

# Iodine as a drinking water disinfectant

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## List of abbreviations

CT (mg-min/L)	product of disinfectant concentration (mg/L) and contact time (min.)
DBP	disinfection by-product
DIAA	diiodoacetic acid
EC <sub>50</sub>	half maximal effective dose
HOCL	hypochlorous acid
HIO	hypoiodous acid
I <sub>2</sub>	iodine
IAA	iodoacetic acid
IO <sub>3</sub> <sup>-</sup>	iodate
IWPD	Individual water purification device
LC <sub>50</sub>	median lethal dose – dose required to kill half the members of a test population after a specified test duration
NTU	nephelometric turbidity unit
OCl <sup>-</sup>	hypochlorite
OI <sup>-</sup>	hypoiodite
PBI	protein bound iodine
PMTDI	provisional maximum tolerable daily intake
POU	point of use
PPM	parts per million
SHBG	sex hormone-binding globulin
THM	trihalomethane
TOC	total organic content
TOI	total organic iodine
TRH	thyrotropin releasing hormone
TSH	thyroid stimulating hormone

# 1 Introduction

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Disinfection of water has been perhaps the single greatest beneficial technology with respect to reducing risks to public health from contaminated drinking water.

Numerous disinfectant techniques have been developed over the centuries that are used in a wide range of applications ranging from large and small public drinking water plants to point-of-use and point-of-entry treatment devices. Chlorine has been used for more than 100 years, and several other disinfectants have been studied extensively, but there are still questions that exist in many cases with respect to optimisation of biocidal effectiveness under a range of conditions (i.e., efficacy), the chemistry of formation and the toxicological significance of disinfectant 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, and has been generally used as an antiseptic for skin wounds, as a disinfecting agent in hospitals and laboratories, and in pharmaceuticals. In terms of disinfection, iodine is commonly used in the form of tablets and solutions for water treatment during emergencies and by travellers (Ongerth et al., 1989; Backer and 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 (= 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 safety of drinking water for troops deployed in the field (Chang and Morris, 1953). Also, in more recent times, iodine (and bromine) has become attractive for particular applications. Elemental iodine ( $I_2$ ) is used, for example, as a drinking water disinfectant aboard space vessels at a residual concentration of around 2 ppm (Atwater et al., 1996). The more general use of iodine is however impeded by the potential for excess iodine intake, cost and the possibility of disinfection by-product (DBP) toxicity.

The emphasis of this literature review is to evaluate available evidence on the efficacy and toxicity of iodine ( $I_2$ ) 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 searches were carried up to September 2015. Further details of the search strategy are included in Appendix 1.

# 2 Disinfectant mode of action and efficacy

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## 2.1 Chemistry basics

Like chlorine and iodine belongs to the halogen group of chemicals. All of the halogens share the common property of being oxidants as they have seven electrons in their outer shell; as oxidising agents, halogens accept an electron to become the analogous halide ion. The suitability of halogens as disinfectants is based on both their oxidising power and substitution reactions. Different halogens however vary in their oxidation potential and disinfection power. The main determinant for their reactivity is the strength to snatch electrons from other molecules. The halogen with the strongest oxidative power is fluorine, followed by chlorine, bromine, and iodine. Their reactivity is directly correlated with their electro-negativities, which are as follows (based on the Pauling nomenclature of electronegativity values):

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

The reactivity of the given halogens therefore decreases from left to right. Nevertheless the usefulness of a particular halogen as a disinfectant is not only determined by its reactivity, but also by its selectivity, chemical stability and other factors including the potential to form by-products. Fluorine, as 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 application. Among the three halogens used for disinfection purposes, iodine has the highest atomic weight and is the only solid at room temperature.

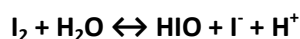
### 2.1.1 Water solubility, taste, odour and colour

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°C, 0.78 mg/L at 50°C and 4.45 mg/L at 100°C (Handbook of Chemistry and Physics, 1984). A saturated aqueous solution of I<sub>2</sub> can be produced by passing water through a column containing crystalline iodine. The iodine concentration achieved will be approximately 200 mg/L at 10°C and 400 mg/L at 30°C (Chang, 1968). This concentrated solution can be diluted to achieve the desired level of iodine.

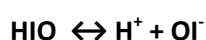
Free halogen residuals usually produce tastes and odours in potable water. Bryan et al. (1973) compared taste threshold determinations of chlorine, iodine and bromine residuals in water. The threshold taste values for chlorine residuals varied with pH; 0.075 mg/L at pH of 5.0; 0.156 mg/L at pH 7.0; and 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 volatilises, especially in the presence of sunlight or higher temperatures, iodine has a low vapour pressure resulting in little loss by volatilisation (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 (Lengyel et al., 1993). 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):



Like hypochlorous acid, HIO can deprotonate to form hypoiodite ( $OI^-$ ) according to the following general reaction:



The different chemical species vary in their disinfection power. The active disinfectants are elemental iodine and hypoiodous acid (Backer and Hollowell, 2000). Other species including iodide ( $I^-$ ), iodate ( $IO_3^-$ ) and hypoiodite ( $OI^-$ ) have mild or little antimicrobial activity (Chang, 1958). Comparing the two disinfection-active chemical species, the oxidizing power of HIO is nearly twice that of  $I_2$  (Handbook of Chemistry and Physics, 1984). A comparison with the equivalent chlorine species is shown in Table 1.

Table 1: Comparison of oxidising potentials of iodine and chlorine species

Chemical species	oxidising potential
$I_2$	0.535 V
HIO	0.987 V
$Cl_2$	1.358 V
HOCl	1.482 V

(Source: Handbook of Chemistry and Physics, 1984)

The disinfection efficacy of the different chemical species depends not only on oxidising potential, but also on penetration power.  $I_2$  has higher penetrating power than HIO (White 1992; cited in Ellis et al. 1993).

A comprehensive study of disinfection efficacy was performed by Chang and 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 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 and Hollowell, 2000). Moreover, iodine and hypoiodous acid contribute to different extents to the disinfection efficacy against different microbes. Chemical speciation is highly pH dependent. 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 mg-min/L - 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 I<sub>2</sub> and HIO are pH-dependent, but the effect is not as pronounced as with chlorine. Table 2, adapted from Chang (1958), Black et al. (1970) and Ellis and van Vree (1989), shows the proportions of elemental iodine, hypiodous acid and iodide for a pH range between 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)

	I <sub>2</sub>	HIO	OI <sup>-</sup>	Cl <sub>2</sub>	HOCl	OCl <sup>-</sup>
<b>pH</b>	%	%	%	%	%	%
<b>5</b>	99	1	0	0.5	99.5	0
<b>6</b>	90	10	0	0	99.5	0.5
<b>7</b>	52	48	0	0	96.5	3.5
<b>8</b>	12	88	0.005	0	21.5	78.5
<b>9</b>				0	1.0	99.0

Higher pH results in a progressive decline in elemental iodine with a shift in the equilibrium toward HIO. As the active disinfectants are elemental iodine and hypiodous 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 I<sub>2</sub> and HIO (Table 2). At a pH of ≥8.0, HIO was reported to be unstable and to slowly decompose into iodate (IO<sub>3</sub><sup>-</sup>) and iodide (I<sup>-</sup>) (Ellis and van Vree, 1989). However, in the absence of a stronger oxidant such as chlorine, IO<sub>3</sub><sup>-</sup> 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 (OCl<sup>-</sup>) formation increases at pH values > 7. Strong evidence has been provided that OCl<sup>-</sup> has less disinfection power that can be influenced by concentrations of anions, such as sodium and potassium (Chang and Morris, 1953; Keirn and Putnam, 1968; Haas et al, 1986; Jensen et al., 1980).

The progressive decline of free iodine residual and increasing proportion of HIO 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 efficiencies for different groups of microbes (Ellis et al., 1993). In generalised terms, elemental iodine is primarily efficient against spores and protozoan cysts, whereas HIO is known to be an effective bactericide and virucide (Ellis et al., 1993). For example Chang (1966) reported I<sub>2</sub> to be 2-3 times more effective against *Entamoeba histolytica* cysts, whereas HIO was found to be approx. 40 times more effective than I<sub>2</sub> against viruses. HIO also had greater germicidal activity against vegetative bacteria than I<sub>2</sub> (for example, HIO was found 3-4 times more effective than I<sub>2</sub> against *E. coli*; Chang, 1966).

The effect of pH on speciation of iodine and the resulting effect on disinfection efficacy is exemplified by a study by Taylor and 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 HIO, which has greater virucidal activity than I<sub>2</sub> (Chang et al., 1966). The virucidal efficacy of HIO was reported to be 4-5 times less than HOCl, and I<sub>2</sub>, 200 times less (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 efficient disinfectant prevails.**

Microbial group	Disinfection efficiencies of different iodine species		Suitable pH range for disinfection
Bacteria (vegetative)	HIO	> I <sub>2</sub>	pH 5-8
Bacteria (spores)	I <sub>2</sub>	> HIO	pH 5-7
Viruses	HIO	> I <sub>2</sub>	pH 8-9
Protozoa <sup>1</sup>	I <sub>2</sub>	> HIO	pH 5-7

Source – Taylor and Butler (1982). 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. 1 – effective against *Giardia* cysts but not effective against *Cryptosporidium Oocysts*.

Where these tendencies hold true for microorganisms suspended in clean water, disinfection efficiencies can be altered in the presence of turbidity and for poor quality water. The underlying reason is that although HIO is more reactive and has a higher oxidation potential, it has less penetrating power than I<sub>2</sub>. 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 HIO (prevalent at pH 8-9) might lead to preferential reaction with oxidisable organic matter (for example, in the case of turbid water with total organic content (TOC)) leaving less residual available for disinfection (Ellis et al., 1993). 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 and van Vree (1989) when increasing the pH from 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, 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 > echo 1 > polio 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 HIO 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 temperature to achieve the same level of disinfection (Chambers et al., 1952). As for 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 and 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 HIO which, in turn, has a higher oxidation potential than I<sub>2</sub>.

## 2.2 Efficacy of iodine

### 2.2.1 Bactericidal efficacy of iodine

Chang and 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  $\geq 0.05$  ppm consistently reduced the culturability of 10<sup>4</sup> bacteria per mL to less than one within 10 min (25°C, pH 8.1-8.5). Other results obtained when exposing 10<sup>6</sup> mL<sup>-1</sup> *E. coli* cells to different iodine concentrations are shown in Table 4 below.

Table 4: Bactericidal efficacy of iodine.

Iodine concentration (in ppm)		Viable cells per 100 mL (log 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 concentration to reduce viability of *E. coli* cells spiked into tap water at an initial concentration of 10<sup>6</sup> mL<sup>-1</sup>. A standard iodine dose between 7 to 9 ppm was used to meet the iodine demand in the tap water and to obtain a bactericidal residual of 4 to 5 ppm. The experiment was performed at 25°C and a pH between 8.1 to 8.5. (adapted from Chang and Morris, 1953).

Chang and Morris (1953) reported stronger inactivation than seen with *E. coli* for other enteric bacteria including, *Salmonella typhimurium*, *Shigella dysenteriae* and *Vibrio cholera*, with 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 4.5-8.1. Similar (but declining) results were obtained with pH values up to 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 disinfection of *E. coli* (Chang and 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 and an increased disinfectant dosage has been reported to be necessary for water with organic colour > 70 ppm; a doubling of the dose was found to be adequate. A study by Ellis and 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 NTU reduced the germicidal effectiveness of iodine (see section 2.2.2 for more details) .

In general, the disinfection capability of iodine solutions 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 hepatitis A virus by iodine at doses of 8 and 16 ml/L was less effective in 'dirty water' (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 pH values of 6, 7.5 and 9 and different temperatures (5, 20, 35°C). 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 for the same contact time. The authors argued that the nature of the turbidity was more important than its density. A reason was hypothesised to lie in the higher organic and nitrogen content in sludge compared to stream sediment. 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, percentage removal 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 removal 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 along with a carrier and stabilising agents to enhance dissolvability (e.g., Globaline, composed of tetraglycine hydroperiodide, sodium acid pyrophosphate and talc) to the water to be disinfected. The U.S. Army has utilised iodine as a drinking water disinfectant, since 1952, issuing iodine- based tablets (Globaline™) to American Soldiers. The Army continues to provide iodine-based tablets in addition to other emergency field drinking water products. Today,

there are several Commercial-Off-The-Shelf (COTS) Individual Water Purification Devices (IWPD) that use iodine for disinfection (e.g. Globaline™).

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 swimming pools in Florida. 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 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 fully effective in meeting bacteriological standards.. The amount of iodine required for pools with high bathing activity was reported to be only slightly higher than required for pools with low bathing load (home-type pool), suggesting that the iodine residual appeared to be less sensitive to bathing load than chlorine residual. The authors considered that this was due to iodine not reacting with ammonium, as chlorine does; 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 home pools or public pools. This translates into a residual concentration of approx. 0.2 ppm (Black et al., 1959).

Available evidence indicates that iodine solution can be an effective<sup>1</sup> disinfectant against bacteria and to a lesser extent viruses. Iodine is least effective against protozoa and in particular, ineffective against *Cryptosporidium parvum* oocysts at practical doses and contact time, which are a major etiological agent of diarrhoeal disease globally (Gerba et al., 1997; Butkus et al., 2005; Kotloff et al., 2013). Recommend dosages range between 4 and 16 mg/L with contact times ranging from 20 – 35 minutes (min), resulting in CTs of 80 – 560 mg-min/L to achieve a 6 log<sub>10</sub> reduction/inactivation of bacteria and a 4 log<sub>10</sub> reduction/inactivation of viruses. When used as a disinfectant against protozoan cysts which are most resistant to iodine, dosages will be higher and contact times longer, resulting in larger CTs (Gerba et al., 1997).

It is important to note however, that existing evidence may not reflect actual use conditions in the field (e.g. water of varying quality, shorter contact times) for all three classes of pathogens which causes diarrhoeal disease. In order to comprehensively assess effectiveness, WHO has set tiered health based log<sub>10</sub> reduction performance targets for household water treatment products for the removal of bacteria, viruses and protozoa (WHO, 2011a). 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<sup>2</sup>. Box 1 gives further information on the Scheme. At the time of this report, iodine has not been tested but could be included in future rounds.

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<sup>2</sup> [http://www.who.int/household\\_water/scheme/en/](http://www.who.int/household_water/scheme/en/)

The objective of the Scheme is to independently and consistently evaluate the microbiological performance of household / point of use water treatment technologies. The evaluation considers both non- and turbid-water, and is carried out to manufacturers' instructions for daily household use ([http://www.who.int/household\\_water/scheme/en/](http://www.who.int/household_water/scheme/en/)). 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.

<b>Performance target</b>	<b>Bacteria</b> (log <sub>10</sub> reduction required)	<b>Viruses</b> (log <sub>10</sub> reduction required)	<b>Protozoa</b> (log <sub>10</sub> reduction required)	<b>Classification</b> (assuming correct and consistent use)
★★★	≥ 4	≥ 5	≥ 4	Comprehensive protection: very high removal of pathogens
★★	≥ 2	≥ 3	≥ 2	Comprehensive protection: high removal of pathogens
★	Meets at least 2-star (★★) criteria for two classes of pathogens			Targeted protection
–	Fails to meet criteria for 1-star (★)			

The performance of HWT products is classified as 3-star (★★★); 2-star (★★); and 1-star (★), denoting descending order of performance, based on log<sub>10</sub> 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

### 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 microorganism 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. Like iodine solutions, available data on iodine resins indicates they are effective disinfectants against bacteria, viruses, and some protozoa. However, the resins have not been proven effective against *Cryptosporidium* oocysts, which may possibly be due to a lack of subjective testing to date.

Iodine release systems comprise (1) organic iodide compounds, (2) iodophors and (3) iodine incorporated resins (Punyani et al., 2006). Iodine resins used in IWPDs are generally combined with other treatment processes such as filtration and modern applications of resins have resulted in an increase in their use. Devices used by NASA for space flights are prominent examples. Controlled release on board of the International Space Station Alpha is achieved through a flow-through device (referred to as Microbial Check Valve, MCV) containing an iodinated polymer (Atwater et al 1996; Gibbons et al. 1990). The I<sub>2</sub> residual concentration released into the water stream flow is around a maximum of 2 mg L<sup>-1</sup>. The released dissolved iodine undergoes a series of hydrolytic reactions resulting in the formation of I<sup>-</sup>, I<sub>3</sub><sup>-</sup>, HIO and OI<sup>-</sup> exerting germicidal action, with different biocidal capabilities associated to each inorganic species (Punyani et al., 2006; Venkobachar and Jain 1983). Another resin employed by NASA consists of the iodine-polyvinyl pyrrolidone (iodine-PVP) complex which releases iodine and I<sup>-</sup> at concentrations of 2-3 mg L<sup>-1</sup> and 1.5 mg L<sup>-1</sup>, respectively (Punyani et al., 2006). Again the dissolved iodine speciates into a variety of different inorganic compounds. Greatest biocidal activity can be attributed to I<sub>2</sub> and HIO (Gazda et al., 2004; Gottardi W., 1991).

A number of other resins have been developed with some promising results, the greatest of which is the controlled release of iodine compared to addition of the chemical to water. 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 IO<sub>3</sub><sup>-</sup> did not exhibit a germicidal effect, polyiodide resins were reported to be efficient for water disinfection (Vasudevan and Tandon 2010).

Table 5. Disinfection capabilities of iodine solutions and resins<sup>1</sup>

Parameter	Iodine solutions	Iodine resins
General	Cysts most resistant. Achieving <i>Giardia</i> cyst inactivation will ensure adequate bacteria and virus inactivation.	Cysts most resistant. Achieving <i>Giardia</i> cyst inactivation will ensure adequate bacteria and virus inactivation.
Bacteria	4 log inactivation at CT's < 10 mg-min/L <sup>2</sup>	Triiodide and pentaiodide resins can potentially provide a 6 log bacterial inactivation under most situations.
Viruses	2 log inactivation at CT's of 15 – 75 mg-min/L <sup>3</sup> Reduction of 4 log <sub>10</sub> for HAV, poliovirus 1 and echovirus 1 by	Triiodide and pentaiodide resins can potentially provide a 4-log virus inactivation under most natural water quality conditions.

	doses of 8 and 6 mg/L in 60 minutes or less, depending on water quality, pH and temperature	
<i>Giardia</i> cysts	3 log inactivation at CT's of 45 – 241 mg-min/L at >20°C. Provide additional contact time and higher CT's at <20°C to achieve 3 log inactivation.	3 log 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
<i>Cryptosporidium</i> Oocysts	Not effective <sup>4</sup>	Not effective <sup>4</sup>
Effect of temperature	Major effect. Increase contact time and/or dose at colder temperatures. CTs up to 720 mg-min/L recommended for <i>Giardia</i> cyst inactivation in colder waters (<5°C).	Major effect. Increase contact time after passing through pentaiodide resin at colder temperatures. Allow up to 40 mins. additional contact time for <i>Giardia</i> 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),

**1** - Note that testing was carried out using iodinated resins only, with no filter applied as would normally be found in IWPDs. 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 washing off of oocysts, which could remain viable. **2** - assuming a contact time of 20 minutes, a 0.5 mg/L iodine residual would be necessary to provide 4-log inactivation 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). **3** - 2-log inactivation at near neutral to alkaline pH levels (6 – 10) and various water temperatures (5 – 30 °C) at CT's of 15 – 75 mg-min/L with the higher CTs occurring at lower pH levels and colder water temperatures. **4** - Gerba et al. (1997).

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 <sup>a</sup>	Residual concentration of iodine
Iodine tablets (tetraglycine hydroperiodide)	1 – 2 tablets	8 – 16 mg/L
2% iodine solution (tincture)	0.25 – 0.5 mL	4 – 8 mg/L
10% providone-iodine solution	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 <sup>b</sup>
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 charcoal	-	0.01 ppm

Modified from Backer and 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 and contact time, as well as a function of water temperature.
- b- mg/L equivalent to ppm.

## 2.2.4 Comparison of efficacy with chlorine

The properties of iodine differ from the ones of chlorine 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 a 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 and 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;
- Works better for water of poor quality.

Disadvantages of iodine compared to chlorine: -these mainly relate 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.

## 3 Safety and toxicity of iodine

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

- European Food Safety Authority (EFSA) in 2014 (available on-line 2013);
- World Health Organisation /Food and Agriculture Organisation (WHO/FAO) in 2004;
- US Environmental Protection Agency (US EPA) in 2006;
- Agency for Toxic Substances and Disease Registry (ATSDR) in 2004;
- World Health Organisation (WHO; Background Document) in 2003;
- Expert Group on Vitamins and Minerals (EVM) in 2003; and
- European Commission Scientific Committee on Food in 2002 (EC, 2002).

In this section, opinions on intake of iodine from expert bodies, as detailed above, are described. In addition a detailed assessment of recent (to November 2013) toxicological literature for iodine was undertaken and relevant findings included here.

### 3.1 Human exposure

Iodine is an essential dietary element for mammals being required for the synthesis and function of the thyroid hormones T4 and 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 iodophores for sanitising 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, eggs and milk are the richest sources of dietary iodine. Chronic excessive iodine intake has been linked to development of goitre (Zhao et al., 2000), early onset of sub-clinical thyroid disorders, hyperthyroidism and hypothyroidism, an increased incidence of autoimmune thyroiditis and increased risk of thyroid cancer (Laurberg et al., 1998; Teng et al., 2006). In Japan, iodine intake exceeds that of most other countries, primarily due to substantial seaweed consumption. Zava & Zava (2011) utilised information from a number of sources to estimate daily Japanese iodine intake including; dietary records, food surveys, urine iodine analysis (both spot and 24-hour samples) and seaweed iodine content. The authors estimated that the Japanese iodine intake averages 1,000-3,000 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 to 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).

In contrast, iodine deficiency remains a major public health concern in many countries, including some European countries (WHO/UNICEF, 2007b; Zimmermann and Andersson, 2011; Andersson et al., 2012). Chronic deficiency has been linked with compensatory thyroid hyperplasia with goitre (enlarged thyroid gland), 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 around 120 countries worldwide (WHO/UNICEF, 2007). Of these 40 are European countries<sup>3</sup> being mandatory in 13 countries, voluntary in 16 and not regulated in the remaining countries; the amount of iodine added varies from 10 to 75 mg/kg salt with a majority of values in the range 15–30 mg/kg.

## 3.2 Guideline values

### 3.2.1. WHO drinking-water quality guidelines

The WHO Guidelines for Drinking-water Quality (WHO, 2011) 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 water disinfection is unlikely (WHO, 2003).

### 3.2.2 Other values

In 1988, The Joint FAO/WHO Expert Committee on Food Additives (JECFA) set a Provisional Maximum Tolerable Daily Intake (PMTDI) for iodine of 1 mg/day (17 µg/kg of body weight 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 recommended nutrient intakes for iodine were (WHO, 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 US National Institute of Medicine recommended the following dietary intake for iodine:

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<sup>3</sup> List of countries available from:

[http://www.who.int/nutrition/publications/VMNIS\\_Iodine\\_deficiency\\_in\\_Europe.pdf](http://www.who.int/nutrition/publications/VMNIS_Iodine_deficiency_in_Europe.pdf)

#### Infants

- 0 - 6 months: 110 µg/day
- 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

#### Pregnancy

- 220 µg/day

#### Lactation

- 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 concentration 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 (NAP, 2001).

In 2002, the European Commission Scientific Committee on Food 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 Gardener et al. (1998) and Paul et al. (1988) but changes were not associated with any adverse clinical outcome. In a five year study, Stockton and 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 per day, since the 97.5 percentile intake in European men is 434 µg per day (CRN, 2013).

The UK's EVM in 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 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 for supplemental iodine and 930 µg for total intake from all sources (CRN, 2013).

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 oral intake of iodine supplements of 500 µg. In 2014, EFSA published Adequate Intake (AI) levels for iodine in different age groups, based 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:

- 70 µg/day for infants below one year of age;
- 90 µg/day for children aged between 1-3 years, 4-6 and 7-10 years;
- 120 µg/day for children aged between 11-14 years;
- 130 µg/day for children aged between 15-17 years;
- 150 µg/day for adults; and
- 200 µg/day for pregnant or breast-feeding women.

For individuals from countries with long-standing iodine deficiency disorder (IDD), the French Expert Committee on Human Nutrition have suggested a provisional maximal tolerable daily intake of 500 µg/day to avoid the occurrence of hyperthyroidism (AFSSA, 2001 – cited in EFSA, 2014).

## 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 I<sub>2</sub> vapour by inhalation showed clearance with a half-life of 10 min, with the majority of iodine being removed by mucociliary clearance to the GI tract (Black and Hounam, 1968; Morgan et al., 1968). Iodine ingested in the form of water-soluble salts shows 100% absorption from the GI tract; inorganic iodine is initially reduced to iodide in the GI tract and then is completely absorbed in the small intestine (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 new-borns 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 (Fish et al., 1987; Hays, 1991) 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 foetus to thyroid hormones, with accumulation of iodine in the foetal thyroid gland commencing at around 70-80 days gestation (Evans et al., 1967; Book and Goldman, 1975 – cited in ATSDR, 2004).

#### 3.3.1.3 Metabolism

Iodine undergoes rapid conversion to iodide (Morgan et al., 1967a; Morgan et al., 1967b; Black and Hounam, 1968) which is then transported by the sodium iodide symporter (NIS) to the thyroid and utilised for the production of T<sub>3</sub> and T<sub>4</sub> hormones. Competition with NIS 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 and Fulwyler, 1963; Hays, 2001).

### 3.3.2 Acute toxicity

Several biological mechanisms protect against 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 gastrointestinal 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 1,200 to 9,500 mg (17–120 mg/kg). Acute oral toxicity is primarily due to irritation of the gastrointestinal 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 excess iodine on human health have been reported.

#### 3.3.3.1 Systemic effects

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

Men who drank iodised water providing iodine doses of 0.17-0.27 mg/kg bw/day for 26 weeks reported no adverse effects (Morgan and Karpen, 1953 – cited in EFSA, 2004).

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. 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 (Paul *et al.*, 1988).

In another study group, 10 males (mean age 27 years) were treated for 2 weeks with either 500, 1500 or 4500 µg iodide/day. 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 T3, T4, 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 subjects were studied, only males were examined, exposure was rather short and the actual dietary intake of iodine was not determined analytically but estimated (Gardner *et al.*, 1988).

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 and thyroid antibody positive (subclinical Hashimoto's thyroiditis) (n=20) or antibody negative (n=30), or 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 mU/L in 3 of the 60-75 year old subjects, while the raised TSH levels increased even further in 2 antibody-positive subjects (Chow *et al.*, 1991).

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 iodised 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 – cited in EFSA, 2014). The use of winter milk 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 and Phillips, 1985). In 32 young Swiss adults with simple goitre (and urinary I excretion of 32 µg/day) administered 200 µg I/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).

Peace Corps volunteers in Niger, West Africa using two-stage iodine-resin water purification devices for 32 months during the period 1995-1998, showed an increased incidence (42%) of thyroid abnormality; effects were reversed when iodinated water consumption ceased. The purification devices delivered a mean concentration of 10mg 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 RDA 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 two-stage water filters, with a positive relation with duration of exposure (adjusted odds ratios 4.6 and 10.9 at 6 and 12 months, respectively) (Pearce *et al.*, 2002).

In a 5-year study using iodinated drinking water (1 mg/L) supplied to 750 male and female prison inmates no hyper- or hypothyroidism, no sensitisation reactions and no iodism were noted. The average dose was 30 µg/kg bw/day. There was a statistically significant decrease in <sup>131</sup>I uptake and an increase in PBI of the thyroid. One-hundred and seventy seven women inmates delivered 181 infants showing no thyroid-related adverse effects. Four hyperthyroid women became more hyperthyroid. 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 (Stockton and Thomas, 1978).

Although most individuals who ingest large amounts of iodine remain euthyroid (i.e. have normal thyroid gland function) some will develop hypothyroidism (diminished production of thyroid hormone) with or without goitre, hyperthyroidism (excessive production and/or secretion of thyroid hormones) 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, gastrointestinal irritation, acneform dermatitis, metallic taste, gingivitis, increased salivation, conjunctivitis and oedema of eye lids. In children aged between 5-15 years of age, 10 µg/kg/day is considered to be a NOAEL based on thyroid effects (subclinical hypothyroidism with thyroid gland enlargement) (Boyages *et al.* 1989; Chow *et al.* 1991 – cited in ATSDR, 2004).

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, 2002; 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 foetuses, newborn infants, and individuals who have thyroiditis has the potential to produce neurological effects. This is particularly applicable to the foetus 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 (Boyages 2000b). 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, periodic paralysis, myasthenia gravis, peripheral neuropathy, tremor, and chorea (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, including inducing 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 (SHBG), 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, 2000b). Hypothyroidism may be associated with impairment in neurological development of the foetus or growth retardation (Boyages, 2000a, 2000b; 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). In mares administered 48-432 mg I/day during pregnancy and lactation produced foals with disturbed metabolism, osteopetrosis of the long bones of the legs and increased serum alkaline phosphatase levels (Silva et al., 1987 – cited in EC 2002).

#### **3.3.2.4 Carcinogenicity**

The American Conference of Governmental Industrial Hygienists (ACGIH) has classified iodine as A4 - not classifiable as a human carcinogen. IARC has not classified non-radioactive iodine.

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 and Williams 1995; Franceschi 1998; Franceschi and 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 LOAEL of 3.5 µg/kg bw/day has been identified based on thyroid cancer prevalence in Salta, Argentina, an endemic goiter area (Harach and 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 because of species differences in basal metabolic rate and in iodine metabolism (US Food and Nutrition Board, 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 and Bair, 1961; Bair, 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 (Thieblemont et al., 1965; Perrault et al., 1967 – cited in ATSDR, 2004).

ADME data from animal studies for iodine exposure via the gastro-intestinal tract, were not apparent from the reviews identified during the literature search.

### 3.4.2 Acute toxicity

The acute oral LD<sub>50</sub> for iodine in rats is 14 g/kg of body weight. In the mouse the LD<sub>50</sub> is 14 g/kg of body weight and in the rabbit, 10g/kg body weight (HSDB)<sup>4</sup>.

### 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 on thyroid function have been reported, with representative studies from different species summarised below;

- Two strains of chickens (CS and OS), genetically vulnerable to autoimmune thyroiditis, were given either 20 or 200 mg KI/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 T3, T4 and thyroglobulin antibody titres (Bagchi *et al.*, 1985).
- In female Wistar rats administered diets containing iodine concentrations of between 0.015 and 0.23 mg/kg bw/day for 10 weeks, significantly enlarged thyroids were found at doses of 0.15 and 0.23 mg/kg bw/day, with a dose-dependent increase at all doses (Fischer *et al.*, 1989).
- Newton and Clawson (1974 – cited in ATSDR, 2004) reported a dose-dependent increase in thyroid weights of pigs administered iodine at concentrations between 3 and 218 mg/kg bw/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; food intake was also decreased. Haematological changes (decreased packed cell volume) and clinical signs of nasal discharge and lacrimation were noted in the high dose and two highest dose groups respectively (Jenkins and Hidirolou, 1990).
- A NOAEL of 10mg/L for the most sensitive endpoint in rats of thyroid hormone imbalance: decrease in T3 levels and increase in T4/T3 ratio (100 day treatment) has been proposed (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 10x more T4/kg than humans).

#### 3.4.3.2 Reproductive and developmental toxicity

Arrington and colleagues 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 (Arrington *et al.*, 1965).

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<sup>4</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+34>

- 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 (Arrington et al., 1965).
- 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 (Arrington et al., 1965).
- 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 (Arrington et al., 1965).

In female rats administered 0, 500, 1000, 1500 and 2000 mg KI/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 foetal development (Ammermann *et al.*, 1964 – cited in EC, 2002). Brain enzymes of pups from pregnant rats administered 11 mg KI/day in their drinking water (37 mg/kg bw/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 – cited in EC, 2002).

In further studies a NOAEL of 10 mg/kg bw/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/day was also established (based on no supported changes at any dose level) (EC, 2002).

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

### 3.4.3.3 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, 2002)

### 3.4.5 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 DNA synthesis was seen in SHE cells.

## 3.5 Vulnerable populations

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

**Table 7 Risk groups for iodine-induced hypothyroidism**

Risk group / subgroup	
<b>No underlying thyroid disease</b>	
Foetus 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 and autoimmune thyroiditis
Chronic non-thyroid illness	Cystic fibrosis Chronic lung disease Chronic dialysis treatment Thalassaemia major Anorexia nervosa
<b>Underlying thyroid disease</b>	
	Hashimoto thyroiditis Euthyroid patients previously treated for Graves' disease with <sup>131</sup> 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

Source WHO, 2009

## 3.6 Toxicity of organiodides produced as DBPs

### 3.6.1 Formation and occurrence of iodinated by-products (I-DBPs)

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

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

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

- dichloriodomethane;
- bromochloriodomethane;
- dibromiodomethane;
- 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, and chloroform during chlorination or chloramination;
- THM formation increased with pH during chlorination but was only slightly elevated at around 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 (TOI) formation was twice that of total organic chlorine (TOCI);
- iodoacetic acid, diiodoacetic acid, and other iodo-acids were also formed with iodine tincture treatment, but at levels <11% of iodoform.
- a POU device combining an iodinated anion exchange resin with activated carbon post-treatment, indicated minimal formation of I-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 by-products

Concern has arisen regarding I-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 I-DBPs, as presented for iodine, is not available at the current time. An exception to this is that iodoform has been tested in NTP bioassays and was not carcinogenic under test conditions. (NCI, 1978)

Following the identification of iodoacids and iodo-THMs in chloraminated and chlorinated drinking waters in the US (section 2.2.6) 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 iodo-THMs (dichloroiodomethane and bromochloroiodomethane) using *in vitro* assays with Chinese Hamster Ovary (CHO) 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 iodo-THMs were much less cytotoxic than the iodo-acids.

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 and 172mM potassium iodide; 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 (TOI) content of the water samples. The cytotoxicity of THMs formed with 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 around 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 I-DBPs when evaluating potential risks, with measurement of iodoacids, in addition to iodoform as the dominant I-DBP, following iodination. Diiodoacetic acid (DIAA) and iodoacetic acid (IAA) were formed at levels <10% of iodoform

following treatment with iodine tincture. However, IAA has greater cytotoxicity (> 2x) in mammalian cells than iodoform, and is genotoxic which iodoform is not.

### 3.7 Summary

- Limited data (both human and from 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. Sensitising 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 (T3, T4 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 the foetus 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 I-DBPs and likely adverse effects at the levels 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.

DRAFT



## 4 Environmental considerations

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The oceans are the most important source of natural iodine in the air, water, and soil. Iodine in the oceans enters the air from sea spray or as iodine gases. Once in the air, iodine can combine with water or with particles in the air and can enter the soil and surface water, or land on vegetation when these particles fall to the ground or when it rains. Iodine can remain in soil for a long time because it combines with organic material in the soil. It can also be taken up by plants that grow in the soil. Cows or other animals that eat these plants will take up the iodine in the plants. Iodine that enters surface water can re-enter the air as iodine gases. Iodine can enter the air when coal or fuel oil is burned for energy; however, the amount of iodine that enters the air from these activities is very small compared to the amount that comes from the oceans.

Environmental considerations are largely beyond the scope of this report, however, as noted in Table 7, the impact of release of iodine into the environment to ‘non-target’ organisms should be considered.

Table 7. Environmental toxicity of iodine to ‘non-target’ species

Group of organisms		Test compound	L(E)C <sub>50</sub>	NOEC	
Fish (freshwater)	Bluegill sunfish ( <i>Lepomis macrochirus</i> )	Iodine (99.8%)	0.61 mg/L	0.16 mg/L	Highly toxic
Invertebrates	Water flea ( <i>Daphnia magna</i> )	Iodine (99.8%)	0.33 mg/L	0.09 mg/L	Very highly toxic

Reproduced from US EPA (2006)

## 5. Discussion

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The use of iodine for water disinfection compared to other 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 acceptable effectiveness against viruses and some but less effectiveness against some protozoans. 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 target and no evaluations have been carried out on the health impacts in low-income settings with microbially contaminated drinking-water.

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

- Water treatment needs little supervision, is simple and cost effective (although more expensive than chlorine);
- Iodine may provide superior disinfection to chlorine for water of poor quality<sup>5</sup> (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 against health. Achieving health gains from household water treatment requires products to be used correctly and consistently, and thus clear product information and use instructions are important. In addition, user preferences, supply chains and availability and cost are important factors to consider. Products such as iodine 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 is not adequate to establish a linear and temporal dose response between iodine intake and altered thyroid function (Backer and Hollowell, 2000).

Current POU water disinfection devices that are both effective in terms of disinfection and can achieve low residual levels (0.01 mg/L; 0.01 ppm) of iodine (such as triiodinated resins including a granular activated charcoal), 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

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<sup>5</sup> 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 greater residual levels.

an adult of 2L per day, residual iodine at this level would result in intakes of around 0.02 mg/day. This is well below the low end range of the recommended upper limit of 0.5 mg/day (500 µg/day; CRN, 2013) even allowing for greater consumption of 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 (>1 mg/L) residual iodine levels (such as iodine tablets which leave residual concentrations from 8-16 mg/L), intake of 2L 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 and 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, as this study was conducted over a two-week period 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 foetus 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. Based on the information presented in table 5, iodine solutions would not meet the WHO minimum performance recommendations for point of use treatment products, while iodine resins (without filters) could achieve the minimum performance recommendations for two of the three pathogen classes (bacteria and viruses);
- Effectiveness 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 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.

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 that result in low residual concentrations of iodine (e.g. those using resins with charcoal filters), few adverse effects are

anticipated. Although there is insufficient evidence to support long-term use of resin-based disinfectants, it is anticipated that these devices could be used over extended periods of time.

- for euthyroid individuals using other iodine disinfection techniques that result in higher residual concentrations of iodine (e.g. solution or tablets and resins without charcoal 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 utilised;
- for high-risk members of the population, water disinfection with iodine is not recommended and an alternative disinfectant should be utilised. However, disinfection should not be compromised due to the public health significance of microbially unsafe water, and therefore if iodine is the only disinfectant available, use should be limited to a short of a time as possible and an alternative disinfectant sought.

On the basis of limited effectiveness against viruses and particularly protozoa, the use of iodine products may be appropriate in targeted situations where the causative agent is known. For instance, iodine is effective against bacteria, and could be used in a cholera outbreak. However, where the causative disease agent is unknown, use should ideally be combined with another household treatment method to provide comprehensive protection.

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# Appendix 1: Methodology

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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))
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## 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.
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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 September 2015).