification devices for 32 months during the period 1995–1998, showed an increased incidence (42%) of thyroid abnormality but effects were reversed when iodinated water consumption ceased (Pearce et al., 2002). The purification devices delivered a mean concentration of 10 mg iodine/L to the drinking-water, which with a daily consumption amongst volunteers of 5–9 L resulted in consumption of 50 mg/iodine per day (300 times the recommended dietary allowance for the USA at that time). The adjusted odds ratio for thyroid dysfunction (abnormal thyrotropin) adjusted for age, sex, and other potential confounding factors, was 3.9 (95% CI 1.1–14.3) ($p < 0.04$) for the devices, with a positive relation with duration of exposure (adjusted odds ratios 4.6 and 10.9 at 6 and 12 months, respectively).

In a 5-year study using iodinated drinking water (1 mg/L) supplied to 750 male and female prison in-mates, no hyper- or hypothyroidism sensitization reactions and iodism (symptoms provided in the following paragraph) were noted (Stockton and Thomas, 1978). The average dose was 30 µg/kg bw per day. There was a statistically significant decrease in iodine uptake and an increase in PBI of the thyroid. One hundred and seventy-seven women in-mates delivered 181 infants showing no thyroid-related adverse effects. In four women who were already hyperthyroid, their symptoms became even more severe. The difficulties with this study were the imprecise estimates of intakes from the diet and fluid consumption of the participating individuals as well as the variable exposure time but the group size and duration of exposure were adequate.

Although most individuals who ingest large amounts of iodine remain euthyroid (i.e. have normal thyroid gland function) some will develop hypothyroidism with or without goitre or hyperthyroidism which can manifest as thyrotoxicosis (inflammation of the gland), and changes in the incidence and types of thyroid malignancies. Very large amounts of iodide may cause iodism, the symptoms of which resemble rhinitis as well as salivary gland swelling, GI irritation, acneform dermatitis, metallic taste, gingivitis, increased salivation, conjunctivitis and oedema of eye lids (ATSDR, 2004; Leung & Braverman, 2014). In children aged between 5–15 years of age, 10 µg/kg bw per day is considered to be a no-observed-adverse-effect level (NOAEL) based on thyroid effects (subclinical hypothyroidism with thyroid gland enlargement) (Boyages et al., 1989; Chow et al., 1991).

It has been proposed that excess iodide intake may be a contributing factor in the development of autoimmune thyroiditis in people who are vulnerable (Brown and Bagchi 1992; Foley 1992; Rose et al., 1997; Safran et al., 1987); however, evidence to support this in humans is incomplete.

3.3.3.2 Neurotoxicity

Iodine-induced hypothyroidism in sensitive populations (including fetuses, newborn infants, and individuals who have thyroiditis) has the potential to produce neurological effects (Boyages, 2000b). This is particularly applicable to fetuses and newborn infants as thyroid hormones are essential to the development of the neuromuscular system and brain. An iodine-induced hypothyroid state can result in delayed or deficient brain and neuromuscular development of the newborn. Iodine-induced hypothyroidism in an older child or adult would be expected to have little or no deleterious effects on the neuromuscular system.

Iodine-induced hyperthyroidism presenting as thyrotoxicosis in sensitive individuals (including those who are initially iodine deficient; those who have thyroid disease; including nodular goitre; Graves'

disease; those who have been previously treated with antithyroid drugs; and those who have developed thyrotoxicosis from amiodarone or interferon-alpha treatments [Roti and Uberti, 2001]) may experience neuromuscular disorders, including myopathy (muscular weakness), periodic paralysis, myasthenia gravis (weakness in skeletal muscles), peripheral neuropathy, tremor, and chorea (involuntary movement disorder) (Boyages, 2000a).

3.3.3.3 Reproductive and developmental toxicity

Chronic exposure to excess iodine has been shown to disrupt reproductive function secondary to thyroid gland dysfunction. Induced changes in the menstrual cycle, including menorrhagia (excessive uterine bleeding) and anovulation (no ovulation); spontaneous abortions, stillbirths, and premature births have also been associated with hypothyroidism (Longcope, 2000a).

Reproductive impairments associated with hyperthyroidism include amenorrhea (no uterine bleeding), alterations in gonadotropin release and sex hormone-binding globulin, and changes in the levels and metabolism of steroid hormones in both females and males (Longcope, 2000b).

Exposure to iodine may give rise to developmental defects secondary to thyroid gland dysfunction (Boyages, 2000a, b). As noted in Section 3.3.3.2, hypothyroidism may be associated with impairment in neurological development of the fetus or growth retardation (Boyages, 2000a, b; Snyder, 2000a).

Hyperthyroidism has been associated with accelerated growth linked to accelerated pituitary growth hormone turnover or a direct effect of thyroid hormone on bone maturation and growth (Snyder, 2000b).

3.3.3.4 Immunotoxicity

No data could be located regarding immunotoxic effects in humans following repeated exposure to iodine.

3.3.3.5 Genotoxicity

No data could be located regarding genotoxic effects in humans following repeated exposure to iodine.

3.3.3.6 Carcinogenicity

The American Conference of Governmental Industrial Hygienists has classified iodine as A4 - not classifiable as a human carcinogen (ATSDR, 2004). The International Agency for Research on Cancer has not classified non-radioactive iodine (ATSDR, 2004).

The results from several epidemiology studies suggest that increased iodide intake may be a risk factor for thyroid cancer in certain populations, in particular, those that are iodine-deficient (Bacher-Stier et al., 1997; Harach & Williams, 1995; Franceschi, 1998; Franceschi & Dal Maso, 1999). Studies of populations in which iodine intakes are sufficient have not found significant associations between iodine intake and thyroid cancer (Horn-Ross et al., 2001; Kolonel et al., 1990).

A lowest-observed-no-effect level of 3.5 µg/kg bw per day has been identified based on thyroid cancer prevalence in Salta, an endemic goitre area in Argentina (Harach & Williams, 1995; Bacher-Stier et al., 1997).

3.4 Animal toxicity studies

Laboratory animals, poultry, pigs and cattle have a high tolerance to large iodine intakes. Animal data are of limited value to humans because of species differences in basal metabolic rate and in iodine metabolism (IOM, 2001).

3.4.1 Toxicokinetics

Rapid absorption of iodine vapour following inhalation exposure observed in humans is supported by studies in rats, mice, dogs and sheep (Willard & Bair, 1961; Bair et al., 1963). Compounds of iodine were also seen to be rapidly absorbed in monkeys when inhaled as vapours or aerosols, with a half-life of 10 min (Thieblemount et al., 1965; Perrault et al., 1967).

Absorption, distribution, metabolism and excretion data from animal studies for iodine exposure via the GI tract, were not apparent from the reviews identified during the literature search.

3.4.2 Acute toxicity

Due to the rapid conversion of iodine to iodide *in vivo*, the acute toxicity of iodine has been poorly studied. Conversely, the acute toxicity of iodides and iodates have been well studied and can be used to estimate the acute toxicity of iodine.

The acute oral median lethal dose (LD_{50})[7] for potassium iodide in rats was 3320 mg iodide /kg bw and in mice, 1425 mg iodide /kg bw (Stokinger, 1981).

3.4.3 Repeat dose toxicity

3.4.3.1 Systemic toxicity

A number of experimental studies on the effects of chronic exposure to excess iodine or iodide, particularly on thyroid function have been reported, with representative studies from different species summarized below:

- Two strains of chickens (CS and OS), genetically vulnerable to autoimmune thyroiditis, were given either 20 or 200 mg potassium iodide/L in their drinking water for the first 10 weeks of their lives. At both levels the incidence of the disease was increased as shown histopathologically, and also by measurements of, T4, T3 and thyroglobulin antibody titres (Bagchi et al., 1985).

- In female Wistar rats administered diets containing iodine concentrations between 0.015 and 0.23 mg/kg bw per day for 10 weeks, significantly enlarged thyroids were found at all doses, with a dose-dependent increase at all doses (Fischer et al., 1989).

- Newton and Clawson (1974) reported a dose-dependent increase in thyroid weights of pigs administered iodine at concentrations between 3 and 218 mg/kg bw per day.

- Female calves fed iodine at concentrations between 0.011 and 3.96 mg/kg feed twice daily for 5 weeks from day 4 of age showed a significant decrease in body weight gain at the highest dose;

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

food intake was also decreased. Haematological changes (decreased packed cell volume) and clinical signs of nasal discharge were noted in the highest dose group and lacrimation was noted in the two highest dose groups (Jenkins & Hidiroglou, 1990).

- A NOAEL of 10 mg/L has been proposed for the most sensitive endpoint of thyroid hormone imbalance in rats. This was based upon a decrease in T3 levels and an increase in T4/T3 ratio after 100 days of iodine treatment (Sherer et al., 1991). When considering the use of rat models, it should be noted that rats are much more sensitive to thyroid hormone imbalance than humans (requiring around 10 times more T4/kg than humans).

3.4.3.2 Neurotoxicity

No data could be located regarding neurotoxic effects in animals following repeated exposure to iodine.

3.4.3.3 Reproductive and developmental toxicity

Arrington and colleagues (Arrington et al., 1965) investigated the reproductive and developmental toxicity of iodine in a series of studies:

- Iodine administered to pregnant Long-Evans rats at a concentration of 2500 mg/kg in the diet for 12 days in the latter part of gestation was associated with an increased incidence of death in the neonates, < 10% of the neonates survived for more than 3 days. Length of labour (parturition) was also increased.

- Syrian hamster pups from mothers fed iodine at 2500 mg/kg in the diet for 12 days in the latter part of gestation showed decreased feed intake (10%) and weaning weights at 21 days were significantly less than controls.

- Pups from pregnant rabbits (Dutch and New Zealand) fed iodine at concentrations between 250 and 1000 mg/kg feed for 2–5 days before parturition showed decreased survival rates.

- Pregnant pigs receiving diets containing 1500 or 2500 mg iodine/kg feed for the 30 days prior to parturition delivered litters that were unaffected by dietary levels of iodine that were toxic to rabbits and rats.

In female rats administered 0, 500, 1000, 1500 and 2000 mg potassium iodide/kg diet throughout gestation, lactation and weaning, pup survival was reduced from 93% in controls to 16% in rats given the highest dose; milk secretion was also diminished. There were no adverse effects on ovulation rate, implantation rate and fetal development (Ammermann et al., 1964). Brain enzymes of pups from pregnant rats administered 11 mg potassium iodide/day in their drinking water (37 mg/kg bw per day) showed transient increases in glutamate dehydrogenase and transient decreases in succinate dehydrogenase. Phosphofructokinase and malate enzymes were increased; however, hexokinases were unaffected. Serum T4 levels were also unchanged compared to controls (Morales de Villalobos et al., 1986).

In further studies a NOAEL of 10 mg/kg bw per day has been derived for reproductive and developmental toxicity in rats administered iodine by oral gavage (based on no observed toxicity at any dose level). A

NOAEL for parental toxicity of 10 mg/kg bw per day was also established (based on no supported changes at any dose level) (EC, 2002).

Mares given 48–432 mg iodine/day during pregnancy and lactation produced foals with disturbed metabolism. The long bones of the legs of the foals showed osteopetrosis (hard, dense bones). Serum phosphate and alkaline phosphatase levels were increased (Silva et al., 1987).

3.4.3.4 Immunotoxicity

No data could be located regarding immunotoxic effects in animals following repeated exposure to iodine.

3.4.3.5 Genotoxicity (*in vivo*)

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

3.4.3.6 Carcinogenicity

Metaplasia of the thyroid was reported in rats given potassium iodide in their drinking water for two years (dose not quoted by authors). This was thought to occur through a non-genotoxic proliferation dependent mechanism (EVM, 2003)

3.4.4 *In vitro* toxicity studies

The mutagenicity data for iodine are generally negative; iodine has been shown to be non-mutagenic using the mouse (TK +/-) lymphoma assay and no induction of unscheduled deoxyribonucleic acid synthesis was seen in Syrian Hamster Embryo cells (ATSDR, 2004).

3.5 Vulnerable populations

Individuals identified as most vulnerable to iodine-induced toxicity in the form of hypothyroidism are shown in Table 7.

Table 7: Risk groups for iodine-induced hypothyroidism (WHO/UNICEF/ICCIDD, 2007)

Risk group / subgroup	
No underlying thyroid disease	
Fetus and neonate, mostly preterm	Secondary to transplacental passage of iodine or exposure of neonate to topical or parenteral iodine-rich substances
Infant	Occasionally reported in infants drinking iodine-rich water (China)
Adult	In Japanese subjects with high iodine intake where Hashimoto thyroiditis has been excluded
Elderly	Reported in elderly subjects with and without possible defective organification (incorporation of iodine into thyroglobulin to produce thyroid hormone) and autoimmune thyroiditis
Chronic non-thyroid illness	Cystic fibrosis Chronic lung disease Chronic dialysis treatment Thalassaemia major Anorexia nervosa
Underlying thyroid disease	
	Hashimoto thyroiditis Euthyroid patients previously treated for Graves' disease with ^{131}I, thyroidectomy, or antithyroid drugs Subclinical hypothyroidism (particularly the elderly) After transient postpartum thyroiditis After subacute painful thyroiditis After hemithyroidectomy for benign nodules Euthyroid patients with a previous episode of amiodarone-induced destructive thyrotoxicosis Euthyroid patients with a previous episode of interferon-induced thyroid disorders Patients receiving lithium therapy

3.6 Toxicity of iodinated disinfection by-products

3.6.1 Formation and occurrence of iodinated disinfection by-products

When present in water, either at background levels or when used as a disinfectant, iodine has the ability to form iodinated DBPs. These have been identified in some chloraminated drinking-water in countries including the USA (Weinberg et al., 2002) and include:

- iodoacetic acid;
- bromoiodacetic acid;
- (*Z*)-3-bromo-3-iodopropenoic acid;
- (*E*)-3-bromo-3-iodopropenoic acid; and
- (*E*)-2-iodo-3-methylbutenedioic acid.

In addition, iodinated trihalomethanes (THMs) identified in chlorinated and chloraminated drinking water (Richardson et al., 2007) have been identified as:

- dichloroiodomethane;
- bromochloroiodomethane;
- dibromoiodomethane;
- chlorodiiodomethane;
- bromodiiodomethane; and
- iodoform.

When chloramine or chlorine is used as a disinfectant, these compounds are usually present in very low concentrations (fractional parts per billion) due to the low background presence of iodide in natural waters.

Smith et al. (2010) compared the formation of DBPs from a number of iodine-based disinfectants (used at the manufacturer's recommended levels) to chlorination and chloramination under overdosing conditions. The authors reported the following findings:

- the predominant THM formed during iodination was iodoform; chloroform predominated during chlorination or chloramination;
- THM formation increased with pH during chlorination but was only slightly elevated at neutral pH during iodination;
- use of iodine tincture was associated with higher levels of iodoform than with iodine tablets;
- iodoform formation with iodine tincture was 20–60% (on a molar basis) of chloroform formation during chlorination;
- total organic iodide formation was twice that of total organic chlorine;
- iodoacetic acid, diiodoacetic acid, and other iodoacids were also formed with iodine tincture treatment, but at levels < 11% of iodoform formation;
- a POU device combining an iodinated anion exchange resin with activated carbon post-treatment, indicated minimal formation of iodinated DBPs, no iodine residual and N-nitrosamine formation below 4 ng/L after the first few flushes of water.

3.6.2 Toxicological evaluations of iodinated disinfection by-products

Concern has arisen regarding iodinated DBPs as they are considered, on current evidence, to be of greater toxicological concern than their brominated and chlorinated analogues (Richardson et al., 2007). However, it should be noted that this view is predominantly based on findings from a very limited dataset of *in vitro* cytotoxicity and genotoxicity assays, which are described below; the applicability of findings from *in vitro* cytotoxicity and genotoxicity assays to humans has not been established at present. A

dataset of basic toxicological information on DBPs, as presented for iodine, is not available at the current time. An exception to this is that iodoform has been tested in National Toxicology Program bioassays and was not carcinogenic under test conditions (NCI, 1978).

Following the identification of iodoacids and iodinated THMs in chloraminated and chlorinated drinking waters in the USA (section 3.6.1), Richardson et al. (2008) assessed the cytotoxicity and genotoxicity of five iodoacids (iodoacetic acid, bromoiodoacetic acid, (*Z*)-3-bromo-3-iodo-propenoic acid, (*E*)-3-bromo-3-iodo-propenoic acid, and (*E*)-2-iodo-3-methylbutenedioic acid) and two iodinated THMs (dichloroiodomethane and bromochloroiodomethane) using *in vitro* assays with Chinese Hamster Ovary cells.

The chronic cytotoxicity of the compounds measured in the study were ranked and compared to other iodinated compounds by the authors. This resulted in a ranking order as follows:

iodoacetic acid > (*E*)-3-bromo-2-iodopropenoic acid > iodoform > (*E*)-3-bromo-3-iodo-propenoic acid > (*Z*)-3-bromo-3-iodo-propenoic acid > diiodoacetic acid > bromoiodoacetic acid > (*E*)-2-iodo-3-methylbutenedioic acid > bromodiiodomethane > dibromoiodomethane > bromochloroiodomethane ~ chlorodiiodomethane > dichloroiodomethane.

With the exception of iodoform, the iodinated THMs were much less cytotoxic than the iodoacids.

Of the iodo-compounds analysed, 7 were genotoxic; their rank order was:

iodoacetic acid >> diiodoacetic acid > chlorodiiodomethane > bromoiodoacetic acid > (*E)*-2-iodo-3-methylbutenedioic acid > (*E*)-3-bromo-3-iodo-propenoic acid > (*E*)-3-bromo-2-iodopropenoic acid.

The authors reported that, in general, compounds containing an iodo-group had enhanced mammalian cell cytotoxicity and genotoxicity as compared to their brominated and chlorinated analogues.

In the study described previously (section 3.6.1), Smith et al. (2010) compared the cytotoxicity of THMs in four natural waters treated with different disinfectants (free chlorine, 20mM monochloramine, 20mM iodine tincture, 72 mM elemental iodine, 172mM potassium iodide as iodine tablets, and a personal POU treatment unit). THMs formed following treatment with iodine tincture were associated with between 19–92 times higher cytotoxicity than for chlorination, with toxicity being driven by total organic iodine content of the water samples. The cytotoxicity of THMs formed with the iodine tablet treatment was around 40% lower than for treatment with iodine tincture. The authors estimated that from an exposure perspective, chlorination may be preferable to iodination for long-term disinfection, where comparable degrees of disinfection are achieved. Use of the personal POU treatment unit was also associated with THM formation, with associated cytotoxicity approximately 10% of that with iodine tincture, but 6-fold higher than for chlorination, with no iodine residuals apparent.

The authors highlight the importance of considering all iodinated DBPs when evaluating potential risks, with measurement of iodoacids, and iodoforms as the dominant DBPs, following iodination. Diiodoacetic acid and iodoacetic acid were formed at levels < 10% of iodoform following treatment with iodine

tincture. However, iodoacetic acid has greater cytotoxicity (> 2 times) in mammalian cells than iodoform, and distinct from iodoform is genotoxic.

3.7 Summary

- Limited data (both from human and animal studies) suggest that the bioavailability of iodine from foods and water is high, with inorganic iodine (usually in the form of iodide) being readily absorbed (92%) from the small intestine. Iodine is rapidly distributed, including across the placenta, and is stored in the thyroid gland for the synthesis of thyroid hormones (T4 and T3). Excess iodine is mainly excreted in the urine, with very small amounts excreted in sweat, faeces and exhaled air and secreted into human breast milk.
- In humans, several mechanisms help regulate iodine levels, to protect against toxicity; these include reduced iodine uptake and preferential production of more heavily iodinated thyroid hormones. Symptoms of acute iodine toxicity include vomiting and diarrhoea, metabolic acidosis, seizure, stupor, delirium, and collapse. Sensitizing reactions include iodine mumps, iododerma, and iodine fever.
- Chronic and sub-chronic iodine toxicity in humans includes disruption of thyroid function, leading to hypothyroidism which can present with or without goitre, hyperthyroidism, and changes in the incidence and types of thyroid malignancies. Responses of this type are associated with a general high iodine intake or where intervention has taken place to compensate for iodine deficiency. Measures of serum thyroid hormone levels (T4, T3 and TSH) are used as indicators of iodine disturbances in humans.
- Iodine-induced hypothyroidism in humans has the potential to produce neurological effects (delayed or deficient brain and neuromuscular development) in sensitive populations, particularly in fetuses and new-born infants. Hyperthyroidism in humans has been associated with accelerated growth.
- Dysfunction of the thyroid in humans has also been associated with reproductive disruptions including changes in the menstrual cycle, menorrhagia, anovulation, spontaneous abortions, stillbirths, and premature births.
- Iodine is not classifiable as a human carcinogen. Chronic iodine exposure has been associated with metaplasia of the thyroid, considered to occur via a non-genotoxic mechanism. Mutagenicity data for iodine are generally negative.
- Acute, sub-chronic, and chronic toxicity studies in animals support the findings from human studies.
- The adverse effects associated with high levels of iodine intake are linked to the disruption of thyroid hormone metabolism, the thyroid-pituitary axis, and the compensatory mechanisms that exist to protect such metabolism against low or high levels of iodine intake. Previous exposures to iodine and the complex effects of pre-existing thyroid conditions also influence the effects of subsequent exposure.
- A threshold level for inducing thyrotoxicosis has not been established and available data are inadequate to establish a dose-response relationship.
- Vulnerable members of the general population to iodine toxicity include pregnant and lactating women, and neonates.

Due to limited available evidence, there are uncertainties regarding both the potential for formation of iodinated DBPs and likely adverse effects at the concentrations predicted to be formed from use of iodine as a drinking-water disinfectant. The applicability of findings from *in vitro* cytotoxicity and genotoxicity assays to humans has not been established at present.

4. Environmental considerations

Environmental considerations are largely beyond the scope of this report; however, as noted in Table 8, the impact of release of iodine into the environment to 'non-target' organisms should be considered.

Table 8: Environmental toxicity of iodine to 'non-target' species (USEPA, 2006)

Group of organisms	Common name (scientific name)	Test compound	L(E)C_{50}[8]	NOEC[9]	Acute toxicity rating
Fish (freshwater)	Bluegill sunfish (*Lepomis macrochirus*)	Iodine (99.8%)	0.61 mg/L	0.16 mg/L	Highly toxic
Invertebrates	Water flea (*Daphnia magna*)	Iodine (99.8%)	0.33 mg/L	0.09 mg/L	Very highly toxic

[8] LC_{50} – median lethal concentration; the dose required to kill half the members of a test population after a specified test duration. EC_{50} – half maximal effective concentration; the effective concentration of a chemical that causes half of the maximum response in a test population after a specified test duration.
[9] No-observed-effect concentration.

5. Discussion and conclusions

The use of iodine for drinking-water disinfection, as with all water disinfectants, should be considered in terms of risk versus benefit. Known issues of water quality in many parts of the world necessitate additional measures to ensure potability. The risk of enteric infection should therefore be weighed against the risk for, and severity of, acquiring thyroid disease from exposure to iodine over a short- and long-term period of exposure, as well as alternative disinfection options.

Ideally a water treatment product (or combination of products) should be effective against all three classes of pathogens, i.e. bacteria, viruses and protozoa. The evidence presented in this review indicates that iodine is most effective against bacteria, has some effectiveness against viruses (particularly iodinated resins) and comparatively less effectiveness against certain species of protozoa. Higher dosages and longer contact times will be required when used as a disinfectant against protozoan cysts such as *Giardia*. Iodine is not effective against *Cryptosporidium* oocysts at practical Ct values. At the time of this publication, iodine has not been tested against WHO HWT performance targets and no evaluations have been carried out on the health impacts in low-income settings with microbiologically contaminated drinking-water.

From a disinfection perspective, iodine offers some advantages over chlorine:

- Water disinfection process requires less supervision, is simple and cost effective (although more expensive than chlorine); and
- Iodine may provide superior disinfection to chlorine for water of poor quality. The reduced overall reactivity of iodine prompts slower reactions with organic material and thus a lower disinfectant demand. The low reactivity with organic nitrogenous contaminants results in improved maintenance of residual iodine concentrations (Backer and Hollowell, 2000).

At the household level, there are a number of additional considerations beyond efficacy for determining whether any product, including iodine, will protect health. Achieving health gains from HWT 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 iodine and other drinking-water disinfectants which require a reliable supply chain can be problematic in resource-limited settings where such systems are not in place.

The lack of knowledge on long-term toxic effects of iodine consumption impedes the use of iodine for disinfection of municipal or community supplies. Considerable controversy exists about the maximal "safe" dietary dose of iodine (in the range of 500 to 1000 µg/day in healthy adults) and the maximum "safe" period of consumption for iodine treated water. Although a number of studies have been carried out, the data are not adequate to establish a linear and temporal dose response between iodine intake and altered thyroid function (Backer & Hollowell, 2000).

Current POU water disinfection devices that are both effective in terms of disinfection and can achieve low residual levels (0.01 ppm) of iodine (such as triiodinated resins including a granular activated carbon filter), are considered to be "safe" from a toxicological perspective to use for long periods of time in euthyroid individuals (see Table 6). Assuming drinking water consumption in an adult of 2 L per day,

residual iodine at this level would result in intakes of approximately 0.02 mg/day. This is well below the low-end range of the recommended upper limit of 0.5 mg/day (CRN, 2013) even allowing for greater consumption of drinking-water and/or intake of iodine from other sources. It is also low in comparison to the AI of 0.15 mg/day for an adult recommended by EFSA (2014). However, for those disinfection devices/methods that produce higher residual iodine levels (> 1 mg/L; such as iodine tablets, which leave residual concentrations from 8–16 mg/L), intake of 2 L of purified water per day would result in intakes of up to 32 mg/day, exceeding the recommended upper limit. Advice is given to limit the use of such devices to a few months (Backer & Hollowell, 2000; WHO, 2011b). Current evidence (outlined in section 3.3) suggests that intake at levels of 18 mg/day and above are associated with changes to serum T4 and TSH levels and TSH response to TRH (Gardner et al., 1988). Although no significant symptoms of thyroid dysfunction were associated with these biochemical changes, this study was conducted over a two-week period; hence, it is unclear if thyroid dysfunction would become apparent with prolonged exposure. Supporting evidence from a study of Peace Corps volunteers (Pearce et al., 2002), which showed a positive relationship between thyroid dysfunction and intake of iodine at 50 mg/day over 32 months, suggests that this would occur.

Iodine use for water disinfection is therefore not recommended for high-risk members of the population including:

- Infants and young children;
- Pregnant women (the fetus is vulnerable to goitre);
- Individuals with known hypersensitivity to iodine;
- Individuals with a history or strong family history of thyroid disease; and
- Individuals from areas of severe iodine deficiency (may lead to hyperthyroidism).

In summary, the current evidence indicates that:

- As a drinking-water disinfectant, iodine can be most effective against bacteria. Iodine is less effective against viruses and least effective against protozoa. Specifically, based on the information presented in Table 5, iodine solutions are less effective against these two pathogen classes compared to iodine resins.
- Effectiveness of iodine is impacted by the temperature, concentration, contact time, pH and organic content of water; however, this is to a lesser extent than for chlorine. In addition, the effectiveness of individual disinfectant products will vary according to manufacturing processes and related quality management.
- Higher dosages and longer contact times for iodine will be required when used as a disinfectant against protozoan cysts; iodine shows some effectiveness against *Giardia* cysts, but does not appear to be effective against *Cryptosporidium* oocysts.

Iodine would not be recommended for use as a primary disinfectant due to the lack of knowledge on long-term toxic effects and the availability of widely used, well-characterized disinfectants.

Use of POU applications of iodine as a water disinfectant may be appropriate under certain circumstances. In POU applications, the potential toxicity associated with iodine consumption from drinking-water will be variable depending on the method employed for disinfection and individual

susceptibility. When considering to use iodine as a drinking-water disinfectant compared to other water disinfectants, recommendations should be considered in the context of overall benefits versus harm from potential iodine toxicity and ingestion of contaminated water, as outlined below:

- For euthyroid individuals using resin-based disinfection devices that result in low residual concentrations of iodine (e.g. those using resins with carbon filters), few adverse effects are anticipated. Although there is insufficient evidence to support long-term use of devices containing resin-based disinfectants and carbon filters, it is anticipated that these devices could be used over extended periods of time. However, activated carbon filters should be replaced at frequencies recommended by the manufacturer. In addition, care should be taken to ensure the treated water is safely stored to prevent recontamination as the finished water will have no residual disinfectant.
- For euthyroid individuals using other iodine disinfection techniques that result in higher residual concentrations of iodine (e.g. solutions or tablets and resins without carbon filters), use should be restricted to as short a period of time as possible. If longer term use of a disinfectant is needed, another disinfectant should be utilized.
- For high-risk members of the population (noted on the previous page), water disinfection with iodine is not recommended and an alternative disinfectant should be utilized. However, disinfection should not be compromised due to the public health significance of microbiologically unsafe water, and therefore if iodine is the only disinfectant available, use should be limited to as short a time as possible, and an alternative disinfectant sought.

On the basis of limited effectiveness against viruses and particularly protozoa, as well as uncertainties around the safety and toxicity, the use of iodine products may be appropriate for short-term use for euthyroid individuals in targeted situations where the causative agent of disease is known. However, where the causative disease agent is unknown, use by euthyroid individuals should ideally be combined with another HWT method (e.g. with a filter) to provide comprehensive protection. The use of POU devices should be appropriately approved or certified to ensure efficacy and safety.

6. References

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Appendix A: Methodology

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

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

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

Box 1- Search strategy for toxicity assessment for iodine

((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(7553-56-2) AND DOCTYPE(ar OR re) AND PUBYEAR > 2004))

Box 2- Search strategy for efficacy assessment for iodine

(TITLE-ABS-KEY(iodine) 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 62 papers relating to iodine toxicity and 155 papers relating to iodine 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 as needed, particularly for identification of "grey" literature, earlier studies and during the period of document preparation (up to 16 December 2016).

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