Iodine in Drinking-water

Draft Background document for development of WHO Guidelines for Drinking-water Quality

26 September 2019
Preface

To be updated by WHO Secretariat
Acknowledgements

The first draft of the background document on chromium in drinking-water for the development of the WHO Guidelines for Drinking-water Quality was prepared by Dr Ruth Bevan, Independent Consultant.

To be updated by WHO Secretariat
## Abbreviations used in the text

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AI</td>
<td>Adequate Intake</td>
</tr>
<tr>
<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry</td>
</tr>
<tr>
<td>bw</td>
<td>body weight</td>
</tr>
<tr>
<td>EAR</td>
<td>Estimated Average Requirements</td>
</tr>
<tr>
<td>EFSA</td>
<td>European Food Safety Authority</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>I</td>
<td>iodide</td>
</tr>
<tr>
<td>I₂</td>
<td>elemental iodine</td>
</tr>
<tr>
<td>HIO</td>
<td>hypoiodous acid</td>
</tr>
<tr>
<td>LD₅₀</td>
<td>median lethal dose</td>
</tr>
<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse-effect level</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-adverse-effect-level</td>
</tr>
<tr>
<td>PMTDI</td>
<td>Provisional Maximum Tolerable Daily Intake</td>
</tr>
<tr>
<td>RDA</td>
<td>Recommended Daily Allowance</td>
</tr>
<tr>
<td>T₃</td>
<td>triiodothyronine</td>
</tr>
<tr>
<td>T₄</td>
<td>thyroxine</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
</tbody>
</table>
Table of Contents

1.0 EXECUTIVE SUMMARY ................................................................. 1
2.0 GENERAL DESCRIPTION ............................................................. 1
  2.1 Identity ..................................................................................... 1
  2.2 Physicochemical properties ....................................................... 1
  2.3 Organoleptic properties ............................................................ 1
  2.4 Major uses ............................................................................... 2
3.0 ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE .................. 2
  3.1 Water ....................................................................................... 2
  3.2 Food ......................................................................................... 2
  3.3 Air ............................................................................................ 2
  3.4 Estimated total exposure and relative contribution of drinking-water 2
4.0 TOXICOKINETICS AND METABOLISM IN ANIMALS AND HUMANS 3
  4.1 Absorption ............................................................................... 3
  4.2 Distribution ............................................................................. 3
  4.3 Metabolism ............................................................................. 3
  4.4 Elimination ............................................................................. 3
5.0 EFFECTS ON HUMANS ................................................................. 3
  5.1 Requirements .......................................................................... 4
  5.2 Acute exposure ....................................................................... 5
  5.3 Short-term exposure (≤ 90 days) ................................................ 5
  5.4 Long-term exposure (≥ 90 days) ................................................ 6
6.0 EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS 8
  6.1 Requirements .......................................................................... 8
  6.2 Acute exposure ....................................................................... 8
  6.3 Short-term and subchronic exposure (≤ 90 days) ....................... 8
  6.4 Long term exposure (≥ 90 days) .............................................. 8
  6.5 In vitro systems ....................................................................... 10
  6.6 Mode of Action ....................................................................... 10
7.0 OVERALL DATABASE AND QUALITY OF EVIDENCE ................... 10
  7.1 Summary of Health Effects ....................................................... 10
  7.2 Quality of Evidence .................................................................. 11
8.0 PRACTICAL CONSIDERATIONS ..................................................... 12
  8.1 Analytical methods and achievability ....................................... 12
  8.2 Source Control ........................................................................ 12
  8.3 Treatment methods and performance ...................................... 12
9.0 CONCLUSIONS ............................................................................ 12
10.0 APPENDICES .............................................................................. 13
  10.1 References ............................................................................. 13
1.0 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 with the diet being 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%).

Guidance levels for iodine intake differ with age, gender and pregnancy/breast-feeding status. Adequate intakes of between 70 and 200 µg/day and upper total intake levels of 1,100 µg/day have been published. The bioavailability of iodine from food and water is high and absorbed iodine is rapidly distributed. The thyroid gland is the main storage organ and target of iodine toxicity, with exposure to excess iodine leading to hypothyroidism (with or without goitre), hyperthyroidism and changes in the incidence and types of thyroid malignancies.

There is currently insufficient toxicological information to identify a threshold in humans and/or animals for the induction of thyrotoxicosis by iodine, from which a guideline value could be derived. It is considered inappropriate to derive such a value using the more robust toxicological dataset for iodide as data from drinking-water studies in rats indicate that the effects of iodine on thyroid hormone concentrations in the blood differ from those of iodide. Levels of iodine found in drinking water are generally low. Although higher levels of exposure may occur in specific instances when iodine is used as a drinking water disinfectant, extended periods of exposure are considered unlikely, and a guideline value for iodine is not recommended at this time.

2.0 GENERAL DESCRIPTION

2.1 Identity

CAS no.: 7553-56-2 Molecular formula: I₂

2.2 Physicochemical properties

Some physicochemical properties of iodine are shown in Table 1.

Table 1. Physicochemical properties of iodine

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling point</td>
<td>184.4 °C</td>
</tr>
<tr>
<td>Melting point</td>
<td>113.5 °C</td>
</tr>
<tr>
<td>Density</td>
<td>4.93 g/cm³ at 25 °C</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>40 Pa at 25 °C</td>
</tr>
<tr>
<td>Water solubility</td>
<td>0.34 g/litre at 25 °C</td>
</tr>
<tr>
<td>Log octanol–water partition coefficient</td>
<td>2.49</td>
</tr>
</tbody>
</table>

¹Sources: Ruth (1986), ATSDR (2004), HSDB (2018), ToxNet (2018); conversion factor in air: 1 ppm = 10 mg/m³

2.3 Organoleptic properties

The taste and odour thresholds for iodine are 0.147–0.204 mg/litre in water and 9 mg/m³ in air (Ruth, 1986).
2.4 Major uses
Iodine is generally used as an antiseptic for skin wounds, as a disinfecting agent in hospitals and laboratories, in pharmaceuticals and in photographic developing materials. 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 & Hollowell, 2000).

3.0 ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE
The oceans are the most important source of natural iodine in the air, water and soil, with weathering of rock and volcanic activity also leading to the release of iodine. Iodine occurs naturally in water in the form of iodide (I⁻), which is largely oxidized to iodine during water treatment. Once elemental iodine (I₂) is added to water, it hydrolyses in a pH-dependent manner to form hypoiodous acid (HOI) and iodide (Lengyel et al., 1993). The overall stoichiometry of iodine hydrolysis between pH 2 and 7 is:

\[ \text{I}_2 + \text{H}_2\text{O} \leftrightarrow \text{HOI} + \text{I}^- + \text{H}^+ \]

3.1 Water
Iodine occurs naturally in water in the form of iodide. The average concentration of iodine in seawater, rain water, and rivers and lakes is 45-60 µg/litre, 0.5-5.0 µg/litre, and 0.5-20 µg/litre, respectively (Whitehead, 1984). Human exposures to iodine through drinking-water are typically too low to provide for significant uptake of iodine. The mean concentration of total iodine in drinking-water in the USA is 4 µg/litre, and the maximum concentration is 18 µg/litre (ATSDR, 2004). This is presumably predominantly iodide.

3.2 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 are not generally the main constituents of the majority of diets, the largest sources of iodine in the human diet come from 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 et al., 2008). The adequate dietary iodine requirement for adults has been recommended as 150 µg/day (EFSA, 2004).

3.3 Air
Iodine in the oceans can enter the air from sea spray or iodine gases where it combines with water or particulates to enter the soil or surface water. Iodine that deposits on vegetation will be washed to the ground during rainfall. Much smaller amounts of iodine can enter the air during the burning of coal or fuel oil. The average concentration of iodine in the atmosphere has been estimated as 10 – 20 ng/m³ (Whitehead, 1984). Normal human respiratory exposure to iodine has been estimated to be 5 µg/day from an atmospheric exposure of 0.7 µg/m³ (ATSDR, 2004).

3.4 Estimated total exposure and relative contribution of drinking-water
The human diet is the major source of exposure to iodine for the general human population.
Additional exposure to iodine may occur through drinking-water and pharmaceuticals. At a concentration of 4 µg/litre in drinking-water, the additional adult human daily intake will be around 8 µg of iodine, on the assumption that 2 litres of drinking-water are consumed per day. The contribution to total exposure from drinking-water is therefore assumed to be low (around 5%).

4.0 TOXICOKINETICS AND METABOLISM IN ANIMALS AND HUMANS

4.1 Absorption
Iodine is readily absorbed through ingestion and inhalation, with dermal absorption being extremely low (< 1% of applied dose). Iodine ingested in the form of water-soluble salts shows 100% absorption from the gastrointestinal (GI) tract; inorganic iodine or 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 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). Iodide absorption is reduced in the presence of humic acids in drinking-water (Gaitan, 1990), and of chlorate, perchlorate thiocyanates, isothiocyanates, nitrates, fluorides, calcium, magnesium and iron in food and water (Übom, 1991).

Dietary iodine is converted into the iodide ion before it is absorbed (FAO/WHO, 2001). Molecular iodine vapour is also converted into iodide before absorption (ATSDR, 2004).

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

4.3 Metabolism
Iodine undergoes rapid conversion to iodide (Morgan et al., 1967a,b; Black & Hounam, 1968) which is then transported by the sodium iodide symporter to the thyroid and utilised for the production of triiodothyronine (T3) and thyroxine (T4) hormones.

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

5.0 EFFECTS ON HUMANS
As an essential element, many authoritative reviews concern the effects of iodine deficiency with the aim of establishing adequate dietary intakes (FAO/WHO, 2001; IOM, 2001; EVM,
2003; EFSA, 2014). The US Agency for Toxic Substances and Disease Registry (ATSDR) has published a toxicological profile for iodine that is focused on the 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 of excess iodine on human health and is used as a basis for the information given below (ATSDR, 2004). It is of note that physiological adaptations to pre-existing background dietary intake of iodine are likely to impact on the responses to increased levels of iodine, as detailed in the following sections.

5.1 Requirements

Iodine is an essential dietary element for mammals that is required for the synthesis and function of the thyroid hormones, T4 and T3, 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; WHO, 2018). Several authoritative bodies have determined upper intake levels for iodine, which can inform potentially toxic levels, as summarised in Table 1 below.

Table 1. Recommended upper intake levels for iodine (adults)

<table>
<thead>
<tr>
<th>Authoritative Body</th>
<th>Upper Level</th>
<th>Basis for UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Council for Responsible Nutrition 2013 (CRN 2013)</td>
<td>500 µg/day supplemental intake (8 µg/kg bw per day for a 60 kg adult); 1000 µg/day total intake (17 µg/kg bw per day for a 60 kg adult)</td>
<td>Absence of adverse effects in healthy adults given 500 µg of supplement (Gardner et al., 1988; Paul et al., 1988; Chow et al., 1991).</td>
</tr>
<tr>
<td>Expert Group on Vitamins and Minerals 2003 (EVM, 2003)</td>
<td>Guidance level – 500 µg/day supplemental intake (8 µg/kg bw per day for a 60 kg adult); 930 µg/day total intake (16 µg/kg bw per day for a 60 kg adult)</td>
<td>Absence of adverse effects in healthy adults given 500 µg of supplement (Gardner et al., 1988; Paul et al., 1988; Chow et al., 1991).</td>
</tr>
<tr>
<td>European Commission Scientific Committee on Food, 2002 (EC, 2002)</td>
<td>600 µg/day total intake (10 µg/kg bw per day for a 60 kg adult)</td>
<td>Elevated TSH(^1) levels at 1,700 µg/day iodine from all sources in a healthy adult population (Laurberg et al., 1998). UL derived by applying a UF of 3 to the LOAEL.</td>
</tr>
<tr>
<td>Institute of Medicine (IOM, 2001)</td>
<td>1,000 µg/day total intake (18 µg/kg bw per day for a 60 kg adult)</td>
<td>Elevated TSH(^1) levels at 1,700 µg/day iodine from all sources in a healthy adult population (Laurberg et al., 1998). UL derived by applying a UF of 1.5 to the LOAEL.</td>
</tr>
<tr>
<td>Joint FAO/WHO Expert Committee on Food Additives (JECFA; WHO, 1988, 1994)</td>
<td>1 mg/day (17 µg/kg bw per day for a 60 kg adult)</td>
<td>Provisional Maximum Tolerable Daily Intake (PMTDI) based on the tolerance of high doses of iodine in healthy iodine-replete adults; does not include neonates or young infants</td>
</tr>
</tbody>
</table>

\(^1\)TSH – thyroid stimulating hormone – 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 over 54 countries\(^1\). The IOM has published Adequate Intake (AI) levels for infants (0–12 months) of between 110 and 130 µg/day of iodine. In addition, gender and age specific Estimated Average Requirements (EAR) and Recommended Daily Allowances (RDA) of between 65 – 150 µg/day of iodine have been established for ages 1 year to adult. In pregnancy and lactation, the EAR and RDA rise to between 160 – 290 µg/day of iodine. Similarly, the European Food Safety Authority (EFSA) have also published AIs of between 70 and 200 µg/day, dependant on age, gender and pregnancy/breast-feeding status (EFSA, 2014).

5.2 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 shock occurring in severe cases (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 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/kg bw) have been reported to be fatal. Exposure to iodine vapour results in lung, eye, and skin irritation, while high concentrations rapidly lead to pulmonary oedema (ATSDR, 2004).

In rare instances, a hypersensitisation 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).

5.3 Short-term exposure (≤ 90 days)

The short-term exposure studies for 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 and regulation of 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, reproductive systems are derived as a result of disorders of the thyroid gland. Effects on the thyroid gland can occur in all ages and are classified into three types:

- Hypothyroidism – refers to the condition whereby thyroid hormone is reduced. Can present with or without goiter which results from hypothyroidism of the thyroid in response to a reduced level of serum TSH. Hypothyroidism is characterised by reduced circulating T4 and/or T3 in the presence of elevated TSH; Hyperthyroidism - refers to an excessive production and/or secretion of thyroid hormones, characterised by elevated circulating levels of T4 and/or T3. The clinical manifestation of hyperthyroidism is thyrotoxicosis; and

\(^1\) [http://www.who.int/nutrition/topics/idd/en/][accessed October 2018]
• Thyroiditis – refers to inflammation of the thyroid gland, often presenting as a result of thyroid gland autoimmunity.

ATSDR reviewed a number of studies that assessed adverse effects following an increased oral intake of iodine over the short-term (≤ 90 days). In healthy euthyroid male adults, dietary iodine intakes up to a total of 800 µgI/day are not associated with suppression of the thyroid gland. Although intakes as high as 4,800 µgI/day did induce statistically significant changes in T3, T4 and/or TSH, these were not outside of normal ranges and did not produce clinically relevant adverse effects (Jubiz et al., 1977; Paul et al., 1988; Gardner et al., 1988; Chow et al., 1991; Namba et al., 1993; Robison et al., 1998; NSF, 2002).

5.4 Long-term exposure (≥ 90 days)

5.4.1 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 per day) is considered by some authors to be excessive, but daily doses of 50–80 mg (0.8–1.3 mg/kg bw per day) are consumed by some Japanese 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 thyroid hormone production and secretion (ATSDR, 2004; Sand 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 iodised bread in The Netherlands raised the daily intake by 120-160 µg iodine resulting in an increase in the incidence of hyperthyroidism (EFSA, 2014). The consumption of milk in the winter (rich in iodine due to farming practices) in Cambridgeshire, 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 in the following spring/summer periods (Nelson & Phillips, 1985).

When considered in isolation, 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 per day for 26 weeks (ATSDR, 2004). In a 5-year study of prison inmates consuming water containing iodine at a concentration of 1 mg/litre (approximately 0.03 mg/kg bw per day), no cases of hyper- or 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 after high intakes of iodine (50 mg/day or approximately 0.8 mg/kg bw per day assuming 60 kg bw) for a prolonged period of over 32 months (Pearce et al., 2004).
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 iodine uptake decreased by 54–99% in patients with thyroid disease but only by 8–54% in normal controls (ATSDR, 2004).

Eight cases 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 per day) in individuals taking iodide as an expectorant in the treatment of asthma. No direct evidence of a cause-and-effect relationship between iodide exposure and health effects during pregnancy was reported.

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).

5.4.2 Neurological effects
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, 2000a). 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 may experience neuromuscular disorders, including myopathy, periodic paralysis, myasthenia gravis, peripheral neuropathy, tremor, and chorea (Boyages, 2000b).

5.4.3 Reproductive and developmental effects
Chronic exposure to excess iodine has been shown to disrupt reproductive function, secondary to 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 et al., 2010).

Reproductive impairments associated with hyperthyroidism include amenorrhea, 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; Krassas et al., 2010).

Exposure to iodine may give rise to developmental defects, secondary to thyroid gland dysfunction (Boyages, 2000a,b). Hypothyroidism may be associated with impairment in neurological development of the foetus or growth retardation (Boyages, 2000a,b; Snyder, 2000a; Krassas et al., 2010).
5.4.4 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 be a contributing factor in 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;).

6.0 EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

6.1 Requirements

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

6.2 Acute exposure

The acute oral 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) (Stokinger, 1981).

6.3 Short-term and subchronic exposure (≤ 90 days)

Increased thyroid weight was reported as a consequence of iodide administration via the diet in female rats (0.15 or 0.23 mg/kg bw per day for 10 weeks); this effect was also noted in the non-standard experimental species of pigs (3 or 218 mg/kg bw per day) and calves (female) (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 the rat and in chickens. An inbred strain of rat, the BB/Wor rat that shows a high rate of spontaneous autoimmune thyroiditis, showed an increase in incidence (77% compared to a control rate of 30%) following exposure to iodide in drinking-water at a concentration of 85 mg/kg bw per day for 8 weeks. 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/litre, 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).

6.4 Long term exposure (≥ 90 days)

6.4.1 Systemic effects

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

6.4.2 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).
6.4.3 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 in the diet for 12 days in the latter part of gestation. Length of labour (parturition) was also increased (Ammerman et al., 1964a). Although no effects were observed on ovulation rate, implantation rate, or foetal development in female rats given doses of 0, 500, 1000, 1500, or 2000 mg of iodide (as potassium iodide) per kg of diet during gestation and lactation, a dose-related decrease in survival rate for 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 between 250 and 1000 mg/kg feed for 2-5 days before parturition. Pregnant hamsters exposed to 2500 mg iodine/kg feed similarly showed a decreased weaning weight of pups due to reduced maternal feed intake. Litters from pregnant pigs receiving diets containing 1500 or 2500 mg iodine/kg feed (i.e. toxic dietary levels in rats and rabbits) for the 30 days prior to parturition (Arrington et al., 1964).

Hyperthyroidism 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). Metabolism was severely disturbed in foals born to mares receiving excess iodine (48–432 mg of iodine per 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).

6.4.5 Genotoxicity and carcinogenicity

Iodine has not been classified as a human carcinogen due to a lack of available data. 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 indicate contrary findings (Zimmermann & Galetti, 2015; Cao et al., 2017).

The carcinogenicity of iodine was evaluated in male Wistar rats fed iodine deficient (0.5 mg/kg), adequate (12 mg/kg) or rich (200 mg/kg) diets for up to 10 months (estimated as 0.05, 1.2 or 20 mg/kg bw per day). From Month 2, rats were also administered weekly injections of the carcinogen N-nitrosobis (2-hydroxypropyl)amine. In the iodine adequate and 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 promoting effect of TSH (Yamashita et al., 1990).

Metaplasia, secondary to lobular impairment, of the thyroid was reported in rats given potassium iodide in their drinking-water for two years, with intakes estimated as 0, 0.6, 5.3 or 53 mg/kg bw per day. The authors considered that the metaplasia lesions may develop into carcinoma via a non-genotoxic, proliferation-dependent mechanism (EVM, 2003).
6.5 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).

6.6 Mode of Action

The mechanism by which excess iodide produces hypothyroidism is not completely understood. It has been proposed that when in 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 thyroid gland suppression (ATSDR, 2004).

7.0 OVERALL DATABASE AND QUALITY OF EVIDENCE

7.1 Summary of Health Effects

Current evidence from human studies suggests that oral intake at levels > 1.8 mg/day for 14-28 days was associated with changes to serum T4 and TSH levels and TSH response to TRH without significant symptoms of thyroid dysfunction (Gardner et al., 1988; Paul et al., 1988; Chow et al., 1991; Robinson et al., 1998), recognizing the limited number of subjects (i.e. sample sizes ranged from 9 to 30 in one or both sexes) and short exposure duration. It is unclear if thyroid dysfunction would become apparent with prolonged exposure due to the lack of longer-term data at this exposure level. 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 may well occur high intakes well above 1.8 mg/day.

Limited data (both human and from animal studies) suggest that the bioavailability of iodine from foods and water is high, with absorbed iodine being rapidly distributed, including across the placenta. Iodine 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.

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, disruption of thyroid function can occur, 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. A NOAEL of 10 mg/L iodine for the most sensitive endpoint in rats of thyroid hormone imbalance following 100 days of treatment was identified based on a decrease in T3 levels and increase in the T4/T3 ratio (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 (McClain, 1992).

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 can be associated with accelerated growth (EC, 2002). Dysfunction of the thyroid in humans has also been associated with reproductive disruptions and a NOAEL of 10 mg/kg bw per day iodine has been derived for reproductive and developmental toxicity in rats administered iodine by oral gavage (based on no observed toxicity at any dose level). A NOAEL for parental toxicity of 10 mg/kg bw per day iodine 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 (IARC). 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 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. Vulnerable members of the general population to iodine toxicity include pregnant and lactating women, and neonates.

### 7.2 Quality of Evidence

The database of information regarding adverse health effects in humans following oral exposure to iodine is fairly robust, with that in animals being less complete. Particular gaps related to iodine include:

- Identification of a threshold level for hyperthyroidism in humans and animals (noting the increased sensitivity of rats to thyroid disturbances);
- Insufficient information relating to reproductive, developmental, neurological, and carcinogenic effects in humans and animals following oral exposure (including dose-response relationships);
- The incomplete knowledge of the mechanisms by which iodine induces thyroid autoimmunity.
- Inadequate information to inform the cases where autoimmunity impacts observed thyroid gland responses; and
- The doses where iodine deficiency causes effects on the thyroid compared to the doses causing toxicity.
8.0 PRACTICAL CONSIDERATIONS

8.1 Analytical methods and achievability
Iodide in water is normally determined by a titrimetric procedure which can be used for solutions containing 2–20 mg of iodide per litre. A leuco crystal violet method may be used for the determination of iodide or molecular iodine in water. This photometric method is applicable to iodide concentrations of 50–6000 µg/litre; the detection limit for iodine is 10 µg/litre (US EPA, 1983; APHA, 1989; EC, 2005).

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

8.3 Treatment methods and performance
Iodine can be used as a disinfectant rather than removed as a contaminant.

9.0 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 was not derived, since exposures to iodine by the general population through drinking-water should be low. It is unlikely to be found at more than trace concentrations in source water and it is not recommended for use as a primary disinfectant, due to the lack of knowledge on long-term toxic effects of iodine consumption, the maximum “safe” dietary dose, and the maximum “safe” period of consumption for iodine treated water (WHO, 2018).

Considerable controversy exists about the maximal “safe” dietary dose of iodine, which is in the range of 500 to 1000 µg/day in healthy adults (8-16 µg/kg bw per day based on 60 kg bw). Further, the available data are inadequate to establish a linear and temporal dose response 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 guideline value could be derived. In addition, there are known differential sensitivities between humans and rats to thyroid hormone imbalance (McClain, 1992) which preclude utilisation of animal data. It is also not considered appropriate to derive a drinking-water health-based value for iodine based on data from drinking-water studies in rats for iodide, as the effects of iodine on thyroid hormone concentrations in the blood differ from those of iodide (Sherer et al., 1991; Thrall & Bull, 1990; Robison et al., 1998).

This document focuses on the health effects information for 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. Iodine however can be used as a point of use (POU)
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 ≤ 0.01 ppm), can be used over extended periods of time 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 use 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, disinfection should not be compromised due to the public health significance of microbiologically unsafe water, and therefore if iodine is the only disinfectant available, use should be limited to as short a time as possible, and an alternative disinfectant sought.

10.0 APPENDICES

10.1 References


HSDB (2017) Hazardous Substances Data Bank of the National Library of Medicine, Bethesda, MD.


Zimmermann, MB & Galetti, V. (2105) Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. Thyroid Res. 8: 8.