

General information

Chemistry

Iodine is a non-metallic group VII element (a halogen). At room temperature it is a blue-black solid which sublimes into a gaseous form. It reacts readily, common compounds being iodides (e.g. potassium iodide) and iodates (e.g. potassium iodate). Iodine can exist in oxidation states -1 , 1 , 5 and 7 , -1 (iodide) being the most common. In this risk assessment, the word iodine refers to both the elemental and ionic forms of iodine.

Natural occurrence

Iodine is present in seawater, igneous rocks and some soils.

Occurrence in foods, food supplements and medicines

High levels of iodine are present in marine fish (up to 2.5 mg/kg), shellfish (up to 1.6 mg/kg) and sea salt (up to 1.4 mg/kg). Levels in cereals and grains vary depending on the iodine content of the soil. The food colour erythrosine is also rich in iodine. In the UK, iodine is also present in cows' milk (average level 0.15 mg/kg), probably as a result of the use of supplemented cattle feeds and iodophors as teat sterilants. The content of iodine in raw food is reduced by cooking. Iodine, as iodide, is present in multi-vitamin and mineral supplements (providing up to 0.49 mg iodine/day) and is a component of kelp products. It is also present in licensed medicines, topical antiseptics and radiographic contrast agents.

Iodine intakes in children are higher than those in adults, because of a greater consumption of milk, and are likely to be higher in the winter than the summer because winter milk contains more iodine.

Other sources of exposure

Iodine intake from water is estimated to be generally less than 0.03 mg/day.

Recommended amounts

COMA established a Lower Reference Nutrient Intake (LRNI) and a RNI for iodine of 0.07 and 0.14 mg/day, respectively (COMA, 1991).

Analysis of tissue levels and iodine status

Urinary iodine excretion, or blood levels of thyroxine (T4) or thyroid stimulating hormone (TSH) have been used to estimate iodine status.

Brief overview of non-nutritional beneficial effects

Iodine is claimed to assist with weight loss, rheumatism, ulcers, hair loss and the maintenance of healthy arteries, nervous tissue and nails.

Function

Iodine forms part of the thyroid hormones, thyroxine (T₄) and triiodothyronine (T₃). Receptors binding T₃ and T₄ have been found in the cell nucleus and in mitochondria. These hormones are involved in the maintenance of metabolic rate, cellular metabolism and integrity of connective tissue. Thyroid hormones are necessary for the development of the nervous system in the foetus and infant.

Deficiency

A variety of mechanisms exist to compensate for low levels of iodine intake. These include enlargement of the thyroid gland (goitre). Only when these mechanisms fail do the clinical signs of hypothyroidism (also known as myxoedema) develop. Symptoms and signs of hypothyroidism include lethargy, weakness, weight gain, poor concentration, oedema, myalgia, dry skin, delayed tendon reflexes and slow heart rate. In pregnancy, iodine deficiency is associated with an increased risk of miscarriage, stillbirth and congenital abnormality. Cretinism is the result of iodine deficiency in the developing foetus, and is characterised by mental retardation, deaf mutism, and spastic diplegia. A less common form of cretinism is the myxoedematous type, which is characterised by hypothyroidism and dwarfism.

Interactions

Iodine interacts with selenium and possibly with vanadium.

Natural goitrogens (which impair thyroid hormone synthesis) may be present in soybeans, peanuts and walnuts, or may be formed (for example, thiocyanate) from foods such as corn, maize, cassava, potato, cauliflower and broccoli. Pollutants derived from coal (such as 2 and 5 methyl resorcinol) have also been reported to act as goitrogens.

Absorption and bioavailability

The few data available suggest that the bioavailability of iodine in food is high.

Inorganic iodine (generally in the form of iodide) is readily absorbed, largely from the small intestine. It can also be absorbed through the skin, absorption being increased when the skin is damaged.

Distribution and metabolism

Once absorbed, iodine is distributed rapidly throughout the extracellular fluid, secreted into saliva, and enters the gastrointestinal system, from where it is reabsorbed. Iodine can cross the placenta and is secreted into human breast milk.

Iodine is taken up and stored in the thyroid gland mainly as iodinated tyrosines and thyronines, within a large protein (thyroglobulin), for the synthesis of thyroid hormones (T4 and T3). Excess iodide is excreted in the urine. T4 and T3 are released into the blood (by passive diffusion) after proteolysis from thyroglobulin, and circulate in protein-bound and free forms. The free forms of the hormones enter tissues, in particular the liver (for T4) and skeletal muscle (for T3). The thyroid gland is the only significant store of iodine.

Excretion

Iodine is largely excreted in the urine, mainly in the form of iodide. Very small amounts of iodine may be excreted in sweat, faeces and exhaled air.

Toxicity

Human data

Several biological mechanisms protect against iodine toxicity; these include reduced iodine uptake and preferential production of the more heavily iodinated thyroid hormones. Not all exposed subjects will react to excess iodine.

Clinical features of acute iodine toxicity that have been produced following accidental or deliberate ingestion, or medical procedures such as wound irrigation, include gastrointestinal disturbance (vomiting and diarrhoea), metabolic acidosis, seizure, stupor, delirium and collapse. Sensitivity reactions, such as iodide mumps, iododerma and iodide fever may also occur following treatment with iodine-containing drugs, or the use of radiographic contrast media.

Chronic and sub-chronic toxicity have also been identified. Excess iodine or iodide intake may disrupt thyroid function, resulting in the induction of hypothyroidism with or without goitre, hyperthyroidism (thyrotoxicosis) and changes in the incidence and types of thyroid malignancies. Responses of this type frequently occur where there is general high iodine intake or where intervention has taken place to correct iodine deficiency.

The pattern of effects changes over time as iodine exposure in the population changes. For example, in the UK, the possibility of iodine induced hyperthyroidism associated with prior iodine deficiency appears to be less common due to recent increases in the iodine intake of the population as a whole.

Supplementation studies

Measures of serum thyroid hormone levels, such as T3, T4 and TSH are used as indicators of iodine disturbances in human studies. Increased TSH and decreased T3 and T4 levels have been noted at supplemental doses of 0.5-1.5 mg/day and above for 2 weeks. Significant reductions in further iodine uptake have been noted with supplemental doses of 2 mg iodine/day. Dietary iodine intakes were uncertain.

Animal data

Symptoms of acute iodide or iodate toxicity include diarrhoea, with alternating periods of hyperactivity, weakness, prostration, convulsions and death.

Symptoms of sub-chronic toxicity include reduced weight gain and haemolysis, in addition to specific effects on the thyroid.

Carcinogenicity and genotoxicity

No data have been identified on the carcinogenicity of iodine. Both iodine deficiency and excess can promote tumour formation in animals pre-exposed to known carcinogens. Metaplasia of the thyroid was reported in rats given potassium iodide in drinking water for two years. This was thought to occur via a non-genotoxic proliferation dependent mechanism. Human epidemiological studies have shown variations in the incidence of thyroid cancer, depending on the levels of iodine available in water supplies in these areas. The type of cancer appears to differ depending on whether iodine levels are deficient or excess. Changes to the pattern of thyroid tumours have been noted after prophylaxis. The mutagenicity data for iodine are generally negative.

Mechanism of toxicity

The adverse effects of high levels of iodine are largely due to the derangement 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.

Dose-response characterisation

The threshold level of iodine necessary to induce thyrotoxicosis is uncertain and appears to vary depending on previous iodine exposure. The available data are inadequate to establish a dose-response relationship.

Vulnerable groups

Pregnant and lactating women, and neonates are considered to be vulnerable groups as iodine freely crosses the placenta and is expressed in breast milk, and goitre and hypothyroidism have been reported to occur in the offspring of mothers exposed to pharmacological doses of iodine and iodide.

Genetic variations

No genetic variation in the uptake and toxicity of excess iodine has been identified.

Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD).

Saxena et al., 1962

This study investigated the minimal effective dose necessary to suppress radioactive iodine uptake. Increasing doses of stable iodine (as sodium iodide) were given to children with normal thyroid function. Doses of 0.1, 0.3, 0.6 or 1 mg iodide/day were given to children aged 1-3, 4-6 or 9-11 years of age. The 24 hour uptake of ¹³¹I was measured every two weeks until uptake declined to 5% or until there was no change between successive uptakes. Iodide was then discontinued. No toxic effects were observed. Thyroid hormone concentrations were not assessed. The length of the study in the particular sub-groups is uncertain, but appears to have been no longer than 3 months. The degree of suppression of radioactive iodine uptake was related to dose, with maximum suppression of ¹³¹I being achieved with a dose of 1.5-2 mg iodide per square meter of body surface. This was equivalent to a dose of 1-2 mg iodide in children and 3-4 mg in adults. ¹³¹I uptake rapidly returned to normal once the iodide was discontinued.

Freund et al., 1966

The health status and thyroid function of representative subjects of a prison population were assessed before and during use of iodinated water for 9 months. The group initially comprised 133 euthyroid prisoners, but was gradually reduced to 70, due to discharge from the institution. Water containing 1 mg iodine/L resulted in a marked decrease in the uptake of test doses of radioactive iodine, to a level of 7%. However, protein bound iodine levels did not change significantly until the iodine concentration of the water was increased to 5 mg/L for 2 months (following 7 months exposure at the lower level), radioactive iodine uptake then fell to 2%. Serum thyroxine concentration did not change regardless of the iodine concentration of the water. No information is provided on individual iodine intake, but water consumption can be assumed to have been approximately 2 L/day. Prisoners continued to receive iodine from the diet, including iodised salt. No effects on thyroid function were reported in non-prison personnel who swam in water iodinated at a level of 5 mg/L. No evidence of iodine allergy was apparent. Two (of fifteen) male inmates had impaired iodine organification, after consuming water (for at least 3 months) containing 1 mg iodine/L, as measured by the change in thyroidal ¹³¹I concentration following administration of perchlorate. The clinical significance of this effect is unclear, since individual T4 concentrations remained unchanged throughout the study i.e. no patients demonstrated iodine-induced hypothyroidism.

Stockton and Thomas, 1978

No significant change in serum thyroxine levels was seen following the iodination of a prison water supply at a concentration of 0.5 to 0.75 mg/L (estimated intake 1-1.5 mg/day) for up to 15. During the same period, 177 women in the prison gave birth to 181 full term infants none of whom had enlarged thyroids. Ninety-nine mothers (of 101 infants) had been in prison for ≥ 122 days, whilst eighty mothers had been imprisoned for < 118 days (10-118). This study has been published as an abstract only.

Sternthal et al., 1980

Single doses of 10-100 mg iodide (as sodium iodide), were given to adult volunteers. In a subsequent experiment, 12 daily doses of 10-100 mg sodium iodide were given. All doses greater than 10 mg suppressed 24-hour uptake of ^{123}I to between 0.7% and 1.5%. Continued daily administration of 15 mg iodide or more resulted in 24-hour uptake values of less than 2% (compared with baseline values of 17 to 23%). Pooling the 24 hour uptake values of the subjects taking 30-100 mg iodide resulted in a significant increase in serum TSH and significant decreases in T3 and T4 levels. These values returned to normal following the withdrawal of treatment. No adverse effects were reported.

Braverman, 1987

Doses of approximately 150 mg iodine given to normal adults for 1-3 weeks induced a small but significant decrease in serum T3 and T4 levels, with a small, significant compensatory increase in serum TSH, and TSH response to thyrotrophin-releasing hormone (TRH). However, the values for these parameters were within the normal range. Similar changes in thyroid function were reported in male volunteers given 200 mg/day of the iodine-rich colour erythrosine for 14 days. The increase in urinary iodine excretion was approximately 1.5 mg daily, which is equivalent to a 2-7 fold increase in dietary iodine intake. No effect was found when the volunteers were given 60 mg erythrosine/day. The effects caused by 200 mg erythrosine/day were reproduced when 1.5 mg/iodine was administered. The author considered that these subtle changes in thyroid function represented physiological adaptation to iodine excess.

Serum T3 and T4 concentrations and free T4 index were unchanged in normal subjects who used iodine-containing mouthwash daily for 6 months. (A small but significant increase in TSH levels was measured; this was within the normal range and considered a normal physiological adaptive response. The amount of iodine absorbed was equivalent to 2- 4 mg/day (based on increased urinary excretion).

Paul et al., 1988

Subjects with a normal functioning thyroid (9 men and 23 women) between the ages of 26 and 56 were given doses of 0.25, 0.5 or 1.5 mg supplemental iodine/day for 14 days. There were small but significant decreases in serum T3 and T4 concentrations following the administration of 1.5 mg/day as well as a small compensatory increase in serum TSH levels and in TSH response to TRH. No effects were observed in the subjects given the lower levels of iodine.

Gardner et al., 1988

Thirty healthy men aged 22-40 were randomly assigned to receive 0.5, 1.5 or 4.5 mg iodide/day for 2 weeks. Several thyroid parameters being measured on day 1 and day 15. Mean serum T4 levels and free T4 index values were decreased at the 1.5 and 4.5 mg/day dose. No changes were observed in serum T3 concentrations at any dose. Doses of 0.5 mg/day resulted in a significant increase in the serum TSH response to TRH and the two larger doses resulted in increases in both basal and TRH-stimulated serum TSH concentrations.

Chow et al., 1991

A randomised controlled trial was performed to investigate the effects of low levels of iodine supplementation in healthy women and in women with sub-clinical Hashimoto's thyroiditis (one of the two major types of autoimmune lymphocytic thyroiditis, characterised by an enlarged thyroid). From a group of 225 women screened for thyroid microsomal antibody, 20 antibody positive women and 30 antibody negative controls were recruited into a trial comparing iodide and placebo. Additional groups

of older subjects from iodine sufficient and iodine deficient areas were also enrolled. The subjects received a supplement of 0.5 mg iodide/day or placebo. Dietary iodine intake was estimated to be approximately 0.25 mg/day. Free thyroxine (T4) and thyrotrophin levels were measured after 14 and 28 days treatment. No changes in thyroid function were seen in the placebo group. All the iodide supplemented groups showed a small decrease in free thyroxine and increase in thyrotrophin levels. In two subjects thyrotrophin levels rose beyond the reference range and in a further three subjects, initially elevated thyrotrophin levels increased further. The effects seen were comparable in the normal and antibody positive subjects. The authors noted that the changes would not be of clinical significance in the general population but that a small shift in the mean value for these indices in a population tended to result in greater effects at the extremes of the distribution. The authors further concluded that dietary intakes in the UK should be monitored since total intakes of 0.75 mg/day could adversely affect thyroid function.

Garber et al., 1993

Healthy hyperlipidaemic subjects (104) were placed on a low fat diet for 12 weeks. Between weeks 4 and 12, they were randomised into a control group (n=53) or were given an iodine enriched egg per day (iodine enriched eggs are produced by hens fed a diet containing kelp and contain an average of 0.71 mg iodine/egg). No information was provided on the iodine content of the rest of the diet. Some subjects from each group continued in the study for an additional 4-8 weeks; there were 19 test subjects and 21 controls by week 16. Plasma and urinary iodine levels were significantly higher in the test subjects compared to the controls. No significant adverse clinical effects were reported (with the exception of one report of an allergic-type response shortly after beginning egg consumption). There were no differences in clinical chemistry values between the two groups. Thyroid function tests (T3, T4, T3 uptake, TSH, thyroid binding globulin and free T4 index) were normal in 17 (of 19) subjects and 20 (of 21) controls. The remaining subjects (2 test and 1 control) had elevated TSH levels. A report was provided for just 1 of these subjects, and revealed high iodine excretion, suggesting exposure to other sources of iodine. Unfortunately, the subject was not followed up and it was unknown whether clinically significant hypothyroidism developed.

Three of the studies cited above (Freund *et al.*, 1966; Saxena *et al.*, 1962; Sternthal *et al.*, 1980) reported on blockage of radioactive iodine uptake following repeated doses of stable iodine. The purpose of these studies was to identify the minimum daily dose of iodine necessary to prevent thyroidal uptake of radioactive iodine in the event of nuclear fallout. The mechanism by which stable iodine blocks thyroidal uptake of radioactive iodine is not well established but may involve isotope dilution, saturation of iodide transport mechanism, interference with intrathyroidal organification of iodide (acute Wolff-Chaikoff effect), or inhibition of hormone release (Zanzonico and Becker, 2000). Thyroid radioactive iodine uptake is inversely proportional to iodine intake (Merck, 2001). In normal subjects the Wolff-Chaikoff effect is transient and overcome by prolonged exposure. Furthermore, when assessed in these studies, serum thyroid hormone concentrations were unaffected. It is therefore unclear whether this minimum inhibition dose can be considered an adverse effect.

Exposure assessment

Total exposure/intake:

Food	Mean: 0.22 mg/day (1986/87 NDNS) 97.5th percentile: 0.43 mg/day
Drinking water	< 0.03 mg/day (estimated intake from 2 litres of water containing < 0.015 g/L)
Supplements	up to 0.49 mg/day (Annex 4)

Estimated maximum intake: $0.43 + 0.03 + 0.49 = 0.95$ mg/day

Children are a potential high intake group, because iodine intakes in children are higher than those in adults due to higher milk consumption.

Risk assessment

The observed effects at lower levels of iodine exposure (as opposed to overt poisoning) seem to result from the derangement of thyroid hormone metabolism and the complex feedback mechanisms that govern it. Changes in thyroid parameters that represent normal compensating mechanisms are difficult to distinguish from those which indicate the onset of adverse or toxic effects in human studies as iodine exposure increases. Small changes in the levels of thyroid hormones may be of little significance, whereas larger changes or phenomena such as blocking of further iodine uptake or increased thyroid weight may be of more significance, suggesting that iodine intakes are at a level where permanent change or more significant symptoms could occur. The response to increased iodine intake also seems to vary depending on previous iodine exposure. Disruption of normal thyroid metabolism by increased iodine intake may manifest as either hyperparathyroidism or hypoparathyroidism (mimicking the hypothyroidism caused by iodine deficiency).

Subjects exposed to pharmacological doses of iodine, frequently as the result of medical treatment, may exhibit effects such as iodine fever or mumps or iododerma. The mechanisms for such reactions are uncertain, as is the nature of any susceptible groups. The relevance of such sensitivity reactions to the risk assessment process is therefore unclear.

Although there are human data available, much are unsuitable for risk assessment purposes since a large number of case reports or epidemiological studies have inadequate, if any, estimates of iodine exposure. Similarly, there are few, if any, good quality animal studies where clear adverse effects can be defined and thus animal studies have not been considered further.

ESTABLISHMENT OF GUIDANCE LEVEL

There are insufficient data from human or animal studies to establish a Safe Upper Level for iodine.

A few studies (Paul *et al.*, 1988; Chow *et al.*, 1991; Gardner *et al.*, 1988) have reported that supplemental doses of 0.5 to 1.5 mg iodine/day produced small changes in the levels of thyroid hormones. Other studies (Saxena *et al.*, 1962; Freund *et al.*, 1966) indicate that supplemental doses of 2 mg/day, in addition to the iodine present in the diet, result in the blockage of further iodine uptake. Although 0.5 mg supplemental iodine/day has been reported to alter thyroid parameters in some studies, the changes are likely to represent normal feedback processes rather than adverse effects.

Taken together the data suggest that, for guidance purposes only, a supplemental intake of 0.5 mg/day (equivalent to 0.003 mg/kg bw in a 60 kg adult), in addition to the iodine present in the diet would not be expected to have any significant adverse effects in adults. No uncertainty factors have been applied as these data come from a number of well-reported, controlled human studies. Assuming an intake of iodine from the diet of 0.43 mg/day, this equates to a total intake, which would be expected to be without adverse effects, of 0.94 mg/day (equivalent to 0.015 mg/kg bw/day in a 60 kg adult). It is possible that some consumers of foods with high levels of iodine, particularly children, may occasionally exceed this guidance level from normal dietary sources, but compensatory mechanisms exist and allay concerns for this potentially vulnerable group.

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