

***CONSIDERATION OF MANDATORY
FORTIFICATION WITH IODINE
FOR AUSTRALIA AND NEW ZEALAND***

***SAFETY ASSESSMENT AND
RISK CHARACTERISATION REPORT***

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Summary

Iodine is an important trace element that is required for the synthesis of the thyroid hormones, thyroxine and triiodothyronine (thyronine). These hormones have a key role in influencing cellular metabolism and metabolic rate. They are also crucial to the development of the brain and nervous system.

Although iodine is an essential component of the diet, intakes in excess of physiological requirements may produce adverse effects, particularly on the thyroid gland (thyroid) and the regulation of thyroid hormone production and secretion.

Ingested iodine, in the form of iodide, is readily absorbed from the gastrointestinal tract into the circulation. The human body contains about 15 –20 g iodine in total, the majority of which is stored by the thyroid. The uptake of iodide by the thyroid is controlled by thyroid-stimulating hormone (TSH), which is highly sensitive to dietary iodine intake. At low intakes representing iodine deficiency, uptake of iodide into the thyroid is increased and at very high intakes, iodide uptake into the thyroid decreases. Once the physiological requirements for thyroid hormone synthesis have been met, the thyroid does not accumulate more iodide and any excess is excreted, primarily in the urine.

Safety Assessment and Risk Characterisation

A large number of human experimental, clinical, and epidemiological studies on the effects of excess iodine on human health have been reported and reviewed in detail by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Scientific Committee for Food (SCF), and the US Agency for Toxic Substances and Disease Registry (ATSDR). These reviews indicate there are three potential types of adverse response to excess iodine:

- disturbance of thyroid activity, which may alter the size of the thyroid and/or affect the production of thyroid hormones;
- sensitivity reactions to iodine, which are unrelated to thyroid function;
- iodine poisoning, resulting from acute intakes of large quantities (grams) of iodine. Cases of iodine poisoning are only rarely seen.

This review has focused principally on effects on the thyroid, which are regarded as the primary and most sensitive indicators of iodine toxicity. Some consideration has also been given to iodine 'allergy' and sensitivity reactions because of the widely held belief that adverse reactions to iodine-containing therapeutic substances can confer a specific cross-reactivity with iodine in foods.

Effects on the Thyroid

Excess iodine can produce an enlargement of the gland (goitre) and/or affect the production of the thyroid hormones. An under production of the thyroid hormones is referred to as hypothyroidism and may be accompanied by goitre. An over production of thyroid hormone is referred to as hyperthyroidism.

The effect on the thyroid depends on the current and previous iodine status of the individual, and any current or previous thyroid dysfunction. For example, individuals with a long history of iodine deficiency may be prone to the development of hyperthyroidism, known as iodine-induced hyperthyroidism when it is triggered by increased iodine exposure.

Particular life stages may also be more vulnerable to excess iodine. For example, the foetus and newborn infants are more susceptible than children and adults to the development of goitre and hypothyroidism. While the foetal and neonatal thyroid has a much higher fractional uptake of iodine compared to the adult thyroid, it is less able to escape the inhibitory effects of excess iodine on thyroid hormone formation, hence the greater susceptibility to goitre and hypothyroidism.

The human response to excess iodine can therefore be quite variable, although in general most people are very tolerant of excess iodine in the diet with many individuals, including young children, being able to tolerate large intakes up to 50 µg/kg/day and above. In contrast, others may respond adversely to levels close to recommended intakes (3-7 µg/kg/day). Individuals responding adversely to relatively low intake levels typically have an underlying thyroid disorder, and, in many cases, a long history of iodine deficiency.

For the majority of healthy individuals, the most sensitive endpoint for iodine toxicity is sub-clinical hypothyroidism. Sub-clinical hypothyroidism is defined as an elevated TSH concentration in the presence of thyroid hormone concentrations within the normal range of values for healthy individuals. The effect is usually transient, even if excess iodine intake continues. While not clinically adverse, such an effect, if persistent, may be regarded as an indicator of an existing risk of overt or clinical hypothyroidism.

Although there is potential for progression to clinical hypothyroidism in certain susceptible individuals, it remains uncertain as to whether a persistent state of sub-clinical hypothyroidism would, in practice, have any clinical consequences in otherwise healthy individuals.

In healthy adults, sub-clinical hypothyroidism has been associated with acute intakes of 1700-1800 µg/day (24-25 µg/kg body weight/day for a 71 kg person), and for children, has been associated with chronic intakes of 1150 µg/day (29 µg/kg/day for a 40 kg child). Chronic iodine intakes of approximately 1000 µg/day however appear to be well tolerated by healthy adults.

In the *Nutrient Reference Values for Australia and New Zealand*¹, the National Health and Medical Research Council specified an Upper Level of Intake (UL)² for iodine of 1100 µg/day in adults.

¹ This document is available online at <http://www.nhmrc.gov.au/publications/synopses/n35syn.htm>

² The highest average daily nutrient intake level likely to pose no adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases.

The UL is based on the endpoint of sub-clinical hyperthyroidism. The value for the UL has been adjusted for different age groups on a bodyweight basis. FSANZ has adopted this UL for the purpose of risk assessment for the general healthy population.

The dietary intake assessment in the Dietary Intake Assessment Report (See Supporting Document 6³) indicates that while estimated mean population intakes will remain well below the UL for iodine following the introduction of mandatory fortification, a small percentage of young children, in particular 1-3 year olds, have the potential to exceed the UL.

Although it is generally not desirable to exceed the UL, in this case the estimated worst-case iodine intakes for young children are calculated to be below a level at which adverse effects may be observed. Furthermore, evidence exists which indicates that young children are able to exceed their respective ULs by 2-3 fold without apparent adverse consequences. This, and the reversible nature of the endpoint (sub-clinical hypothyroidism), means such intakes are unlikely to represent a health and safety risk to young children, though a reduced margin of safety exists. Overall, the potential for adverse effects in the small number of young children that are estimated to exceed the UL for iodine is considered low.

For those individuals with thyroid disorders or a long history of iodine deficiency, the UL may not be applicable since these individuals may respond adversely at lower levels of intake. It has been reported that intakes in the range 3-7 µg/kg/day may be sufficient to precipitate or aggravate hyperthyroidism in these individuals. Iodine-induced hyperthyroidism typically occurs in individuals with an underlying autonomously functioning thyroid caused by either multinodular goitre or by Graves' disease. The health risk for these individuals needs to be considered separately from the general population.

An increased incidence of iodine-induced hyperthyroidism is reported to be the most common adverse effect encountered following the introduction of iodine fortification. Once iodine deficiency has been corrected however the incidence of iodine-induced hyperthyroidism typically reverts to normal levels or even below normal levels after several years. The incidence of iodine-induced hyperthyroidism is said to be significantly reduced or avoided by appropriate quality control and monitoring of the fortification programme.

In terms of the risk to the Australian and New Zealand population, the evidence indicates that mild to moderate iodine deficiency has only emerged in recent years. As a consequence, the number of individuals with autonomous multinodular goitres is expected to be quite small. Therefore, while an increase in the detectable occurrence of iodine-induced hyperthyroidism is a recognised risk following the introduction of iodine fortification, in the Australian and New Zealand context it is likely to be a rare event.

A small but finite risk exists for individuals with Graves' disease, however, such individuals will typically be under the care of a medical professional, therefore should

³ SD6: FSANZ (2008) *Dietary Intake Assessment Report – Main Report*. Available from: <http://www.foodstandards.gov.au/standardsdevelopment/proposals/proposalp1003mandato3882.cfm>

there be any exacerbation of the condition this should be detected quickly and remedial action taken.

Iodine 'Allergy' and Sensitivity Reactions

Exposure to iodine (in the form of iodide), and certain iodine-containing therapeutic/diagnostic substances, can produce a range of adverse reactions in certain sensitive individuals that are unrelated to thyroid function. Although the reactions observed appear to have an immunological basis, they are rarely IgE-mediated, therefore they cannot be regarded as true allergic reactions.

In certain sensitive individuals, oral exposure to very large doses of free iodide (>300 mg/day) has been associated with a range of adverse reactions including hives, skin lesions, oedema, and fevers. The symptoms usually cease once the excess intake is discontinued. In many cases, pre-existing disease and related drug therapy are believed to have contributed to the reaction. While these reactions appear to be a true sensitivity to iodine, they occur at very high dose levels that would not be typical from the diet, even with mandatory fortification.

A variety of mild to very severe reactions (including rare cases of anaphylactic reactions) have also been observed in certain individuals following exposure to particular iodine-containing therapeutic/diagnostic substances, such as iodinated contrast material (ICM) and iodine-based antiseptics (e.g. povidone-iodine). Despite iodine being common to both types of substances, testing has shown that the adverse reactions observed are almost certainly a reaction to the iodine-containing molecule as a whole, and not to iodine itself.

It has been suggested that a cross reactivity may exist between contrast material sensitivity and seafood allergy as a consequence of the presence of iodine. Little scientific evidence is available however to support this hypothesis. When investigated, the vast majority of adverse reactions to seafood are allergic (IgE-mediated) reactions to specific proteins, and are completely unrelated to the presence of iodine.

In conclusion, increased dietary iodine intake as a result of mandatory iodine fortification is highly unlikely to increase the risk of iodine sensitivity reactions occurring, and nor is it likely to provoke cross-reactions in people who are sensitive to iodinated contrast materials or iodine-based antiseptics or who are allergic to seafood.

1. Introduction

Although iodine is an essential component of the diet, intakes in excess of physiological requirements may produce adverse effects, particularly on the thyroid gland (thyroid) and the regulation of thyroid hormone production and secretion. This in turn can have downstream impacts on a wide variety of other organ systems, producing an array of debilitating effects in the affected individual.

The purpose of this review is to examine the potential adverse effects associated with an increased iodine intake and to identify vulnerable groups.

2. Physical and Chemical Properties

Iodine (I) is a non-metallic element belonging to the halogen family and has a molecular mass of 126.9. Iodine is a bluish-black, lustrous solid, which sublimes at room temperature into a blue-violet gas with a sharp characteristic odour. Iodine dissolves readily in alcohol, benzene, chloroform, carbon tetrachloride, ether or carbon disulfide but is only slightly soluble in water (0.03 g/100 ml at 20°C).

The chemistry of iodine can be quite complex as it can exist in a number of different valence states, is chemically reactive (although less so than other halogens) and forms various organic and inorganic compounds. The most common compounds formed are the iodides (I^-) and iodates (IO_3^-).

Thirty-six isotopes are recognised with fourteen of these yielding significant radiation. The only naturally occurring isotopes are ^{127}I , which is stable, and ^{129}I , which is radioactive. This report will concentrate on adverse effects associated with increased intake of stable iodine.

3. Toxicokinetics

3.1 Absorption

Gastrointestinal absorption of iodine is generally considered to be close to 100% after an ingested dose of soluble iodide salts, such as potassium or sodium iodide. This conclusion is based on several studies in human subjects receiving oral doses of radioiodine compounds (Fisher *et al.*, 1965; Ramsden *et al.*, 1967).

Although some absorption occurs in the stomach, the small intestine appears to be the principal site of absorption in both humans and rats (Riggs 1952, Small *et al.* 1961). The mechanism by which iodide is transported across the intestinal epithelium is not known.

Gastrointestinal absorption appears to be similar in children, adolescents and adults, as assessed from measurements of 24-hour thyroid uptakes of radioiodine

administered orally (Cuddihy, 1966; Oliner *et al.*, 1957; Van Dilla and Fulwyler, 1963). Absorption in infants however may be lower than in children and adults. Suggestive evidence for this comes from studies in which thyroid uptake of radioiodine was measured and compared in neonates who received tracer doses of radioiodine orally or by injection.

The very rapid changes in iodine status and biokinetics in the first few weeks of postnatal life however generates some uncertainty with the interpretation of these study findings (ATSDR, 2004).

Iodine incorporated into food is said to be nearly completely absorbed, however most of the dietary balance studies have only been undertaken with milk (ATSDR, 2004). Assessments of gastrointestinal absorption of iodine in other foods are not available. Little information is available on the gastrointestinal absorption of forms of iodine other than iodide. Iodine compounds such as I_2 and iodates (such as $NaIO_3$) may undergo reduction to iodide before being absorbed in the small intestine and absorption may not be complete (ATSDR, 2004).

3.2 Distribution

Once absorbed, iodide enters the circulation and is distributed throughout the extracellular fluid where it is taken up by those tissues with specialised transport mechanisms for iodide (Cavalieri, 1980). The human body contains about 15-20 g iodine in total, the majority of which (>90 %) is stored by the thyroid (Cavalieri, 1997). The concentration of iodine in serum is about 50-100 $\mu\text{g/L}$ under normal circumstances, with about 5% being in the inorganic form as iodide and the remaining 95% consisting of various organic forms of iodine, principally protein complexes of the thyroid hormones.

Other tissues that accumulate iodide include the salivary glands, gastric mucosa, choroid plexus, mammary glands, placenta, and sweat glands. The tissue distribution of iodide and organic iodine are very different and are interrelated by metabolic pathways that lead to the iodination and de-iodination of proteins and thyroid hormones.

The uptake of iodide by the thyroid is controlled by thyroid-stimulating hormone (TSH), which is secreted from the anterior lobe of the pituitary gland. In addition to stimulating iodide transport from the blood into thyroid cells, thyroid-stimulating hormone is also responsible for stimulating the oxidation of iodide to iodine, and iodine binding to tyrosine.

Iodide taken up by the thyroid is used for the production of the thyroid hormones, which are stored in the gland. Approximately 90% of the thyroid iodine content is in the organic form and includes iodinated tyrosine residues comprising the thyroid hormones thyroxine and thyronine, and their various synthesis intermediates and degradation products.

Once requirements for thyroid hormone synthesis have been met, the thyroid does not accumulate more iodide and any excess is excreted in the urine (Bender and Bender, 1997).

Children (1 and 10 year olds) appear to have a similar fractional uptake of iodide in the thyroid gland compared to adults (ATSDR, 2004). This contrasts to the situation with neonates, who have much greater fractional uptakes, although this quickly declines to the levels of adults by 5 days of age. After the first few weeks, uptake changes very little with age.

The percent turnover rates of iodine in the thyroid however does change with age, with 0-4 year olds having an apparent half-life of 20 days compared to 33 days in 4-8 year olds and 83 days in 8-12 year olds. Iodine concentration in the thyroid also increases with age with 1-2 year olds having between 95-130 μg iodine/g thyroid tissue compared to 400 μg /g in adults (Stather & Greenhalgh, 1983).

Iodide uptake into the thyroid gland is highly sensitive to iodide intake. At low intakes representing iodine deficiency, uptake of iodide into the thyroid gland is increased (Delange and Ermans, 1996). At very high intakes, iodide uptake into the thyroid gland decreases, primarily as a result of decreased iodothyronine synthesis (the Wolff-Chaikoff effect) and iodide transport into the gland (Nagataki and Yokoyama, 1996; Saller, 1998).

3.3 Metabolism

Once in the thyroid, iodide is oxidised to elemental iodine by the enzyme thyroid peroxidase (Saller, 1998). This reaction is the rate-limiting step for protein iodination and hormone synthesis. Once oxidised, iodine enters the biosynthetic pathway for thyroid hormone synthesis.

Initially iodine is incorporated into monoiodotyrosine and diiodotyrosine, which are then coupled together to form the thyroid hormones thyronine (coupling of a monoiodotyrosine and diiodotyrosine residue) and thyroxine (coupling of two diiodotyrosine residues). These reactions occur within a large glycoprotein called thyroglobulin, which is synthesised only in the thyroid gland.

TSH regulates every step in the biosynthesis of the thyroid hormones, from the concentration of iodide to the proteolysis of thyroglobulin (Cavalieri, 1980).

There is a sensitive feedback mechanism between the thyroid and the pituitary gland to maintain the levels of thyroid hormones. This is influenced by the hypothalamus, with thyrotropin-releasing hormone mediating the secretion of TSH from the pituitary.

De-iodination reactions are carried out by a family of selenoproteins. Iodotyrosine dehalogenase regenerates iodide from monoiodotyrosine and diiodotyrosine for re-use within the thyroid or release into blood, accounting for the iodide leak in the state of chronic iodine excess or certain thyroid conditions (Cavalieri, 1997). The liver contains a considerable amount of thyroxine, some of which is converted into thyronine and some excreted into the bile, and ultimately reabsorbed or excreted (Cavalieri, 1980).

3.4 Excretion

All absorbed iodine is excreted primarily in the urine and faeces, but is also excreted in breast milk, exhaled air, sweat and tears (Cavalieri, 1997). Urinary excretion normally accounts for 97% of the elimination of absorbed iodine, while faecal excretion accounts for about 1-2% (Larsen *et al.*, 1998).

The fraction of the absorbed iodide dose excreted in breast milk varies with functional status of the thyroid.

A larger fraction of the absorbed dose is excreted in breast milk in the hypothyroid state compared to the hyperthyroid state. In the hypothyroid state, uptake of absorbed iodide into the thyroid is depressed, resulting in greater availability of the absorbed iodide for distribution to the mammary gland and breast milk.

4. Toxicity of Iodine

A large number of human experimental, clinical, and epidemiological studies on the effects of excess iodine on human health have been reported. These studies will not be reviewed again in detail as they have already been subject to significant reviews by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (WHO, 1989), the European Scientific Committee for Food (SCF, 2002) and the Agency for Toxic Substances and Disease Registry (ATSDR, 2004).

JECFA concluded there are three potential types of adverse response to excess iodine. The first is disturbance of thyroid activity, which may alter the size of the gland and/or affect the production of thyroid hormones. There is also evidence to indicate that iodine (or the lack of it) may alter the pattern of thyroid malignancy. The second type of response involves sensitivity reactions, which are unrelated to thyroid gland function. The third type of response results from acute intakes of large quantities (grams) of iodine (iodine poisoning). Cases of iodine poisoning are only rarely seen.

This review will largely focus on effects on the thyroid gland, which is regarded as the primary and most sensitive indicator of iodine toxicity (ATSDR, 2004).

4.1 Disturbance of Thyroid Function

The primary effects of excessive stable iodine ingestion are on the thyroid gland and regulation of thyroid hormone production and secretion. Adverse effects on the pituitary and adrenal glands are secondary to disorders of the thyroid gland. Excess iodine can result in goitre, hypothyroidism (with or without goitre), or hyperthyroidism (thyrotoxicosis) (see Box 1 for definitions of the various terms used). The effect produced depends on the current and previous iodine status of the individual and any current or previous thyroid dysfunction (WHO, 1989).

For example, individuals exposed to low levels of iodine early in life may be prone to the development of iodine-induced hyperthyroidism if iodine exposure increases later in life. Those with underlying thyroid disease also respond more to increased iodine intake, and it appears that females are more likely to respond to excess iodine than males. The foetus and neonates are also more susceptible to excess iodine than other life-stage groups.

The most common cause of hyperthyroidism is Graves' disease (diffuse toxic goitre), an autoimmune disease where the immune system produces antibodies that stimulate the thyroid-stimulating hormone receptors of the thyroid gland resulting in the non-suppressible overproduction of thyroid hormone. This causes the thyroid gland to become enlarged. In the elderly, a condition called toxic nodular goitre may cause hyperthyroidism.

Toxic nodular goitre occurs when one or more small benign tumours in the thyroid gland produce excess thyroid hormones.

Terminology

Goitre refers to an enlargement of the thyroid that is usually visible as a swelling in the anterior portion of the neck. A number of different types of goitres are known to occur.

Simple or non-toxic goitre is an enlargement of the thyroid gland that is not associated with overproduction of thyroid hormone, inflammation or malignancy, whereas *toxic goitre* is one involving excessive production of thyroid hormone. Thyroid enlargement can be uniform (diffuse goitre) or the gland can become enlarged as a result of the occurrence of one or more nodules (nodular goitre).

The two most common causes of simple or non-toxic goitre are iodine deficiency or the ingestion of large quantities of goitrogenic foods or drugs, i.e. substances that inhibit the absorption and/or utilisation of iodine by the thyroid, or otherwise interfere with normal thyroid hormone synthesis. In these cases, the thyroid gland is unable to meet the demands of the body (i.e., because of an inadequate supply of iodine) and enlarges to compensate. Enlargement of the gland is usually sufficient to overcome mild impairment to hormone production.

Goitre can also be associated with both **hypothyroidism** and **hyperthyroidism**.

Hypothyroidism refers to the diminished production of thyroid hormone leading to clinical manifestations of thyroid insufficiency and can occur with or without goitre. Typical biomarkers of hypothyroidism are a depression in the circulating levels of thyroxine and/or thyronine below their normal ranges. This is usually, but not always, accompanied by an elevation of TSH above the normal range.

The most common cause of hypothyroidism is Hashimoto's disease (or lymphocytic thyroiditis). Hashimoto's disease is an autoimmune disease in which abnormal antibodies are produced that impair the ability of the thyroid to produce thyroid hormone. The pituitary gland responds by producing more TSH; this may cause the thyroid gland to enlarge.

Hyperthyroidism is where accelerated thyroid hormone biosynthesis and secretion by the thyroid gland produce thyrotoxicosis. The term *thyrotoxicosis* refers to the hypermetabolic clinical syndrome resulting from serum elevations in thyroid hormone levels, specifically free thyroxine, triiodothyronine, or both.

The terms hyperthyroidism and thyrotoxicosis are often used interchangeably but are not synonymous. That is, while many patients have thyrotoxicosis caused by hyperthyroidism, other patients may have thyrotoxicosis caused by inflammation of the thyroid gland, which causes release of stored thyroid hormone but not accelerated thyroid hormone synthesis. Thyrotoxicosis may also be caused by ingestion of exogenous thyroid hormone.

4.1.1 Iodine-Induced Hypothyroidism

The human body has a number of adaptive mechanisms for dealing with excess iodine. These mechanisms tend to be inhibitory in nature and generally do not significantly affect thyroid function.

The most well known of these is the *Wolff-Chaikoff effect* (Wolff *et al.*, 1949), where large dietary or therapeutic intakes of iodine can inhibit organic iodine formation (the binding of iodine to tyrosine in the thyroid), producing a decrease in the circulating thyroid hormone levels, and a subsequent increase in TSH.

The effect is typically transient, even if the excess intake continues, with most people being able to escape from the inhibition without a clinically significant change to circulating hormone levels. Escape is thought to be the result of the down regulation of the sodium-iodide symport, i.e. the iodide transport mechanism in the thyroid gland, leading to a decrease in intrathyroidal iodine and the resumption of normal thyroid hormone synthesis (ATSDR, 2004). Most individuals are therefore able to adapt to excess iodine.

Some individuals fail to escape from the Wolff-Chaikoff effect and typically develop goitre and may also become hypothyroid. These effects result from a persistent inhibition of thyroid hormone synthesis and release. A failure to escape the Wolff-Chaikoff effect is thought to occur primarily in susceptible individuals (ATSDR, 2004). Susceptible individuals include: fetuses and neonates; patients who have autoimmune thyroiditis; patients with Grave's disease previously treated with iodine; women who have post-partum thyroiditis; or those who have subacute thyroiditis. The hypothyroidism resolves once the excess iodine intake is discontinued. Spontaneous recovery usually occurs within 2-3 weeks, although some individuals may develop primary hypothyroidism.

4.1.1.1 Effects in Adults

A number of studies have examined the acute effects of increased intakes of iodine on the thyroid hormone status of adults (Gardner *et al.*, 1988; Georgitis, *et al.*; 1993; Namba *et al.*, 1993; Paul *et al.*, 1988; Robison *et al.*, 1998). These studies suggest that acute (14 days) iodine exposures of 1500 µg/day (21 µg/kg/day) above the pre-existing dietary intake can be tolerated without producing a clinically adverse change in thyroid hormone levels, although such doses may produce a reversible depression in serum thyroxine concentration and a small rise in serum TSH concentrations, both within the normal range for healthy individuals.

Changes in thyroid hormone levels within normal ranges are not considered to be clinically adverse; however, they are indicative of a subtle suppression in thyroid hormone release. Based on estimates of the background dietary intakes of the subjects in these studies, in most cases estimated from measurements of urinary iodide excretion, the total iodide intakes producing sub-clinical hypothyroidism in healthy adults were around 1700-1800 µg/day (24-25 µg/kg/day) (Gardner *et al.*, 1988; Paul *et al.*, 1988).

Acute intakes of approximately 700 µg/day (10 µg/kg/day) had no detectable effect on thyroid hormone status in healthy individuals. One study also found no evidence

of disturbances in thyroid hormone status in 6 healthy euthyroid⁴ males who received doses of 20 mg/day (0.3 mg/kg/day) (Robison *et al.*, 1998), suggesting that, at least under certain conditions, exposure levels >10-24 µg/kg/day may be tolerated by some individuals.

Two studies have been conducted in prison populations exposed to iodine through iodination of the water supply. In a study by Freund *et al.*, (1966), the health and thyroid function of representative subjects of a prison population were assessed before and during usage of iodinated water for nine months. Water containing 1000 µg/L iodine induced a marked decrease in the uptake of radioactive iodine but protein bound iodine levels did not increase significantly until the iodine concentration was increased to 5000 µg/L. No information on actual intake is provided but it has been assumed that water consumption would have been about 1-2 litres/day (WHO, 1989). In another study, iodination of a prison water supply at a concentration of 500-750 µg/L (estimated intake 1000-2000 µg/day) for up to 15 years did not result in any change to serum thyroxine levels (Thomas *et al.*, 1978).

These studies suggest that 1000 µg iodine/day is safe for the majority of the population and support the findings from short-term studies. On the basis of these long-term studies, JECFA set a provisional maximum tolerable daily intake (PTDI) of 17 µg/kg bodyweight for iodine from all sources (WHO, 1989).

A study was initiated in China in 1999 to investigate iodine-induced thyroid dysfunction following the introduction of salt iodisation in 1996 (Teng *et al.*, 2006). The introduction of salt iodisation had resulted in median urinary iodine excretion increasing from 165 µg/L in 1995 to 306 µg/L in 1999. Cohorts in three regions with different levels of iodine intake were investigated: a region regarded as mildly iodine deficient with a median urinary iodine excretion of 84 µg/L (Panshan); a region with more than adequate iodine intake having a median urinary iodine excretion of 243 µg/L (Zhangwu); and a region with excessive iodine intake, having a median urinary iodine excretion of 651 µg/L (Huanghua). The study examined the prevalence and cumulative incidence of various thyroid disorders within each cohort. The investigators found that more than adequate or excessive iodine intake was associated with a slightly increased cumulative five-year incidence of sub-clinical hypothyroidism and autoimmune thyroiditis, but not of overt hypothyroidism or hyperthyroidism. For the majority, the sub-clinical hypothyroidism and autoimmune thyroiditis were not sustained.

4.1.1.2 Effects in the Elderly

Very little data are available for the elderly. Sub-clinical hypothyroidism has been shown to be induced by an acute increase of 500 µg/day (7 µg/kg/day) (Chow *et al.*, 1991) and in epidemiological studies has been associated with chronic intakes of 160-800 µg/day (4-12 µg/kg/day) (Laurberg *et al.*, 1998). This possibly suggests that the elderly may be less tolerant of excess iodide than younger adults.

4.1.1.3 Effects in Children

⁴ Where thyroid-stimulating hormone levels are in the normal range and the thyroid is neither hypothyroid nor hyperthyroid and considered 'normal'.

Some data are available on adverse effects of chronic exposure to high iodine intakes in school-age children but very little data are available for younger children.

Very large iodine intakes have been reported in children residing in certain coastal areas of Japan (Suzuki *et al.*, 1965). In coastal Hokkaido in Japan the traditional local diet is high in iodine-rich seaweed. Urinary iodide excretion in children consuming the local diet was approximately 23,000 µg/day, estimated to be equivalent to an iodine intake of >10,000 µg/day. The overall prevalence of visible goitre in the children was 3-9%, although in some villages, about 25% of the children had visible goitre.

Most of the goitres responded to the administration of thyroid hormone, restriction of dietary iodine intake, or both. TSH assays were not available, but it was suggested that the increase in serum TSH was involved in the generation of goitre. No cases of clinical hypothyroidism were reported.

Results from an epidemiological study of children in China suggest that chronic exposure to excess iodine (1150 µg/day, 29 µg/kg/day) can result in or contribute to the development of sub-clinical hypothyroidism (Li *et al.*, 1987; Mu *et al.*, 1987; Boyages *et al.*, 1989). The study compared thyroid status in groups of children, aged 7-15 years, who resided in two areas of China with different drinking water iodine concentrations, providing estimated iodine intakes of 29 and 10 µg/kg/day. Both groups were euthyroid with normal values for serum thyroid hormones and TSH concentrations; although TSH was significantly higher in the high iodine group. These chronic intake levels therefore did not induce clinical hypothyroidism. The high iodine intake group had a 65% prevalence of goitre compared to 15% in the low iodine intake group. This study was used by the ATSDR to establish a chronic-duration minimal risk level (MRL)⁵ for iodine of 10 µg/kg/day (about 400 µg/day for a 40 kg child) based on a no-observed-adverse-effect level (NOAEL)⁶ of 10 µg/kg/day and a lowest-observed-adverse-effect-level (LOAEL)⁷ of 29 µg/kg/day for sub-clinical hypothyroidism in healthy human children (ATSDR, 2004). In their evaluation, the ATSDR noted that the thyroid gland enlargement can be considered a 'less-serious' LOAEL and is not indicative of significant functional impairment.

In the United States, which is iodine replete, very high iodine intakes – such as estimated intakes of up to 980 µg/day in infants (7 kg bodyweight) and 1350 µg/day for toddlers (15 kg bodyweight) – have been observed in young children without any apparent adverse effects (Park *et al.*, 1981).

A recent study of an international sample of 6-12 year old children (n = 3319) from five continents was undertaken to determine whether chronic high iodine intakes are associated with greater thyroid size in school age children (Zimmermann *et al.*, 2005). The MUIC ranged from 115 µg/L (range 2 – 450 µg/L) in central Switzerland

⁵ An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.

⁶ The highest tested dose of a substance that has been reported to have no harmful (adverse) health effects on people or animals.

⁷ The lowest tested dose of a substance that has been reported to cause harmful (adverse) health effects in people or animals.

(equivalent to an estimated iodine intake of 120 µg/day) to 728 µg/L (range 38 – 11,100 µg/L) in coastal Hokkaido, Japan (equivalent to an estimated iodine intake of 740 µg/day). In the entire sample, 31% of children had urinary iodine concentrations (UIC) >300 µg/L, with 11% being >500 µg/day. This contrasts to figures for children from coastal Hokkaido, where 59% had UIC >500 µg/L, and 39% had UIC >1000 µg/L. The study found that chronic intakes of approximately twice those recommended, indicated by UI concentrations in the 300-500 µg/L, do not increase thyroid volume in children.

UIC ≥500 µg/L were associated with increasing thyroid volume in children from coastal Hokkaido but not in children from central Hokkaido or the United States (the two other sites with a high prevalence of UI concentrations >500 µg/L).

The authors concluded that moderately high dietary iodine intakes in the range 300-500 µg/day appear to be well tolerated by healthy children, although such intakes are of no benefit. Uncertainty still remains regarding higher intakes.

Therefore, while chronically high iodine intakes have been associated with an increased prevalence of thyroid enlargement and goitre, as well as an increased prevalence of sub-clinical hypothyroidism, in children residing in coastal areas of Japan or certain regions of China, this is not true for all populations with chronically high iodine intake, for example in the United States. Such effects have also not been observed in children following the introduction of iodine fortification programmes (Delange and Hetzel, 2005).

4.1.1.4 Effects in Pregnant Women

Maternal exposures to excess iodine, generally in the order of several hundred milligrams of iodine/day, during pregnancy have been shown to produce goitre and hypothyroidism in the foetus and neonates.

The susceptibility of the foetus and neonates to the development of goitre and hypothyroidism has a toxicokinetic basis. Iodine uptake into the foetal thyroid commences at approximately 70-80 days of gestation and generally reaches its peak at approximately 6 months of gestation (Aboul-Khair *et al.*, 1966; Book & Goldman, 1975; Evans *et al.*, 1967). The foetal and neonatal thyroid has a much higher fractional uptake of iodine compared to the adult thyroid, although the fractional uptake generally declines to that of adults 5 days after birth. The foetal thyroid is also less able to escape the inhibitory effects of iodine on thyroid hormone formation.

In one clinical case, hypothyroidism and life-threatening goitre occurred in an infant born to a woman who consumed approximately 200 mg iodine/day (2.8 mg/kg/day) as sodium iodide for two years, including during pregnancy (Iancu *et al.*, 1974). The infant was treated with levothyroxine and reverted to normal gland and thyroid status within three weeks after birth and did not require further hormone therapy. In another case, a woman ingested approximately 260-390 mg iodine/day (4.6 mg/kg/day) during pregnancy resulting in the foetus developing goitre *in utero*. (Vicens-Calvet *et al.*, 1998). The foetus was subsequently successfully treated *in utero* with levothyroxine and was born with a normal gland and thyroid status.

Such doses, however, are atypical and clinical experience with lower doses of iodine supplementation given during pregnancy for the purpose of correcting or preventing iodine deficiency and for the management of Grave's disease indicates that oral doses of 4-5 µg/kg/day can be tolerated without any indication of thyroid dysfunction in the newborn (Pedersen *et al.*, 1993, Liesenkötter *et al.*, 1996).

During the course of a study conducted in prison populations (described above), where the prison water supply was iodinated at a concentration of 500 to 750 µg/L (estimated intake 1000-2000 µg/day) for up to 15 years, 177 women in the prison gave birth to 181 full-term infants without any enlargement of the thyroid in the infants being noted (Stockton and Thomas, 1978).

4.1.1.5 Effects on Individuals with Thyroid Disorders

In individuals with thyroiditis, frequently caused by Graves' or Hashimoto's disease, high intakes of iodine may exacerbate the condition, producing either sub-clinical or clinical hypothyroidism. The hypothyroidism is usually transient with thyroid function returning to normal in 2-3 weeks once the iodine intake is discontinued, although transient thyroxine replacement therapy may be required in some individuals (Markou *et al.*, 2001).

The impact of large scale iodine supplementation programmes on the occurrence of clinically significant iodine-induced thyroiditis does not appear to have been systematically or extensively studied, however, there is little evidence from the epidemiological surveys done to date that iodine supplementation per se is associated with a significant risk of autoimmune thyroiditis (Delange and Lecomte, 2000), although a recent study by Teng *et al* (2006) (discussed above) suggests that increasing iodine intakes from mildly deficient to more than adequate may increase the incidence and prevalence of autoimmune thyroiditis.

4.1.2 Iodine-Induced Hyperthyroidism

Oral exposure to excess iodine can, under certain circumstances, lead to hyperthyroidism. This condition is referred to as 'jodbasedow' although it is not thought to be a single aetiological entity (Fradkin and Wolff, 1983). The occurrence of iodine-induced hyperthyroidism is most common in iodine deficient populations following the introduction of iodine supplementation programs. The degree of vulnerability depends on the duration of the deficiency, with the most vulnerable being those over 40 years of age who have been iodine deficient since birth (Hetzl and Clugston, 1998). Other vulnerable groups include those with thyroid diseases such as Graves' disease or postpartum thyroiditis.

The clinical features of iodine-induced hyperthyroidism are said to be similar to that of Graves' disease, however, in contrast to the diffuse goitres associated with Grave's disease, iodine-induced hyperthyroidism is generally associated with nodular goitres. Nodular goitres are fairly common in elderly people and are the result of longstanding iodine deficiency. Many of these nodules are autonomous, meaning they are independent of regulation by thyroid-stimulating hormone and produce thyroid hormone in direct response to dietary iodine. Thus excess iodine may precipitate or aggravate hyperthyroidism in these subjects.

Frequently, iodine-induced hyperthyroidism is mild and follows a self-limited course, but in some cases it is more severe, even lethal. Iodine-induced hyperthyroidism can be prevented in the next and subsequent generations by correction of iodine deficiency (Delange and Lecomte, 2000).

4.1.2.1 Iodine Deficient populations

A number of epidemiological studies have been conducted in Europe and Africa to monitor the incidence of iodine-induced hyperthyroidism in iodine deficient populations following the introduction of iodine supplementation programs (DeLange *et al.*, 1999; Mostbeck *et al.*, 1998, Lind *et al.*, 1998; Stanbury *et al.*, 1998). A review of these studies indicates that iodine intakes in the range of 3-7 µg/kg/day may be sufficient to produce an increase in hyperthyroidism in iodine deficient populations (ATSDR, 2004). In countries with long-standing iodine deficiency it has been recommended that iodine intake not exceed 500 µg/day to avoid the occurrence of iodine-induced hyperthyroidism (SCF, 2002).

Iodine-induced hyperthyroidism has been reported in almost all iodine supplementation programmes (Stanbury *et al.*, 1998) but is said to be rare in cases where the supplementation programme is well executed (Delange and Hetzel, 2005). For example, in Iran the incidence of hyperthyroidism 4 years after the commencement of iodine fortification was very similar to the incidence of spontaneous thyrotoxicosis in the population prior to the intervention (Azizi and Daftarian 2001; Azizi *et al.*, 2005). In a recent study by Teng *et al.* (2006) (discussed in section 4.1.1), there were no significant differences in the cumulative incidence of either overt hyperthyroidism or Graves' disease in the cohorts studied following the introduction of salt iodisation.

One of the most well documented cases of iodine-induced hyperthyroidism occurred in Tasmania, Australia, following the introduction of iodised bread in 1966 and the addition of iodophors to milk by the dairy industry (Connolly *et al.*, 1970). Milk iodine (from the seasonal use of feed supplements) has also been a factor in outbreaks of hyperthyroidism in Europe (Barker and Phillips 1984; Phillips, 1983).

In the Tasmanian case, a 2- to 4-fold increase in hyperthyroidism occurred within a few months after diets were supplemented with iodide for the prevention of endemic goitre from iodine deficiency (Connolly *et al.*, 1970). The supplemental dose was 80-200 µg/day from the addition of potassium iodate to bread, but mean urinary iodide excretion rates suggested a total post-supplementation iodide intake of about 230 µg/day (range 94-398), equivalent to 3.3 µg/kg/day, some of which came from other sources such as milk (Connolly 1971a, 1971b).

The highest incidence of hyperthyroidism after the iodine supplementation began occurred in people over 40 years of age (Stewart 1975, Stewart & Vidor 1976). Stewart (1975) noted that the small increase in the incidence of hyperthyroidism that occurred in people under 40 years of age was largely due to Graves' disease.

While an increased incidence of iodine-induced hyperthyroidism is a common finding following iodine supplementation, its occurrence is said to be almost entirely avoided

by adequate and sustained quality control and monitoring of the supplementation programme, which should also confirm adequate iodine intake (Delange and Lecomte, 2000). If an increase in the incidence of iodine-induced hyperthyroidism does occur, it typically reverts to normal or even below normal after one to ten years of iodine supplementation (Delange and Hetzel, 2005). A decline in the number of cases of hyperthyroidism, following an initial increase in their number after the introduction of iodine fortification, has been observed in a number of separate studies.

In a prospective epidemiological study conducted in Denmark, all new cases of overt hyperthyroidism in two areas with previously mild and moderate iodine deficiency were recorded prior to and during voluntary and subsequent mandatory fortification, which were introduced in 1998 and 2000, respectively (Pederson *et al.*, 2006). There was an initial rise in the incidence of hyperthyroidism after the introduction of voluntary fortification from 102.8 to 122.8 cases/100,000 people/year, a further rise to 140.7/100,000/year following mandatory fortification, and a small decline to 138.7/100,000/year 3-4 years following the introduction of mandatory fortification. Hyperthyroidism increased in both sexes and in all age groups, with the most pronounced increase being observed in young adults aged 20-39 years.

The increase in occurrence of hyperthyroidism was more pronounced in the area with previously moderate iodine deficiency.

In an epidemiological study conducted in Austria, the annual incidence of hyperthyroidism was evaluated in 392,820 patients examined at nuclear medicine centres before and after the level of table salt iodisation was increased from 7.5 to 15 mg/kg in 1991 to address persistent mild iodine deficiency (Mostbeck *et al.*, 1998). The mean urinary iodide concentration before the adjustment was 42-78 µg/g creatinine and after the adjustment was 120-140 µg/g creatinine. The monitoring revealed an initial 53% increase in the annual incidence of hyperthyroidism which then declined to 21% above baseline after five years.

An epidemiological study in Switzerland examined the incidence of hyperthyroidism before and after the iodine content of salt was increased from 7.5 to 15 mg/kg to address persisting mild iodine deficiency in the population (Baltisberger *et al.* 1995, Bürgi *et al.* 1998). The study population consisted of 109,000 people. The intervention proved to be successful, with the mean urinary iodine concentration increasing from 90 µg/g creatinine to 150 µg/g creatinine. During the first year after the increased salt level, the combined annual incidence of hyperthyroidism, diagnosed as either Graves' disease or toxic nodular goitre, increased by 27% (from 62.3/100,000 to approximately 80/100,000). However, over the next eight years, the total incidence of hyperthyroidism steadily declined to 44% of the pre-supplementation rates, with most of the decrease resulting from a decline in the incidence of toxic nodular goitre.

Healthy Individuals

Cases of iodine-induced hyperthyroidism in people who were euthyroid and without apparent thyroid disease have been reported (Rajatanavin *et al.*, 1984; Savoie *et al.*, 1975; Shilo and Hirsch, 1986; O'Connell *et al.*, 2005); however only a few have

provided dose information. The most recent case, reported by O'Connell *et al*, (2005), occurred in New Zealand and consisted of a cluster of thyrotoxicosis in adult men as a result of the consumption of a soy milk product with very high iodine concentrations (9.14 mg/kg) from added kelp. In cases reporting dose information, effects were observed following doses in the range 0.05–23 mg/kg/day.

4.1.3 Thyroid Cancer

In humans, the only well established cause of thyroid cancer is external radiation of the thyroid gland (NNT, 2002).

The relationship between iodine intake and thyroid cancer has been examined in several large-scale epidemiology studies. The results of these studies suggest that increased iodine intake may be a risk factor for thyroid cancer in certain populations, particularly populations in iodine deficient, endemic goitre regions (ATSDR, 2004). Not all the studies have found an increased risk of cancer; however, a recurrent observation in these studies is an apparent shift in histopathology toward a higher prevalence of papillary cancers, relative to follicular cancers, after increased iodine intake in otherwise iodine-deficient populations. Papillary carcinomas are said to be less aggressive, tend to be diagnosed at earlier stages and have a better prognosis than follicular cancers (Delange and Lecomte, 2000; SCF, 2002).

Therefore, increased iodine intake may alter the pattern of thyroid cancer in iodine deficient, endemic goitre regions; resulting in a trend towards less aggressive forms of thyroid cancer.

There is little evidence to indicate that either the pattern or incidence of thyroid cancer is affected by iodine intake in regions exhibiting only mild or moderate iodine deficiency (Sehestedt *et al*, 2006). Likewise, 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).

4.2 Sensitivity Reactions

Exposure to iodine, and certain iodine-containing substances, can produce a range of adverse reactions in certain sensitive individuals.

While there is a tendency for such reactions to be referred to as 'iodine allergy', in most cases, these reactions, which are unrelated to thyroid function, do not appear to be true allergic reactions (i.e. they are not IgE-mediated), although they do seem to have an immunological basis, with both humoral and cell-mediated responses being involved (Curd *et al.*, 1979; Rosenburg *et al.*, 1972; Stone, 1985).

Sensitivity reactions have been observed following oral exposure to iodide, dermal application of iodine-based antiseptics and administration of iodinated contrast materials (ICM). This review will largely focus on sensitivity reactions following oral exposure to free iodide, as this is the most relevant exposure route.

However, because of the widely held belief that adverse reactions to iodine-containing substances such as ICM and iodine-based antiseptics can confer a specific cross-reactivity with iodine in foods, some consideration will also be given to these reactions, and their causes.

4.2.1 Reactions to Free Iodide

In certain individuals, oral exposure to excess iodine can produce urticaria (hives), acneiform skin lesions (iododerma), and fevers (Kubota *et al.*, 2000; Kurtz and Aber, 1982; Rosenberg *et al.*, 1972; Stone, 1985). Cases of more serious reactions involve angioedema (localised oedema), vasculitis, peritonitis and pneumonitis, and complement activation (Curd *et al.*, 1979; Rosenberg *et al.*, 1972; Stone, 1985). In general, such reactions have occurred in association with repeated oral doses of iodide exceeding 300 mg/day. Such doses are vastly in excess of typical dietary iodine intake.

Iododerma is thought to be a form of cell-mediated hypersensitivity (Rosenburg *et al.*, 1972; Stone, 1985). Characteristic symptoms include acneiform pustules, which can coalesce to form vegetative nodular lesions on the face, extremities, trunk, and mucous membranes. The lesions regress and heal when the excess iodide intake is discontinued. The literature reports cases of iododerma occurring following oral doses of iodide 300-1000 mg/day (5-14 mg/kg bw/day) (Baumgartner, 1976; Khan *et al.*, 1973; Kint and Van Herpe 1977; Rosenberg *et al.*, 1972; Shelly, 1967; Soria *et al.*, 1990).

However, in many of these cases, pre-existing disease and related drug therapy may have contributed to the reaction to iodide; the dose-response relationship for iododerma in healthy people remains highly uncertain (ATSDR, 2004).

Oral exposures to iodide >1000 mg/day have been associated with the occurrence of fevers, which cease once exposure to the excessive iodide intake is discontinued (Horn and Kabins, 1972; Kurtz and Aber, 1982). Reported clinical cases have almost always involved a pre-existing disease, usually pneumonia or obstructive lung disease in which potassium iodide was administered along with other drugs, such as antibiotics, barbiturates and methylxanthines; therefore the dose-response relationship for healthy people is highly uncertain (ATSDR, 2004).

4.2.2 Reactions to Iodine-Containing Substances

The administration of ICM has been associated with both immediate and delayed reactions. The immediate reactions, which can vary from mild to severe and life threatening, are primarily anaphylactoid⁸ in nature, although rare cases of anaphylactic reactions have also been documented (Laroche *et al.*, 1999). Delayed reactions are mainly mild to moderate in nature, typically manifesting as various types of skin reactions. The delayed reactions appear to be T-cell mediated (Christiansen *et al.*, 2000).

⁸ Immediate systemic reactions that mimic anaphylaxis but are not caused by an IgE-mediated immune response. Anaphylaxis and anaphylactoid reactions are clinically indistinguishable.

The contrast materials used are tri-iodinated benzoic acid derivatives that in solution contain a small amount of free iodide.

Studies have shown that individuals who have reacted to ICM fail to react to free iodide following subsequent testing, indicating that the sensitivity reactions observed are almost certainly a response to the contrast molecule as a whole, and not to free iodide (Coakley and Panicek, 1997).

Dermal exposures to iodine-based antiseptics, such as povidone-iodine (polyvinylpyrrolidone -iodine, or PVP-I), have produced both localised and systemic reactions in humans.

Several case reports exist describing contact dermatitis in individuals treated with topical applications of povidone-iodine (Nishioka *et al.*, 2000; Okano, 1989; Tosti *et al.*, 1990). The vast majority of these reactions appear to be the result of skin irritation (manifesting as irritant contact dermatitis) rather than an allergic response (Coakley and Panicek, 1997). Systemic effects are rare and have only been reported in instances of intravaginal applications of povidone-iodine (Moneret-Vautrin *et al.*, 1989; Waran and Munsick, 1995).

In cases of both systemic and localised reactions, patients typically react to subsequent skin challenge tests to povidone-iodine, but not to potassium iodide (Van Ketel and Van den Berg, 1990), indicating the response is caused either by povidone-iodine as a whole, or by povidone itself.

Often, individuals who have a history of a previous reaction to ICM or a topical solution of povidone-iodine or other iodine-based antiseptics and who have subsequently developed an allergy to shellfish or other seafood, or conversely who are allergic to seafood and have subsequently reacted to iodine-containing substances such as ICM, are described as having 'iodine allergy' (Kubota *et al.*, 2000). While it is true that iodine is a common component in these cases, the term 'iodine allergy' is misleading because it implies that the reactions observed are directly in response to the presence of iodine, and also that they are IgE-mediated.

At present, there is little evidence that iodine is able to provoke an IgE response, either by itself or by acting as a hapten and there is also little evidence that the sensitivity reactions to ICM or povidone-iodine are provoked by the iodine component (Coakley and Panicek, 1997). In addition, when adverse reactions to seafood, such as shellfish, are investigated, they are invariably the result of an IgE-mediated reaction to a specific protein (Daul *et al.*, 1993), and are unrelated to the presence of iodine (Huang, 2005).

There is therefore little available evidence to support the belief that adverse reactions to iodine-containing substances can confer a specific cross-reactivity with iodine in foods, or vice versa. Such cross-reactions, should they exist, would be extremely rare.

4.3 Iodine Poisoning

The effects from acute exposure to high iodine concentrations are largely due to the strong oxidising effect of iodine on the gastrointestinal tract and resultant shock. It is these properties of iodine that make it effective as a topical antiseptic and antimicrobial disinfectant. The mechanism of toxicity is not understood although direct chemical injury to the gastrointestinal tract and related secondary consequences including fluid and electrolyte loss, massive acute extracellular fluid volume contraction and cardiovascular shock may contribute to the widespread systemic effects that have been observed in lethal and near lethal poisonings.

Cases of iodine poisoning are rare however and are typically associated with intakes of many grams. Symptoms observed in lethal or near-lethal poisonings have included abdominal cramps, bloody diarrhoea and gastrointestinal ulcerations, oedema of the face and neck, pneumonitis, haemolytic anaemia, metabolic acidosis, fatty degeneration of the liver, and renal failure (Clark, 1981; Dyck *et al.*, 1979; Finkelstein and Jacobi, 1937; Tresch *et al.*, 1974).

Death has occurred from 30 minutes to 52 days after ingestion, although death generally occurs within 48 hours. Where the dose was known, it ranged from 1.1 to 9 g iodine (18-150 mg/kg for a 60 kg adult), although there is a single case report of a 54-year-old male surviving the accidental ingestion of 15 g iodine (Tresch *et al.*, 1974).

5. Upper Level for Oral Intake

A number of adverse health effects have been associated with increased iodine intakes (WHO, 1989). The most relevant of these in the context of the expected increase in iodine intake following fortification of the food supply is the potential for disturbance of normal thyroid activity.

The effect produced – iodine induced hyperthyroidism or iodine induced hypothyroidism – depends on the current and previous iodine status of the individual and any current or previous thyroid dysfunction.

For the majority of healthy individuals, the most sensitive endpoint for iodine toxicity is sub-clinical hypothyroidism. Sub-clinical hypothyroidism is defined as an elevation in thyroid-stimulating hormone concentration while serum thyroid hormone concentration is maintained within the normal range of values for healthy individuals. The effect is usually transient, even if excess iodine intake continues.

While not clinically adverse, such an effect, if persistent, may lead to thyroid gland enlargement, which is an indicator of an existing risk of clinical or overt hypothyroidism (SCF, 2002).

In healthy adults, sub-clinical hypothyroidism has been associated with acute intakes of 1700 and 1800 µg/day (24-25 µg/kg body weight/day for a 71 kg person), and for children, has been associated with chronic intakes of 1150 µg/day (29 µg/kg/day for a 40 kg child).

The level of 1700 µg/day for sub-clinical hypothyroidism has been used by the Institute of Medicine as a lowest-observable-adverse-effect level (LOAEL) (Institute of Medicine, 2001). There was considered to be little uncertainty regarding the range of iodine intakes that are likely to induce elevated thyroid-stimulating hormone concentrations above baseline, therefore an uncertainty factor of 1.5 was considered sufficient to derive an Upper Intake Level (UL)⁹.

A higher uncertainty factor was not considered necessary because of the mild and reversible nature of the endpoint on which the UL is based.

The LOAEL of 1700 µg/day was divided by the uncertainty factor of 1.5 to obtain a UL of 1133 µg/day of iodine, which was rounded down to 1100 µg/day.

The ULs for other age groups were derived by adjustment of the adult UL on a bodyweight basis, as follows:

1-3 years	200 µg/day
4-8 years	300 µg/day
9-13 years	600 µg/day
14-18 years	900 µg/day
≥19 years	1,100 µg/day

There is also no evidence to indicate altered susceptibility of pregnant or lactating women to excess iodine, therefore the UL is the same as that for non-pregnant and non-lactating females. For infants, a UL was judged not determinable because of insufficient data on adverse effects in this age group and concern about the infant's susceptibility to excess iodine intake.

FSANZ has adopted these ULs for the purpose of risk assessment for the general healthy population. The National Health and Medical Research Council also subsequently adopted these levels in Australia as part of their recent review of nutrient reference values (NHMRC, 2006).

While the occurrence of sub-clinical hypothyroidism may lead to progression to clinical hypothyroidism in certain susceptible individuals, it remains uncertain as to whether a persistent state of sub-clinical hypothyroidism would, in practice, have any clinical consequences in otherwise healthy individuals. A body of evidence exists which indicates that healthy adult individuals are able to tolerate quite large intakes (up to 50 µg/kg bw/day) (ATSDR 2004) and in some cases intakes as high as 138 µg/kg bw/day in young children have been reported with no evidence of any adverse consequences (Park et al 1981). These levels of intake are vastly in excess of the ULs described above and suggest that healthy individuals, including young children, may exceed their respective ULs by 2-3 fold without any apparent adverse consequences.

For those individuals with thyroid disorders or a long history of iodine deficiency, the UL may not be applicable since these individuals may respond adversely at levels of

⁹ The tolerable upper intake level is the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects in almost all individuals. The UL is not intended to apply to individuals who are receiving iodine under medical supervision.

intake below the UL. It has been reported that intakes in the range 3-7 µg/kg/day may be sufficient to produce an increase in hyperthyroidism in chronically iodine deficient individuals. The health risk for these individuals needs to be considered separately from the general population.

6. Risk Characterisation

6.1 Implications of Exceeding the Upper Level of Intake

Following introduction of mandatory iodine fortification, it is estimated that a small percentage of young children may exceed the UL (see Dietary Intake Assessment Report (Supporting Document 6³). The level of exceedance is greatest for 1-3 year old children but disappears in later childhood (>8 years). No other age groups are estimated to exceed their respective ULs. The magnitude of the exceedance is influenced by the amount of discretionary iodised salt in the diet.

In considering if the estimated intakes for young children are likely to represent a health and safety risk, a number of factors need to be taken into account.

The age-specific ULs for iodine are not absolute thresholds for toxicity but rather represent intake limits, which provide a comfortable margin of safety. While it is not desirable to routinely exceed the UL, such occurrences do not automatically mean an adverse effect will result because of the safety margin that is incorporated when ULs are derived. In the case of iodine, the UL includes an uncertainty factor of 1.5. Intakes above the UL, while reducing the margin of safety, may be considered acceptable providing they remain within the safety margin.

The toxicological endpoint on which the UL for iodine is based is sub-clinical hypothyroidism. In most individuals, a state of sub-clinical hypothyroidism represents a transient, adaptive response to increased levels of iodine (ATSDR, 2004). Usually, this state does not persist, even if the excess intake continues.

In some populations however an excessively high iodine intake has been shown to result in a persistent state of sub-clinical hypothyroidism, leading to an increased prevalence of thyroid gland enlargement (goitre) (Zimmerman, *et al.*, 2005). In certain susceptible individuals, (e.g. the foetus, neonates) there may also be progression to clinical hypothyroidism (SCF, 2002; ATSDR, 2004).

While the foetus and newborn infants are considered to have increased susceptibility to excess iodine, due to the immaturity of their thyroid, this is not believed to extend beyond a few weeks of age (ATSDR, 2004). Young children therefore are only more vulnerable than adults to excess iodine as a result of their lower body weight. Differences in bodyweight are taken into account in the derivation of ULs for different age groups. The UL for 4-8 year olds is 300 µg/day and for 1-3 year olds is 200 µg/day.

The effects of chronic high iodine intakes on young children appear to be variable. Some groups of children with excessively high chronic intakes of >10 mg/day (in some coastal areas of Japan) have shown an increased prevalence of thyroid

enlargement, but no evidence of clinical hypothyroidism (Suzuki *et al*, 1965; Zimmermann *et al*, 2005). Whereas others with intakes up to 1.35 mg/day (e.g., in toddlers in the United States) do not appear to be adversely affected (Park *et al*, 1981). It therefore remains uncertain whether chronically high iodine intakes would, in practice, have any clinical consequences in otherwise healthy children.

Although a small number of young children are estimated to exceed the UL following the introduction of mandatory iodine fortification, the estimated intakes are still below a level at which adverse effects might be observed. Therefore, while the estimated intake level for young children exceeds the UL, the maximum estimated intake still remains within the margin of safety.

The addition of discretionary iodised salt to the diet, such as in cooking and added to food at the table, has the potential to significantly increase the estimated iodine intakes. Considerable uncertainty exists regarding the extent of discretionary salt use by the population, including by young children. However, added salt is generally not recommended for young children. It also seems unlikely that a young child would add the same amount of salt to food at the table as an adult, if at all.

Because of this, the estimated iodine intakes for the majority of young children are expected to be closer to the lower end of the range of estimated intakes. The estimated intakes at the high end of the range would represent a worst-case situation that in reality is unlikely to be realised in the vast majority of young children. Even so, these worst-case estimates are still below an intake level where adverse effects might be observed.

Overall, the potential for adverse effects in the small number of young children that are estimated to exceed the UL for iodine is considered low. While it is generally not desirable to exceed the UL, in this case the estimated worst-case iodine intakes for young children are calculated to be below a level at which adverse effects may be observed. This, and the reversible nature of the endpoint, means such intakes are unlikely to represent a health and safety risk to young children, though a reduced margin of safety exists.

6.2 Vulnerable Groups

The UL may not be applicable to individuals with thyroid disorders or a long history of iodine deficiency, therefore the health risk for these individuals needs to be considered separately from the general population. The main health risk for these individuals is the occurrence of iodine-induced hyperthyroidism.

Iodine-induced hyperthyroidism typically occurs in individuals with an underlying autonomously functioning thyroid caused by either multinodular goitre or by Graves' disease.

An increased incidence of iodine-induced hyperthyroidism is reported to be the most common adverse effect encountered following the introduction of iodine fortification (Stanbury *et al.*, 1998). Because of this clear link with iodine deficiency, iodine-

induced hyperthyroidism is regarded as one of the Iodine Deficiency Disorders (Delange and Hetzel, 2005).

It affects principally the elderly, who are the population group most likely to have developed multinodular goitres as a result of long-standing iodine deficiency (Hetzel & Clugston 1998). Many of the nodules are autonomous, meaning they are independent of regulation by TSH and produce thyroid hormone in direct response to dietary iodine (ATSDR, 2004). Thus, excess iodine may precipitate or aggravate hyperthyroidism in these subjects.

While the highest incidence of hyperthyroidism following the introduction of iodine fortification is usually found in the elderly population, small increases in incidence have also been documented in people under 40 years of age due largely to Graves' disease (Stewart, 1975).

Graves' disease is an autoimmune disease caused by the stimulation of the thyroid by antibodies, which bind to TSH receptors resulting in the non-suppressible overproduction of thyroid hormone. Excess iodine can precipitate active Graves' disease by providing more substrate for thyroid hormone synthesis and possibly also by disturbing immune function (Topliss and Eastman, 2004).

While an increase in the incidence of iodine-induced hyperthyroidism is regarded as a unavoidable consequence of the correction of iodine deficiency, it has been demonstrated that its incidence can be significantly reduced or even avoided by appropriate quality control and monitoring of the fortification programme (Delange and Lecomte 2000).

The incidence of iodine-induced hyperthyroidism is said to revert to normal or even below normal after 1-10 years of iodine supplementation (Delange and Hetzel, 2005).

In terms of the risk to the Australian and New Zealand population, the evidence indicates that mild to moderate iodine deficiency has only emerged in the last 10 to 15 years. As a consequence, the number of individuals with autonomous multinodular goitres is expected to be quite small. Therefore, while an increase in the detectable occurrence of iodine-induced hyperthyroidism is a recognised risk following the introduction of iodine fortification, in the Australian and New Zealand context it is likely to be a rare event.

A small but manageable risk exists for individuals with Graves' disease, however, such individuals will typically be under the care of a medical professional, therefore should there be any exacerbation of the condition this should be detected quickly and remedial action taken.

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