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Iodine in drinking-water

Background document for development of WHO *Guidelines for drinking-water quality*

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Preface

Access to safe drinking-water is essential to health, a basic human right and a component of effective policy for health protection. A major World Health Organization (WHO) function to support access to safe drinking-water is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...", including those related to the safety and management of drinking-water.

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International standards for drinking-water*. It was revised in 1963 and 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for drinking-water quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects, reviewing selected microorganisms, was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006, and the second addendum to the third edition was published in 2008. The fourth edition was published in 2011, and the first addendum to the fourth edition was published in 2017.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation relating to aspects of protection and control of drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other information to support the GDWQ, describing the approaches used in deriving guideline values, and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a background document evaluating the risks to human health from exposure to that chemical in drinking-water was prepared. The draft health criteria document was submitted to a number of scientific institutions and selected experts for peer review. The draft document was also released to the public domain for comment. Comments were carefully considered and addressed, as appropriate, taking into consideration the processes outlined in the *Policies and procedures used in updating the WHO guidelines for drinking-water quality* and the WHO *Handbook for guideline development*.

The revised draft was submitted for final evaluation at expert consultations.

During preparation of background documents and at expert consultations, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents; the International Agency for Research on Cancer; the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Meeting on Pesticide Residues; and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO website and in the current edition of the GDWQ.

Acknowledgements

The background document on iodine in drinking-water for the development of the World Health Organization (WHO) *Guidelines for drinking-water quality* (GDWQ) was prepared by Dr Ruth Bevan, independent consultant, United Kingdom. Much of the information in this background document has been taken from the WHO 2018 review *Alternative drinking-water disinfectants: bromine, iodine and silver*.

The work of the following experts was crucial in the development of this document and others in the second addendum to the fourth edition:

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The draft text was discussed at the expert consultations for the second addendum to the fourth edition of the GDWQ, held on 28–30 March 2017 and 13–14 July 2018. The final version of the document takes into consideration comments from both peer reviewers and the public, including P Callan, independent consultant, Australia; F Lemieux, Health Canada; J MacAulay, Health Canada; and M Templeton, Imperial College London, United Kingdom.

The coordinator was Ms J De France, WHO, with support from Dr V Bhat, formerly of NSF International, United States of America. Strategic direction was provided by Mr B Gordon, WHO. Dr A Tritscher, formerly of WHO, and Dr P Verger, WHO, provided liaisons with the Joint FAO/WHO Expert Committee on Food Additives and the Joint FAO/WHO Meeting on Pesticide Residues. Dr R Brown and Ms C Vickers, WHO, provided liaisons with the International Programme on Chemical Safety. Dr M Perez contributed on behalf of the WHO Radiation Programme. Dr Andina Faragher, Biotext, Australia, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document are greatly appreciated.

Acronyms and abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
bw	body weight
FAO	Food and Agriculture Organization of the United Nations
GDWQ	*Guidelines for drinking-water quality*
GI	gastrointestinal
GV	guideline value
I_2	iodine
I^-	iodide
NOAEL	no-adverse-effect level
T3	triiodothyronine
T4	thyroxine
TSH	thyroid-stimulating hormone
USA	United States of America
WHO	World Health Organization

Contents

Executive summary

Iodine occurs naturally in water in the form of iodide. When added to water, elemental iodine hydrolyses in a pH-dependent manner to form hypoiodous acid and iodide.

Iodine is an essential dietary element for mammals. The diet is the major source of exposure to iodine for the general human population; the contribution to total exposure from drinking-water is assumed to be low (around 5%). The bioavailability of iodine from food and water is high, and absorbed iodine is rapidly distributed in the body.

Guidance levels for iodine intake differ with age, sex and pregnancy/breastfeeding status. Adequate intake levels of 90–200 µg/day and upper total intake levels of 1100 µg/day have been published.

The thyroid gland is the main storage organ for iodine. It is also the target of iodine toxicity. Exposure to excess iodine can lead to hypothyroidism (with or without goitre – enlargement of the thyroid), hyperthyroidism, and changes in the incidence and types of thyroid malignancies.

Insufficient toxicological information is currently available to identify a threshold in humans or other animals for the induction by iodine of thyrotoxicosis (excessive production of thyroid hormone), from which a guideline value (GV) could be derived. Such a value cannot be derived using the more robust toxicological dataset for iodide because data from drinking-water studies in rats indicate that the effects of iodine on thyroid hormone concentrations in the blood differ from the effects of iodide.

A GV for iodine is not recommended at this time because:

- levels of iodine found in drinking-water are generally low; and
- although higher levels of exposure may occur when iodine is used as a drinking-water disinfectant at the point of use, extended periods of such exposure are unlikely.

1 General description

1.1 Identity

CAS no.: 7553-56-2

Molecular formula: I_2

1.2 Physicochemical properties

Some physicochemical properties of iodine are shown in Table 1.1.

Table 1.1. Physicochemical properties of iodine

Property	Value
Boiling point	184.4 °C
Melting point	113.5 °C
Density	4.93 g/cm^3 at 25 °C
Vapour pressure	40 Pa at 25 °C
Water solubility	0.34 g/L at 25 °C
Log octanol–water partition coefficient	2.49

Note: Conversion factor in air: 1 ppm = 10 mg/m^3
Sources: Ruth (1986), ATSDR (2004), HSDB (2017)

1.3 Organoleptic properties

The taste and odour thresholds for iodine are 0.147–0.204 mg/L in water and 9 mg/m^3 in air (Ruth, 1986).

1.4 Major uses and sources

Iodine is used as an antiseptic for skin wounds, as a disinfecting agent in hospitals and laboratories, in pharmaceuticals and in photographic developing materials. For disinfection, iodine tablets and solutions are commonly used for water treatment during emergencies and by travellers (Ongerth et al., 1989; Backer & Hollowell, 2000).

2 Environmental levels and human exposure

The oceans are the most important source of natural iodine in air, water and soil; weathering of rock and volcanic activity also lead to the release of iodine.

When elemental iodine (I_2) is added to water, it hydrolyses in a pH-dependent manner to form hypoiodous acid (HOI) and iodide (I^-) (Lengyel, Epstein & Kustin, 1993). The overall stoichiometry of iodine hydrolysis between pH 2 and 7 is:

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

2.1 Water

Iodine occurs naturally in water in the form of iodide, which is largely oxidized to iodine during water treatment. The average concentrations of iodine in seawater, rainwater, and rivers and

lakes are 45–60 µg/L, 0.5–5.0 µg/L and 0.5–20 µg/L, respectively (Whitehead, 1984). Human exposures to iodine through drinking-water are typically too low for significant uptake of iodine. The mean concentration of total iodine in drinking-water in the United States of America is 4 µg/L, and the maximum concentration is 18 µg/L (ATSDR, 2004). This is presumably mainly iodide.

2.2 Food

The main natural sources of dietary iodide are seafood (200–1000 µg/kg) and seaweed (0.1–0.2% iodide by weight). However, as these foods are not generally the main constituents of most diets, the largest sources of iodine in the human diet are vegetables (320 ± 100 µg/kg), meat products (260 ± 70 µg/kg), eggs (260 ± 80 µg/kg) and dairy products (130 ± 10 µg/kg) (ATSDR, 2004). Iodide may be added to table salt (100 µg of potassium iodide per gram of sodium chloride) to ensure an adequate intake of iodine (Dasgupta, Liu & Dyke, 2008).

2.3 Air

Iodine in the oceans can enter the air from sea spray or iodine gases. In the air, iodine combines with water or particulates to enter the soil or surface water. Iodine that deposits on vegetation is washed to the ground by rain. Much smaller amounts of iodine can enter the air during the burning of coal or fuel oil. Normal human respiratory exposure to iodine has been estimated as 5 µg/day based on an atmospheric concentration of 0.7 µg/m^3 (ATSDR, 2004).

2.4 Estimated total exposure and relative contribution of drinking-water

Diet is the major source of exposure to iodine for the general human population. Additional exposure may occur through drinking-water and pharmaceuticals. A concentration of 4 µg/L of iodine in drinking-water (mean noted in section 3.1 for the USA) will provide an additional intake of around 8 µg of iodine for an adult, assuming consumption of 2 L of drinking-water per day. The contribution to an adequate dietary iodine intake (see section 5.1) from drinking-water is therefore assumed to be low at the average level of 4 µg/L (around 5%).

3 Toxicokinetics and metabolism in animals and humans

3.1 Absorption

Iodine is readily absorbed via ingestion and inhalation. Dietary iodine is converted into iodide before it is absorbed (FAO/WHO, 2002). Molecular iodine vapour is also converted into iodide before absorption (ATSDR, 2004). Absorption through the skin is extremely low (<1% of applied dose).

Iodine ingested in the form of water-soluble salts shows 100% absorption from the gastrointestinal (GI) tract; iodine ingested in forms other than iodide is initially reduced to iodide in the GI tract and then is completely absorbed in the small intestine (Fischer, Voorhess & Gardner, 1965). Absorption of iodide from the GI tract is similar in adults, adolescents, children and older infants, whereas uptake in newborns is reported to be 2–20% lower (Ogborn, Waggener & VanHove, 1960; Morrison et al., 1963). Iodide absorption is lower in the presence of humic acids in drinking-water (Gaitan, 1990), and in the presence of chlorate, perchlorate thiocyanates, isothiocyanates, nitrates, fluorides, calcium, magnesium and iron in food and water (Ubom, 1991).

3.2 Distribution

The highest concentration of iodine in the human body is found in the thyroid, which contains 70–80% of the body's total iodine content of 15–20 mg. Muscle and eyes also contain high iodide concentrations (ATSDR, 2004). Maternal exposure to iodine results in accumulation of iodine in the fetal thyroid gland, from around 70–80 days gestation (ATSDR, 2004).

3.3 Metabolism

Iodine undergoes rapid conversion to iodide (Morgan, Morgan & Arkell, 1967; Morgan et al., 1967; Black & Hounam, 1968). Iodide is then transported by the sodium iodide symporter to the thyroid, and used to produce the hormones triiodothyronine (T3) and thyroxine (T4).

3.4 Elimination

Around 97% of iodine is excreted in the urine as iodide, with partial reabsorption from the tubules following glomerular filtration (ATSDR, 2004); faecal elimination of 1–2% also occurs (Larsen, Davies and Hay, 1998; Hays, 2001). Small amounts of iodine can be excreted in breast milk, saliva, sweat, tears and exhaled air (Cavalieri, 1997). The elimination half-life of absorbed iodine varies considerably between individuals and has been estimated as 31 days for healthy adult males, on average (Van Dilla & Fulwyler, 1963; Hays, 2001).

4 Effects on humans

Because iodine is an essential element, many authoritative reviews have examined the effects of iodine deficiency, with the aim of establishing adequate dietary intakes (FAO/WHO, 2001; IOM, 2001; EVM, 2003; EFSA, 2014). The United States Agency for Toxic Substances and Disease Registry (ATSDR) has published a toxicological profile for iodine that focuses on the adverse effects (mainly in humans) that are apparent at the lowest levels of exposure; this profile details a large number of experimental, clinical and epidemiological studies and is used as a basis for the information given below (ATSDR, 2004). It is of note that physiological adaptations to background levels of dietary intake of iodine are likely to affect the responses to increased levels of iodine, as detailed in the following sections.

4.1 Requirements

Iodine is an essential dietary element for mammals that is required for the synthesis and function of the thyroid hormones T4 and T3. It is also the precursor of iodotyrosines. Through the thyroid hormones, iodine plays an important role in energy-yielding metabolism and the expression of genes that affect many physiological functions, from embryogenesis to growth and development, and neurological and cognitive functions (EFSA, 2014; WHO, 2018).

Several authoritative bodies have determined upper intake levels for iodine (Table 1.2), which can inform potentially toxic levels.

Table 4.2. Recommended upper intake levels for iodine (adults)

Authoritative body	Upper level	Basis for upper level
Council for Responsible Nutrition (Hathcock 2013)	500 µg/day supplemental intake (8 µg/kg bw/day for a 60 kg adult); 1000 µg/day total intake (17 µg/kg bw/day for a 60 kg adult)	Absence of adverse effects in healthy adults given 500 µg of supplement (Gardner, Centor & Utiger, 1988; Paul et al., 1988; Chow et al., 1991)
Expert Group on Vitamins and Minerals (EVM, 2003)	Guidance level: 500 µg/day supplemental intake (8 µg/kg bw/day for a 60 kg adult); 930 µg/day total intake (16 µg/kg bw/day for a 60 kg adult)	Absence of adverse effects in healthy adults given 500 µg of supplement (Gardner, Centor & Utiger, 1988; Paul et al., 1988; Chow et al., 1991)
European Commission Scientific Committee on Food (EC, 2002)	600 µg/day total intake (10 µg/kg bw/day for a 60 kg adult)	Elevated TSH[a] levels at iodine intake of 1700 µg/day from all sources in a healthy adult population (Laurberg et al., 1998). UL is derived by applying a UF of 3 to the LOAEL
Institute of Medicine (IOM, 2001)	1100 µg/day total intake (18 µg/kg bw/day for a 60 kg adult)	Elevated TSH[a] levels at iodine intake of 1700 µg/day from all sources in a healthy adult population (Laurberg et al., 1998). UL is derived by applying a UF of 1.5 to the LOAEL
Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1989; WHO, International Council for the Control of Iodine Deficiency Disorders & UNICEF 1994; FAO/WHO, 2002)	1000 µg/day (17 µg/kg bw/day for a 60 kg adult)	PMTDI based on the tolerance of healthy iodine-replete adults to high doses of iodine; does not include neonates or young infants

bw: body weight; LOAEL: lowest-observed-adverse-effect level; PMTDI: provisional maximum tolerable daily intake; TSH: thyroid-stimulating hormone; UF: uncertainty factor; UL: upper limit

[a] TSH is produced by the pituitary gland when levels of T3 and T4 are low, and stimulates the thyroid gland to secrete larger amounts of T3 and T4.

Iodine deficiency is a prevalent health issue in more than 54 countries (WHO, n.d.). In 2004, the World Health Organization and the Food and Agriculture Organization of the United Nations recommended the following nutrient intakes for iodine (WHO/FAO, 2004):

- infants and children 0–59 months – 90 µg/day
- children 6–12 years – 120 µg/day
- adolescents and adults, from 13 years of age through adulthood – 150 µg/day
- pregnant women – 200 µg/day
- lactating women – 200 µg/day.

Other authoritative bodies have also published adequate intake levels, including the Food and Nutrition Board at the United States National Institute of Medicine (IOM, 2001) and the European Food Safety Authority (EFSA, 2014).

4.2 Acute exposure

Several biological mechanisms protect against iodine toxicity, and not all exposed subjects will react to excess iodine. Acute oral toxicity is primarily due to irritation of the GI tract, marked fluid loss and, in severe cases, shock (ATSDR, 2004). Clinical features include GI disturbance (vomiting and diarrhoea), metabolic acidosis, seizure, stupor, delirium and collapse. Oral doses of 2000–3000 mg of iodine – about 30–40 mg/kg body weight (bw) – are estimated to be lethal to humans, but survival has been reported after ingestion of 10 000 mg. Doses of 30–250 mL of tincture of iodine (about 16–130 mg of total iodine per kg bw) have been reported to be fatal. Exposure to iodine vapour results in lung, eye and skin irritation, and high concentrations rapidly lead to pulmonary oedema (ATSDR, 2004).

In rare instances, a hypersensitization reaction may occur immediately after, or within several hours of, oral or dermal exposure to iodide. The most striking symptoms are angio-oedema (acute, transitory swelling of the face, hands, feet or viscera) and swelling of the larynx, which may cause suffocation (ATSDR, 2004). Iodide has been used in the past as an expectorant in the treatment of asthma and related conditions, at a typical dose of 3.3 mg/kg bw (ATSDR, 2004).

4.3 Short-term and subchronic exposure

Studies of short-term exposure to iodine have been critically reviewed elsewhere (ATSDR, 2004). The principal systemic effects of repeated exposure to excess iodine through ingestion are on the thyroid gland, leading to effects on thyroid hormone production and secretion. Secondary effects on the endocrine system (pituitary and adrenal glands) and many other organs (including skin, cardiovascular system, pulmonary system, kidneys, GI tract, liver, blood, neuromuscular system, skeleton and reproductive systems) result from disorders of the thyroid gland. Effects on the thyroid gland can occur in all ages and are classified into three types:

- Hypothyroidism refers to reduced production of thyroid hormones. It can present with or without goitre (enlargement of the thyroid), which results from hypertrophy of the thyroid in response to a reduced level of serum thyroid-stimulating hormone (TSH). Hypothyroidism is characterized by reduced circulating T4 and/or T3 in the presence of elevated TSH.
- Hyperthyroidism refers to excessive production and/or secretion of thyroid hormones. It is characterized by elevated circulating levels of T4 and/or T3. The clinical manifestation of hyperthyroidism is thyrotoxicosis.
- Thyroiditis refers to inflammation of the thyroid gland, often as a result of thyroid gland autoimmunity.

The United States Agency for Toxic Substances and Disease Registry reviewed a number of studies that assessed adverse effects following increased oral intake of iodine over the short term (≤90 days). In healthy male adults with normal thyroid function (euthyroid), dietary iodine intakes up to a total of 800 µg/day are not associated with suppression of the thyroid gland. Iodine intakes as high as 4800 µg/day did induce statistically significant changes in T3, T4 or TSH, but these were not outside normal ranges and did not produce clinically relevant adverse effects (Jubiz et al., 1977; Gardner, Centor & Utiger, 1988; Paul et al., 1988; Chow et al., 1991; Namba et al., 1993; Robison et al., 1998; NSF, 2002).

4.4 Long-term exposure

4.4.1 Systemic effects

Chronic iodide exposure results in iodism; the symptoms resemble those of a sinus cold but may also include salivary gland swelling, GI irritation, acneiform skin, metallic or brassy taste, gingivitis, increased salivation, conjunctival irritation, and oedema of eyelids (ATSDR, 2004). Chronic ingestion of 2 mg of iodide per day (0.03 mg/kg bw/day) is considered by some authors to be excessive, but daily doses of 50–80 mg (0.8–1.3 mg/kg bw/day) are consumed by some Japanese people without ill effect (ATSDR, 2004).

As with short-term repeated exposure, the principal systemic effect of chronic (>6 months) exposure to excess iodine through ingestion (via water and food) is on the thyroid gland, and production and secretion of thyroid hormones (ATSDR, 2004; Sang et al., 2013; Leung & Braverman, 2014). Chronic consumption of iodine at levels >0.03 mg/kg bw is considered to be associated with adverse health effects (ATSDR, 2004). The introduction of iodized bread in the Netherlands raised the daily iodine intake by 120–160 µg, resulting in an increase in the incidence of hyperthyroidism (EFSA, 2014). Winter consumption of milk – rich in iodine as a result of farming practices – in Cambridgeshire, United Kingdom, raised the iodine intake of women to 236 µg/day and of men to 306 µg/day; this was also associated with a peak in the incidence of hyperthyroidism in the following spring and summer (Nelson & Phillips, 1985).

By itself, chronic consumption of iodinated drinking-water has not been shown to cause adverse health effects in humans. Although some changes in thyroid status have been observed, these were without clinical significance. No adverse health effects were reported in men who drank water providing iodide at doses of 0.17–0.27 mg/kg bw/day for 26 weeks (ATSDR, 2004). In a 5-year study of prison inmates consuming water containing iodine at a concentration of 1 mg/L (approximately 0.03 mg/kg bw/day, assuming a body weight of 60 kg and drinking-water intake of 2 L), no cases of hyperthyroidism, hypothyroidism, urticaria or iodism were seen. However, a small but statistically significant decrease in radioactive iodine uptake by the thyroid and an increase in protein-bound iodine concentrations were reported (ATSDR, 2004). A study of Peace Corps volunteers showed a positive relationship between thyroid dysfunction and high intakes of iodine (50 mg/day or approximately 0.8 mg/kg bw/day, assuming a body weight of 60 kg) for a prolonged period of more than 32 months (Pearce et al., 2002).

Exposure to iodine by any route may aggravate certain pre-existing thyroid disease conditions. In one study, the rate of radioactive iodide uptake by the thyroid was measured in 22 individuals with thyroid disease and 10 with normal thyroid function, before and after administration of 2.0 mg of iodide. Radioactive iodide uptake decreased by 54–99% in patients with thyroid disease but by only 8–54% in normal controls (ATSDR, 2004).

Incidences of congenital goitre and hypothyroidism in children were reported to be associated with maternal ingestion of iodide (ATSDR, 2004). Estimates of maternal iodide exposure ranged from 12 to 1650 mg/day (about 0.02–27 mg/kg bw/day) in individuals taking iodide as an expectorant for the treatment of asthma. No direct evidence was reported of a cause-and-effect relationship between iodide exposure and health effects during pregnancy.

Hypothyroidism has also been reported in infants of mothers receiving multiple topical applications of povidone–iodine (about 1% free iodine) during pregnancy and lactation (ATSDR, 2004).

4.4.2 Neurological effects

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

Sensitive individuals with iodine-induced hyperthyroidism presenting as thyrotoxicosis may experience neuromuscular disorders, including myopathy, periodic paralysis, myasthenia gravis, peripheral neuropathy, tremor and chorea (Boyages, 2000b).

4.4.3 Reproductive and developmental effects

Chronic exposure to excess iodine has been shown to disrupt reproductive function, as a result of thyroid gland dysfunction. Changes in the menstrual cycle, including menorrhagia (excessive uterine bleeding) and anovulation (no ovulation), spontaneous abortions, stillbirths and premature births have been associated with hypothyroidism (Longcope, 2000a; Krassas, Poppe & Glinoer, 2010).

Reproductive impairments associated with hyperthyroidism include amenorrhea (absence of menstruation), alterations in gonadotrophin-releasing hormone and sex hormone-binding globulin, and changes in the levels and metabolism of steroid hormones in both females and males (Longcope, 2000b; Krassas, Poppe & Glinoer, 2010).

Exposure to iodine may give rise to developmental defects, as a result of thyroid gland dysfunction (Boyages, 2000a,b). Hypothyroidism may be associated with impairment in neurological development of the fetus, as noted above, or growth retardation (Boyages, 2000a,b; Snyder, 2000a; Krassas, Poppe & Glinoer, 2010).

Hyperthyroidism in humans was 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).

4.4.4 Immunological effects

Immunological effects following chronic oral exposure to excess iodine in humans have been reported as thyroid gland autoimmunity or immune reactions such as ioderma; Rosenberg et al. (1972) reported ioderma following oral intake of potassium iodide at a dose of 14 mg/kg bw/day for 1 year. Excess iodide intake may contribute to the development of autoimmune thyroiditis in people who are susceptible (Safran et al., 1987; Brown & Bagchi, 1992; Foley, 1992; Rose et al., 1997; Rose, 2002).

4.4.5 Genotoxicity and carcinogenicity

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

Evidence from human studies is equivocal; in iodine-deficient populations, increased iodide intake has been reported as a risk factor for thyroid cancer (Harach & Williams, 1995; Bacher-Stier et al., 1997; Franceschi, 1998; Franceschi & Dal Maso, 1999). However, more recent studies have produced contrary findings (Zimmermann & Galetti, 2015; Cao et al., 2017).

5 Effects on experimental animals and in vitro test systems

5.1 Requirements

Iodine is an essential element in animals; it is required for the synthesis of the thyroid hormones T4 and T3, through the precursor protein thyroglobulin and the action of the enzyme thyroid peroxidase.

5.2 Acute exposure

The acute oral median lethal dose (LD_{50}) for potassium iodide in rats has been reported as 4340 mg/kg bw (3320 mg of iodide per kg bw), and the lowest oral lethal dose in mice as 1862 mg/kg bw (1425 mg of iodide per kg bw) (ATSDR, 2004).

5.3 Short-term and subchronic exposure

Iodine administration via the diet in female rats (0.15 or 0.23 mg/kg bw/day for 10 weeks) was report to cause increased thyroid weight; this effect was also noted in pigs (3 or 218 mg/kg bw/day) and female calves (0.011 or 3.96 mg/kg bw twice daily for 5 weeks) (ATSDR, 2004).

The effects of iodide on the development of autoimmune thyroiditis have been investigated in rats and chickens. When exposed to iodide in drinking-water at a concentration of 85 mg/kg bw/day for 8 weeks, an inbred strain of rat (BB/Wor) that has a high rate of spontaneous autoimmune thyroiditis showed an increase in incidence of this condition (77% compared with a control rate of 30%). Additional evidence is available from a study in two strains of chickens (CS and OS) known to be genetically susceptible to this disease. Administration of iodide in drinking-water (20 or 200 mg/L, as potassium iodide) during the first 10 weeks of life increased the incidence of the disease, as determined by histological examination of the thyroid and measurement of T3, T4 and thyroglobulin antibodies (ATSDR, 2004).

5.4 Long-term exposure

6.4.1 Systemic effects

As in humans, the main direct effect of excessive iodine ingestion in animals is on the thyroid gland, and production and secretion of thyroid hormones.

5.4.2 Neurological effects

Studies in laboratory animals suggest that iodine deficiency has an early effect on neuroblast multiplication, which could be important in the pathogenesis of the neurological form of endemic cretinism (Hetzel & Mano, 1989).

5.4.3 Reproductive and developmental effects

Decreased survival of pups was reported following administration of iodine to pregnant Long–Evans rats at a concentration of 2500 mg/kg of feed for 12 days in the latter part of gestation. Length of labour (parturition) was also increased (Ammerman et al., 1964). No effects were

observed on ovulation rate, implantation rate or fetal development in female rats given doses of iodide (as potassium iodide) of 0, 500, 1000, 1500 or 2000 mg/kg feed during gestation and lactation. However, a dose-related decrease in survival rate of pups was observed, ranging from 93% (controls) to 16% (2000 mg/kg). Milk secretion was absent or greatly diminished in females exposed to iodide, and the high mortality in pups was attributed to the dams' lactational failure (Ammerman et al., 1964a).

Decreased survival rates were also observed in pups from pregnant rabbits fed iodine at concentrations of 250–1000 mg/kg feed for 2–5 days before parturition. Pregnant hamsters exposed to iodine at 2500 mg/kg feed similarly showed a decreased weaning weight of pups, due to reduced maternal feed intake. Litters from pregnant pigs receiving diets containing iodine at 1500 or 2500 mg/kg feed (i.e. toxic dietary levels in rats and rabbits) for the 30 days before parturition were unaffected (Arrington et al., 1965).

Metabolism was severely disturbed in foals born to mares receiving excess iodine (48–432 mg/day) in the diet during pregnancy and lactation. The long bones of the legs of foals showed osteopetrosis (abnormally dense bones); phosphorus and alkaline phosphatase levels in the blood were elevated (EC, 2002).

5.4.5 Genotoxicity and carcinogenicity

The carcinogenicity of iodine was evaluated in male Wistar rats fed diets that were iodine deficient (0.5 mg/kg), adequate (12 mg/kg) or rich (200 mg/kg) for up to 10 months (estimated as 0.05, 1.2 or 20 mg/kg bw/day). From month 2, rats were also administered weekly injections of the carcinogen *N*-nitrosobis(2-hydroxypropyl)amine. In the iodine-adequate and iodine-rich groups, papillary carcinomas were reported in 33% and 29% of the animals, respectively. In the iodine-deficient group, all animals developed papillary and follicular carcinomas. The authors suggest that the effect is due to the goitrogenic and/or goitre-promoting effect of TSH (Yamashita et al., 1990).

Metaplasia, as a result of lobular impairment, of the thyroid was reported in rats given potassium iodide in their drinking-water for 2 years, with intakes estimated as 0, 0.6, 5.3 or 53 mg/kg bw/day. The authors considered that the metaplasia lesions may develop into carcinoma via a non-genotoxic, proliferation-dependent mechanism (EVM, 2003).

5.5 In vitro systems

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 (EVM, 2003).

Silver iodide was negative in the *Salmonella* reverse mutation assay with strains TA102, TA1535, TA97 and TA98 in both the presence and absence of metabolic activation (Eliopoulos & Mourelatos, 1998). Povidone–iodine, iodine and potassium iodide were negative in the L5178 Y mouse lymphoma assay in the absence of activation; however, iodine and povidone–iodine showed marginal activity in the presence of activation (Kessler et al., 1980). No significant transforming activity was shown by povidone–iodine, iodine or potassium iodide in the Balb/c 3T3 transformation assay (Kessler et al., 1980). Silver iodide did not cause an increase in sister chromatid exchange in human lymphocytes (Eliopoulos & Mourelatos, 1998).

5.6 Mode of action

The mechanism by which excess iodide produces hypothyroidism is not completely understood. It has been proposed that excess iodide inhibits the iodination of thyroglobulin in the thyroid gland, and inhibits the release of T4 and T3 from the gland (Pisarev & Gärtner, 2000). As a consequence, TSH release is stimulated, leading to increased serum levels. Hypertrophy of the thyroid gland is an additional potential effect that is known to accompany iodide-induced suppression of the thyroid gland (ATSDR, 2004).

6 Overall database and quality of evidence

6.1 Summary of health effects

Current evidence from human studies suggests that oral intake of iodine at levels greater than 1.8 mg/day for 14–28 days is associated with changes in serum T4 and TSH levels and TSH response to thyrotropin-releasing hormone without significant symptoms of thyroid dysfunction (Gardner, Centor & Utiger, 1988; Paul et al., 1988; Chow et al., 1991; Robison et al., 1998). However, these studies used a limited number of subjects (sample sizes ranged from 9 to 30, with one or both sexes) and short duration of exposure. A lack of longer-term data at this exposure level means that it is unclear whether thyroid dysfunction would become apparent with prolonged exposure. However, a study of Peace Corps volunteers (Pearce et al., 2002), showed a positive relationship between thyroid dysfunction and intake of iodine at 50 mg/day over 32 months. This provides supporting evidence for an effect on thyroid function of high intakes of iodine (well above 1.8 mg/day).

Limited data (from both human and animal studies) suggest that the bioavailability of iodine in foods and water is high, with absorbed iodine being rapidly distributed, including across the placenta. Iodine is stored in the thyroid gland and used for the synthesis of thyroid hormones (T4 and T3). Excess iodine is mainly excreted in the urine; very small amounts are excreted in sweat, faeces and exhaled air, and secreted into human breast milk.

The thyroid is the main target of iodine toxicity. However, a threshold level for inducing thyrotoxicosis has not been established, and available data are inadequate to establish a dose–response relationship. Following chronic exposure to excess iodine, thyroid function can be disrupted, leading to hypothyroidism (with or without goitre), hyperthyroidism, and changes in the incidence and types of thyroid malignancies. Measures of serum thyroid hormone levels (T3, T4 and TSH) are used as indicators of iodine disturbances. In rats, a no-adverse-effect level (NOAEL) for iodine of 10 mg/L for the most sensitive end-point of thyroid hormone imbalance following 100 days of treatment was identified based on a decrease in T3 levels and an increase in the T4:T3 ratio (Sherer, Thrall & Bull, 1991). It should be noted that rats are much more sensitive to thyroid hormone imbalance than humans (McClain, 1992).

Iodine-induced hypothyroidism in humans can produce neurological effects (delayed or deficient brain and neuromuscular development) in sensitive populations, particularly in the fetus and newborn infants. Hyperthyroidism in humans can be associated with accelerated growth (EC, 2002). Dysfunction of the thyroid in humans has also been associated with reproductive disruptions. A NOAEL for iodine 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 in the same study (based on no supported changes at any dose level) (EC, 2002).

Iodine is not classifiable as a human carcinogen, according to the International Agency for Research on Cancer. Chronic iodine exposure has been associated with metaplasia of the thyroid, considered to occur via a non-genotoxic mechanism.

The adverse effects associated with high levels of iodine intake are linked to disruption of thyroid hormone metabolism and the thyroid–pituitary axis, and the compensatory mechanisms that protect this metabolism from 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. Members of the general population who are vulnerable to iodine toxicity include pregnant and lactating women, and neonates.

6.2 Quality of evidence

The database of information regarding adverse health effects following oral exposure to iodine is fairly robust for humans, but less complete for animals. Knowledge gaps related to iodine include:

- a threshold level for hyperthyroidism in humans and animals (noting the greater sensitivity of rats to thyroid disturbances);
- reproductive, developmental, neurological and carcinogenic effects in humans and animals following oral exposure (including dose–response relationships);
- the mechanisms by which iodine induces thyroid autoimmunity;
- knowledge to inform cases in which autoimmunity affects observed thyroid gland responses; and
- the doses at which iodine deficiency causes effects on the thyroid compared with the doses causing toxicity.

7 Practical considerations

7.1 Analytical methods and achievability

Iodide concentrations in water are normally determined by a titrimetric procedure, which can be used for solutions containing iodide at 2–20 mg/L. A leuco crystal violet method may also be used to determine iodide or molecular iodine in water. This photometric method is applicable to iodide concentrations of 50–6000 µg/L; the detection limit for iodine is 10 µg/L (US EPA, 1983; APHA, 1989; ATSDR, 2004).

7.2 Source control

Source control measures are not warranted, since iodine is unlikely to be found at more than trace levels in source water.

7.3 Treatment methods and performance

Iodine can be used as a disinfectant rather than removed as a contaminant; see WHO (2018) for more information. As noted above, iodine occurs naturally in water in the form of iodide. Disinfection of iodide-containing water by adding chlorine or chloramine can result in the production of iodinated disinfection by-products (I-DBPs); most often, these are formed during chloramination when complete oxidation is prevented. I-DBPs are occasionally detected in drinking-water from treatment plants located in coastal saltwater areas (Weinberg, Krasner & Richardson, 2002). As with all disinfection by-products (DBPs), their concentrations in drinking-water can be reduced at the treatment plant by removing the natural organic matter

from the water before the disinfection process occurs. It is critical that any method used to control DBP levels does not compromise the effectiveness of disinfection.

8 Conclusions

Iodine is an essential dietary element for mammals. It is required for the synthesis and function of the thyroid hormones T4 and T3, and is the precursor of iodotyrosines. A guideline value (GV) was not derived, since exposures of the general population to iodine through drinking-water should be low. Iodine is unlikely to be found at more than trace concentrations in source water. It is not recommended for use as a primary disinfectant, because of the lack of knowledge on long-term toxic effects of iodine consumption, on the maximum "safe" dietary dose and on the maximum "safe" period of consumption for iodine-treated water (WHO, 2018).

Considerable controversy exists about the maximum "safe" dietary dose of iodine, which is in the range of 500–1000 µg/day in healthy adults (8–16 µg/kg bw/day for a 60 kg adult). Further, the available data are inadequate to establish a linear and temporal dose–response relationship between iodine intake and altered thyroid function in humans (WHO, 2018). Currently, therefore, there is insufficient toxicological information to identify a threshold in humans and/or animals for the induction of thyrotoxicosis by iodine, from which a GV could be derived. In addition, humans and rats differ in their sensitivity to thyroid hormone imbalance (McClain, 1992), precluding use of animal data. It is also not appropriate to derive a drinking-water health-based value for iodine based on data from drinking-water studies in rats for iodide, because the effects of iodine on thyroid hormone concentrations in the blood differ from those of iodide (Thrall & Bull, 1990; Sherer, Thrall & Bull, 1991; Robison et al., 1998).

This document focuses on information on the health effects of iodine to derive a GV. An evaluation of iodine for use as a drinking-water disinfectant is included in WHO (2018) and is briefly summarized here. As noted above, since iodine is not recommended for use as a primary disinfectant (WHO, 2018), lifetime exposure to iodine from water disinfection in municipal supplies is unlikely. However, iodine can be used as a point-of-use disinfectant for drinking-water. Resin-based disinfection devices that result in low residual concentrations of iodine (e.g. those using resins with carbon filters achieving residual levels of 10 µg/L) can be used over extended periods by euthyroid individuals. Use of other iodine disinfection techniques that result in higher residual concentrations of iodine (e.g. solutions or tablets, and resins without carbon filters) should be for shorter-term use and only by euthyroid individuals. Iodine disinfectants should not be used by high-risk members of the population, including pregnant women, infants and young children, and another disinfectant should be sought (for further information, see WHO, 2018). However, because of the public health significance of microbiologically unsafe water, disinfection should not be compromised. If iodine is the only disinfectant available, its use should be limited to as short a time as possible, and an alternative disinfectant sought.

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