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**Opinion
of the Scientific Committee on Food
on
the Tolerable Upper Intake Level of Iodine**

(expressed on 26 September 2002)

B-1049 Bruxelles/Brussels - Belgium

Telephone: direct line (+32-2) 29 599.10, exchange 299.11.11. Fax: (+32-2) 299.48.91

Telex: COMEU B 21877. Telegraphic address: COMEUR Brussels.

http://europa.eu.int/comm/food/fs/sc/scf/index_en.html

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FOREWORD

This opinion is one in the series of opinions of the Scientific Committee on Food (SCF) on the upper levels of vitamins and minerals. The terms of reference given by the European Commission for this task, the related background and the guidelines used by the Committee to develop tolerable upper intake levels for vitamins and minerals used in this opinion, which were expressed by the SCF on 19 October 2000, are available on the Internet at the pages of the SCF, at the address http://www.europa.eu.int/comm/food/fs/sc/scf/index_en.html.

1. INTRODUCTION

Iodine is a reactive Periodic Group VII element (halogen) existing in the valency states -1 to +7 but not occurring free in nature. Iodides and iodates, its mineral forms, occur ubiquitously in igneous rocks and soils, most commonly as impurities in saltpetre and natural brines. It is liberated by weathering and erosion, particularly following glacial erosion during the ice ages, and, being water-soluble, it leaches by rainwater into surface water, the sea and oceans, leaving behind mountainous regions with soils low in iodide. Liberated elemental iodine evaporates into the atmosphere because of its volatility and is precipitated by rainfall onto the land surface. The iodides in the sea accumulate in sea weeds, sea fish and shellfish. On land small amounts of iodide are taken up by plants, which have no essential nutritional requirement for this element, the plants being subsequently ingested by herbivores. In many areas of the world the surface soil becomes progressively poorer in iodide through these leaching processes (Whitehead, 1984).

Iodine is an essential dietary element for mammals being required for the synthesis of the thyroid hormones thyroxine (T₄, 3,5,3',5'-tetraiodothyronine), containing 65% by weight of iodine, and its active form T₃ (3,5,3'-triiodothyronine), containing 59% by weight of iodine, as well as the precursor iodotyrosines. The only natural sources for humans and animals are the iodides in food and water. Examples of anthropogenic sources are medicinal products, sanitising solutions and iodophores.

2. NUTRITIONAL BACKGROUND

2.1 Levels in the environment and food

Atmospheric iodine derives from vaporisation from seawater and is present at levels of 3-50 ng/m³, the average global value being 10-20 ng/m³ (WHO, 1988; NNT, 2002). Unpolluted surface water contains <3 µg iodide/L, drinking water <15 µg/L but in the US the average drinking water contains 4 µg iodide/L (WHO, 1988). Sea water levels amount to 50 µg iodide/L.

The iodide content of foods and total diets differs depending on geochemical, soil, and cultural conditions. The major natural food sources are marine fish (mean 1220 µg/kg, up to 2.5 mg I/kg), shellfish (mean 798 µg/kg, up to 1.6 mg I/kg), marine algae, seaweed (1000-2000 µg/kg) and sea salt (up to 1.4 mg I/kg). In industrialised countries the most important sources of iodides are dairy products, e.g. whole cow's milk (mean 27-47 µg/kg), UK winter milk (mean 210 µg/kg), UK summer milk (90 µg/kg), eggs (mean 93 µg/kg), and grain and cereal products (mean 47 µg/kg depending on the soil). Other food sources are freshwater fish (mean 30 µg/kg), poultry and meat (mean 50 µg/kg), fruits (mean 18 µg/kg), legumes (mean 30 µg/kg) and vegetables (mean 29 µg/kg) (WHO, 1996; Souci *et al.*, 2000; MAFF, 2000; EGVM, 2002).

Milk and dairy products contain relatively high amounts derived from iodinated cattle feed supplements, from iodophor medication, iodine-containing sterilizers of milking equipment, teat dips and udder washes. Some of the iodide in cereal products derives from iodate-containing dough conditioners. Other sources of iodide in food are iodised salt (Germany: 15-25 mg I/kg as KIO₃; Austria 20 mg I/kg as KI; Switzerland 25 mg I/kg as KI), bread and sugar supplemented with iodide in some countries, and iodine-containing herbicides/fungicides. Cooking reduces the iodine content of food, frying by 20%, grilling by 23% and boiling by 58% (WHO, 1996).

Non-food sources are iodine-containing medication, topical medicines, antiseptics (povidone-iodine), X-ray contrast media (~5000 mg/dose yielding 1-4 g in cholecystography, >10 g in urography), iodised oil for oral or i.m. use, mineral dietary supplements (up to 190 mg iodide/dose), tablets or capsules of seaweed-based dietary supplements (0.045-5 mg iodide/dose) and kelp tablets as dietary supplement (up to 57 mg iodide/dose) (Pennington, 1990). Marine macroalgae produced in China, Japan, the Philippines, North and South Korea are products grown in aquaculture from brown, red and green algae and can have an extremely high iodine content, particularly in marketed products derived from dried material (up to 6500 mg iodine/kg dry product). A product known as Kombu-powder contains about 0.5% iodine (BGVV, 2001).

2.2 Intake estimates

The intake of iodine generally corresponds to the amount entering the local food chain from the geochemical environment, and is normally low from food. If seaweed is consumed or if iodine-containing mineral supplements or medicinal products are ingested, it can rise to several mg/day (WHO, 1988; US Food and Nutrition Board, 2001). Individual intake from air may average 0.5 µg/person/day (NNT, 2002), that from water (assuming a consumption of 1.5-2 L/day) about 8-30 µg/person/day (WHO, 1988), that from food about 3-75 µg/serving (US Food and Nutrition Board, 2001). Ingestion of marine food or processed food containing iodised salt, calcium iodate, potassium iodate or cuprous iodide also increase the iodine intake.

Breast milk was reported in the 1980s to contain 12 µg/L in Eastern Germany, 27 µg/L in Italy, 95 µg/L in France, the median US value being 178 µg/L (Gushurst *et al.*, 1984). More recent reports quote for Germany 36 µg/L in 1992, 86 µg/L in 1994 and 95 µg/L in 1995-6 (Meng and Schindler, 1997). In general breastfeeding women produce daily 500-800 mL (average 780 mL) breast milk (SCF, 1993).

According to NHANES III the US median intake of iodine from dietary supplements was 140 µg/male or female adult. In 1986 some 12-15% of the US population were taking dietary

iodine supplements (US Food and Nutrition Board, 2001). According to FDA surveys the daily US median adult iodine intake was 240-300 µg for males and 190-210 µg for females, the highest intake of any life stage and gender for the 95th percentile excluding supplements being 1 mg/day and including supplements 1.15 mg/day (US Food and Nutrition Board, 2001).

In Germany the median daily iodine intake varied from about 64-118 (mean 45.3) µg I/day for males aged 4-75 years and from 59-114 (mean 44.2) µg I/day for females aged 4-75 years (Schneider *et al.*, 1995). For infants aged 6 months, children and young adults up to the age 18 years the mean iodine intakes varied from 31-64 µg/day for males and from 28-56 µg/day for females (Alexy and Kersting, 1999). In those taking iodine supplements once/week the corresponding mean levels were 124 µg I/day for males and 109 µg I/day for females compared to 107 µg I/day for males and 102 µg I/day for females not taking any supplements (Mensink and Ströbel, 1999). In Denmark the median intake was about 119 µg I/day for males and 92 µg I/day for females. In The Netherlands the median intake was about 145 µg/day for males and 133 µg/day for females (TNO, 1992). In Great Britain the median dietary intake from all sources was 226 µg/day for males and 163 µg/day for females, the 97.5th percentile reaching 434 µg/day in males and 359 µg/day in females. Survey data in young children aged 1½-4½ years show for high milk consumers in winter 247 µg/day to 309 µg/day, suggesting that some pre-school children are likely to have intakes exceeding the JECFA PMTDI (EGVM, 2002).

Dietary iodine absorption and incorporation is reduced by smoking, thiocyanates, isothiocyanates, nitrates, fluorides, Ca, Mg and Fe in food and water (Ubom, 1991). Glucosinolates (goitrogenic thioetherglycosides yielding on hydrolysis a thioglucose and the aglycones isothiocyanate, nitrils or thiocyanate) and goitrins block the incorporation of iodine into the tyrosine precursors of thyroid hormones and suppress thyroxine secretion (Cornell University, 2001). Degradation of cyanoglycosides (liberating cyanide on enzymatic hydrolysis in the gut which is subsequently metabolised to thiocyanate), glucosinolates and goitrins present in vegetables like brassica, crucifera, rape, cabbage, cauliflower, broccoli, Brussels sprouts, kale, kohlrabi, turnips, maize, lima beans, bamboo shoots, peanuts, walnuts, sweet potatoes, millets and cassava (linamarin is the cyanogenic glycoside in cassava) block the thyroidal uptake of iodine after ingestion thereby decreasing the production of thyroid hormones. Soya flour also inhibits the absorption of iodide by interference with the enterohepatic circulation of thyroxine. Hence goitre and hypothyroidism have appeared in infants fed entirely on soya-based infant formula. The latter is now enriched in the EU to a minimum content of 5 µg iodine/100 kcal intake. Water from polluted wells contains humic substances which also block the iodination process. Vitamin A-, Se-, Zn-, Cu-, Fe- and vanadium-deficiency can result in hypothyroidism and may exacerbate the effects of preexisting iodine deficiency. Large amounts of absorbed iodine, e.g. from radiological contrast media, from iodide liberated from erythrosine, from water purification tablets, from amiodarone (an antiarrhythmic drug), from skin disinfectants and dental disinfectants, also reduce iodine uptake causing the production of iodine deficiency symptoms.

2.2.1 Iodine excess

Excessive intake of iodine can occur as a result of ingestion of large amounts of seaweed, kelp, marine fish, ground beef containing thyroid tissue, iodised water, bread or salt and iodide-containing dietary supplements. The ingestion of iodine-rich algal products made from marine macroalgae grown in aquaculture in the Far East, particularly dried products, can lead to dangerously excessive iodine intakes, if such products contain more than 20 mg I/kg dry

matter and the exposed population lives in an area of endemic iodine deficiency. This would not apply to countries with traditional adequate dietary iodine intake (BGVV, 2001)

Excessive intakes can also follow the ingestion of iodide-containing pharmaceuticals for the treatment of asthma, bronchitis, cystic fibrosis, chronic obstructive pulmonary disease, and of goitre, after the use of amiodarone for the treatment of arrhythmias, of iodine-containing topical antiseptics, mouthwashes and vaginal solutions, and the treatment of burns and wounds with povidone-iodine. However the degree of absorption and incorporation of iodine from these sources is not known. Much circumstantial evidence links excessive iodine intake with the risk of increased incidence of autoimmune thyroiditis but environmental contaminants may also play a part (NNT, 2002).

2.3 Nutritional status

The nutritional status, and consequently the iodine requirements, of a population group can be assessed in various age groups by analysing the following indicators:

1. the fraction of an oral dose of ^{131}I concentrated in the thyroid gland;
2. the average daily iodine turnover (uptake and release) calculated following i.v. administration of ^{131}I ;
3. the urinary iodine excretion as determined in 24-hour samples, measured in $\mu\text{g/L}$ or $\mu\text{g/g}$ creatinine, representing more than 90% of the dietary intake. The minimum European urinary excretion should amount to 100 $\mu\text{g/day}$ (DGE, 2002), deficiency being indicated by iodine levels of $<50 \mu\text{g/L}$ (50 $\mu\text{g/g}$ creatinine). US data show 138-155 $\mu\text{g/L}$ for adult males and 110-129 $\mu\text{g/L}$ for adult females. Using a median 24-hour urine volume of 0.9 mL/hr/kg bw for children aged 7-15 years and a median 24-hour urine volume of 1.5 mL/hr/kg bw for adults, and assuming 92% bioavailability, allows calculation of the iodine intake from such urinary measurements (US Food and Nutrition Board, 2001);
4. the goitre incidence rate and size, the latter determined from ultrasound measurements rather than palpation. In mild Iodine Deficiency Disease (IDD) goitre prevalence in school children is 5-20% with a mean urinary iodine excretion of $>50 \mu\text{g/g}$ creatinine. In moderate IDD it is up to 30% with a mean urinary iodine excretion of 25-50 $\mu\text{g/g}$ creatinine. In severe IDD goitre prevalence is $>30\%$ with a mean urinary iodine excretion of $<25 \mu\text{g/g}$ creatinine;
5. the iodine balance estimates are only of limited use. The techniques are crude and the control of intake assessment is limited because some iodine sources always remain unknown (US Food and Nutrition Board, 2001);
6. the serum levels of TSH (thyroid stimulating hormone), Tg (thyroglobulin), T4 and T3 are the soundest parameters providing an indirect measure of iodine nutritional status. The best parameter is the TSH serum level especially if hypothyroidism is to be detected in pregnant women and neonates. Estimates can be performed on blood spots. The normal serum TSH range is 0.1-5 mU/L. The sensitivity can be increased by previous stimulation with TRH. An exaggerated response to TRH suggests an inadequate hormone availability, hypothyroidism and iodine deficiency. Elevated serum Tg levels are useful for detecting metastases of differentiated thyroid cancer,

hyperplasia of the thyroid and IDD. The serum level of Tg on adequate iodine intake is 10 ng/mL. Serum levels of T4 and T3 are less sensitive and unreliable for estimating iodine nutritional status. The normal T4 serum level is 100 nmol (80 µg)/L but is lower in IDD. The T3 serum level is normally 1.8 nmol (1.2 µg)/L but is lower in fasting individuals or those suffering from malnutrition (US Food and Nutrition Board, 2001).

2.4 Nutritional requirements

The recommended mean population intake for iodine is 100-150 µg/day (WHO, 1996). This is adequate to maintain normal thyroid function, growth and development. In the presence of goitrogens in the diet iodine intake should be raised to 200-300 µg/day. Vegetarians, sufferers of milk allergy, lactose intolerance, fish allergy or persons on low salt diet are liable to develop dietary iodine deficiency and therefore need iodine supplements. Pregnant and breastfeeding women need a higher iodine intake because the higher renal blood flow increases the urinary loss of iodine. Various international and national authoritative bodies have established requirements for iodine intake (SCF, 1993; US Food and Nutrition Board, 2001; DGE, 2002): In Germany and Austria the recommended adult daily intake is 200 µg and during pregnancy 230 µg, in Switzerland it is 150 µg and in pregnancy 200 µg. The SCF recommends as average requirement for adults 100 µg/day, as Population Reference Intake for adults and in pregnancy 130 µg/day, and in lactation 160 µg/day (SCF, 1993).

2.5 Metabolic fate of iodine and interrelationship with thyroid hormones

The biological function of the thyroid hormones T4, T3 and of iodotyrosines encompasses the regulation of energy metabolism and endocrine function by cellular oxidation, calorogenesis, thermoregulation, intermediate metabolism, protein and enzyme synthesis, nitrogen retention, gluconeogenesis and pituitary gonadotropins. Thyroid hormones also play a role in the intestinal absorption of glucose and galactose, in lipolysis and in the uptake of glucose by adipocytes, in the integrity of the connective tissue, and are necessary for optimum cellular metabolism particularly during early growth, development and maturation of most organs especially the brain. The target organs are the developing brain, muscle, heart, pituitary and the kidney. Additional functions of the thyroid hormones include a beneficial effect on mammary dysplasia and fibrocystic breast disease, support of the myeloperoxidase of leucocytes in the inactivation of bacteria and support of the immune response, while iodine lack may be associated with an increased incidence of gastric cancer (US Food and Nutrition Board, 2001).

The biological action of T3 and T4 is mediated through T3 receptors which bind free T3. These receptors are situated on inner mitochondrial membranes and in the nucleus. The nuclear receptors increase transcription for membrane protein and enzyme synthesis. These receptors belong to a superfamily together with steroid hormones, vitamin D and retinoid receptors, and are especially found in the pituitary, the liver and neonatal testis but are rare in the spleen. T3 and T4 may interact at receptor and gene expression level with sex hormones. They may upregulate hepatic oestrogen receptor levels in the rat. They also regulate the same subset of genes involved in lipid homeostasis (NNT, 2002).

Ingested inorganic iodine and iodate are reduced to iodide in the gut and almost completely absorbed by the small intestine. T3, T4 and the drug amiodarone are absorbed intact, while the metabolism of iodinated X-ray contrast media, e.g. lipiodol, is not entirely clear (US Food and Nutrition Board, 2001). The bioavailability of oral inorganic iodide is >90%, that of oral

T4 about 75%, some 15% of ingested iodide is taken up by the thyroid within 24 hours. Iodine can be absorbed dermally from topically applied material, the absorbed iodide is distributed in the extracellular fluid.

Some 30% of absorbed iodide is concentrated in the thyroid, the excess being excreted by the kidneys in the urine. About 80% of iodine stored in the thyroid is in the form of iodinated tyrosine, some 20% as thyronines and 1% as iodide (NNT, 2002). Minor tissue sites for iodide uptake from blood plasma are the salivary glands, the choroid plexus, the mammary gland, the kidneys, and the gastric mucosa. Iodide is able to cross the placenta. The biosynthesis of the biologically active thyroid hormones T3 (triiodothyronine), the most active, T4 (thyroxine), and the hormonally inactive T1 (monoiodo-3)- and T2 (diiodo-3,5)- derivatives of the precursor amino acid tyrosine utilises the circulating plasma iodide. T3 is produced by the deiodination of T4 in the liver and kidney of man and probably also in the thyroid of the rat. Plasma iodide is actively taken up by the basal membrane of the thyroidal follicular cells using a sodium-dependent, carrier-mediated pathway and concentrated 20-50 times in these cells. These follicular cells synthesise intracellularly the thyroglobulin (Tg), a glycoprotein of molecular weight 660,000. This Tg meets the iodide at the apical surface where the intracellular iodide is oxidised by thyroperoxidase (TPO), a Se-containing enzyme, in the presence of H_2O_2 to an iodonium ion which simultaneously attaches to the tyrosyl functional groups of Tg. Further action of TPO leads to the formation of T1, T2, and the coupling of 2 T2 to give T4 or of T1+T2 to give T3, all these thyronines remaining attached to the Tg. The iodinated Tg is stored extracellularly in the colloid of the thyroid follicles, about 1/3 of the iodine being present in T3 and T4, the rest in T1 and T2. When needed, T3 and T4 are released into the circulation from Tg by endosomal and lysosomal cellular proteases.

Thyroid function is regulated by a feedback process in which thyrotropin-releasing hormone (TRH) of the hypothalamus and thyroid-stimulating hormone (TSH) of the anterior pituitary are released in response to a decrease in circulating T3 and T4 levels. TSH stimulates within minutes the secretion of thyroid hormones, causes an increased iodide uptake and an increased Tg breakdown. Iodothyronine secretion, including T3 and T4, is also controlled by interaction between growth factors, their receptors and signal transition pathways. Epidermal and insulin-like growth factor also stimulate follicular cells (NNT, 2002). Iodine interacts with selenium and possibly with vanadium (EGVM, 2002).

Persistent action of TSH causes hypertrophy and hyperplasia of the thyroid gland, reduces the colloid and the stored iodine. TSH secretion of the anterior pituitary is stimulated also by TRH, a protein of molecular weight 28,000. TRH secretion is stimulated by α -noradrenergic impulses and inhibited by dopaminergic impulses but is also responsive to circulating levels of T3 and T4. The autonomous regulation of thyroidal iodine metabolism occurs independent of TSH (Forth *et al.*, 1987).

T1, T2, T3 and T4 are metabolised by specific deiodinases, a family of selenoproteins, the freed iodide entering either the plasma pool or being reutilised by the follicular cells. T4 is produced only by the thyroid gland, T3 is primarily produced (80% in man) by extrathyroidal deiodination in liver and kidney, brain, pituitary and brown fat and some (20% in man) by deiodination in the thyroid. In rats the deiodination of T4 takes place mainly in the thyroid (NNT, 2002).

TPO is inhibited by thioamides, the deiodinases forming the active hormone T3 are inhibited by thiouracil, propylthiouracil, propranolol, and glucocorticoids or may be genetically deficient. Monkey TPO is less sensitive to inhibition than rat TPO. Deiodinases show reduced

activity in Se-deficiency with consequent impaired hormonal activity (Forth *et al.*, 1987). Deiodinase activity is lower in human liver than in the rat.

Circulating T3 and T4 are in a reversible equilibrium attached to binding proteins synthesised by the liver, e.g. thyroxine binding globulin (Tg), transthyretin (prealbumin) (TTR), albumin and lipoproteins. In humans T4 is mainly bound to Tg, in rodents to TTR (NNT, 2002). Glucuronidation of T3 and T4 is less important in man. Less than 1% of T3 and T4 is free in plasma (NNT, 2002). Most biological action in the target tissues is probably mediated by T3 receptors. The bound T4 is enzymatically deiodinated to its active form T3, the liberated iodine entering the serum pool as iodide and being either reused by the thyroid or being excreted in the urine. T3 being less tightly bound enters cells more easily. In neonatal animals, in protein starvation, liver and kidney disease, and pyrexia T4 is mostly converted to T3.

The synthesis of normal quantities of thyroid hormones requires an adequate dietary intake of iodide but excess intakes may inhibit thyroid function by either inhibition of iodide organification (Wolff-Charkoff effect) or by inhibition of thyroglobulin proteolysis with reduction in hormone secretion. Plasma concentrations above 20-30 µg I/100 mL inhibit organic iodine uptake of the thyroid and intrathyroidal iodine is transformed from its inorganic form into organic iodine derivatives. Thiocyanate and perchlorate reduce thyroidal iodine transport and inhibit the conversion of the inorganic form of intrathyroidal iodide into its organic form, causing its discharge into the extracellular fluid (Forth *et al.*, 1987).

The average adult thyroid contains about 8-15 mg iodine, the total body iodine amounts to about 10-20 mg of which 70-80% is found in the thyroid, some also appearing in muscle and the eye. The thyroid store at birth is 0.1 mg. Some 70% (100-150 µg) of ingested iodide are excreted daily by adults on adequate iodine intake in the urine with partial reabsorption occurring in the renal tubules, about 20% (15-20 µg) are excreted in the faeces, about 5-10 µg appear in the sweat, saliva and the bile (US Food and Nutrition Board, 2001). Lactating women excrete 10-15% of the daily iodine intake into breast milk (Saller, 1998). In a 5-day old infant urinary excretion varies from 2.8-11 µg/100 mL. In Germany adult urinary iodine excretion varies from 20-65 µg/day, in Denmark males excrete 64 µg/day and females 73-100 µg/day (Vitti *et al.*, 1999). The renal iodide clearance is 34 mL/minute.

The placenta traps maternal excess serum iodide and transfers maternal T4 to the foetus until the foetus produces its own T4. Therefore iodine supply to the mother must be adequate to prevent foetal goitre formation (Glinioer *et al.*, 1995).

Administration of iodide to the rat also causes transient inhibition of intrathyroid organification of iodine and reduces hormone synthesis. Escape from this effect occurs through reduction in iodide transport mechanism until intrathyroid concentration of iodide is below the level necessary to maintain biosynthesis inhibition.

Many environmental agents interfere with thyroid function, the most prominent effect being the development of goitre but decreases in T3 and T4 may also alter brain maturation and testis development. Direct toxic effects include 1) inhibition of iodide transport into and uptake by the thyroid; 2) inflammation and degeneration of follicular cells; 3) damage to DNA of follicular cells; 4) accumulation of iodotyrosines in the gland. Indirect toxic effects manifest themselves by 1) changes in plasma transport of hormones e.g. by displacement from TTR; 2) increased iodotyrosine excretion by increased activity of hepatic microsomal enzymes; 3) inhibition of iodotyrosine deiodinases; 4) interference with the intestinal

absorption of T3 and T4 with faecal loss; 5) interference at the level of TSH or TTR (NNT, 2002).

2.6 Iodine deficiency

Several mechanisms compensate for low dietary iodine intake. If these mechanisms are insufficient clinical symptoms of iodine deficiency appear. These clinical effects are seen at all stages of development and are particularly noticeable in the foetus, the neonate and the infant as goitre, this being the commonest cause of human thyroid disease. Inadequate iodine intake and the resulting IDD are widespread in Europe and the developing countries of Asia, Africa and South America. They arise from a depletion of the thyroid iodine stores of the body with consequent fall in daily T4 and T3 production and their plasma levels, which trigger an increased secretion of TSH and hyperactivity of the thyroid coupled with thyroid epithelial cell hyperplasia, goitre formation, and faster iodine turnover. Simultaneously, tests show an increased uptake of ^{131}I (WHO, 1996). About 1600 million people are at risk of iodine deficiency disorders worldwide because they inhabit iodine-deficient environments. IDD is a public health problem in 118 countries. In Europe about 140 million are at risk. Worldwide some 700 million have goitre. Thyroid hypofunction can also be induced by thyroiditis and exposure to antithyroid compounds.

2.6.1 Iodine deficiency disorders (IDD) in adults

This is associated with goitre, low serum T4 and suboptimal brain function. In some areas apathy and low capacity for initiative and decision making is also seen. Goitrous enlargement of the thyroid gland occurs at intake levels of $<50 \mu\text{g I/day}$. It is the common feature of iodine deficiency (WHO, 1996). Goitre is initially diffuse but later becomes nodular with appearance of autonomous nodules, which may cause hyperthyroidism by production of T4 uncontrollable by TSH. The appearance of large goitres may cause obstruction of the trachea and the oesophagus and increases the risk of thyroid disease and thyroid cancer.

Hypothyroidism (myxoedema), another form of IDD, also results from hormone deficiency and is associated with reduced metabolic rate, cold intolerance, weight gain, puffy face, oedema, hoarse voice and mental sluggishness.

2.6.2 Foetal iodine deficiency

This results from maternal iodine deficiency. It is accompanied by higher rates of stillbirths, abortions and congenital abnormalities. Low maternal T4 levels ($<25 \mu\text{g/mL}$) are correlated with adverse pregnancy outcome, perinatal mortality and cretinism. The major hazard is endemic cretinism associated with iodine intakes of $<25 \mu\text{g/day}$. It is characterised by very low serum T4, T3, and a very high serum TSH (40-50 mU/L). The more common neurological type is characterised by mental deficiency, deaf mutism, spastic diplegia, the less common myxoedematous type by apathy, hypothyroidism, puffy features, growth retardation, delayed bone maturation, retarded sexual maturation and dwarfism. Endemic cretinism can disappear spontaneously without supplementary iodization measures but usually needs preventive treatment by iodised oil injection before pregnancy. Congenital hypothyroidism can occur despite adequate dietary intakes of iodine. Its incidence is 1/3000 to 1/4000 and is due to congenital maldevelopment or aplasia of the thyroid. In the US and in many European countries all neonates are screened by blood spot tests for TSH or T4 levels in order to detect any cases of congenital hypothyroidism due to thyroid aplasia (US Food and Nutrition Board, 2001).

2.6.3 Neonatal iodine deficiency

This is associated with increased perinatal and neonatal mortality and more frequent congenital abnormalities. It constitutes a threat to early brain development with consequent physical and mental retardation and possible later depressed cognitive and motor performance. This is a more serious socio-economic risk for children than the incidence of cretinism.

2.6.4 Iodine deficiency in children

Mild deficiency is associated with goitre in 5-20% of school children, appearing more frequently in girls, and is accompanied by a median urinary iodine concentration of 43.5 nmol I/nmol creatinine. School performance and IQs are impaired even if allowance is made for confounding factors. Growth is reduced and psychomotor development lags behind normal children noticeable already from age 2.5 years onward. Moderate iodine deficiency is associated with a median urinary iodine level of 21.5-43.5 nmol I/nmol creatinine, and a goitre frequency of 30%. Severe iodine deficiency is associated with a median urinary iodine level of <21.5 nmol I/nmol creatinine, with >30% goitre frequency and 1-10% incidence of endemic cretinism (WHO, 1996). A metaanalysis of 18 studies has shown that iodine deficiency alone may reduce the mean IQ scores by 13.5 points (US Food and Nutrition Board, 2001).

2.6.5 Iodine deficiency in animals

In animals reproductive, neurological and other defects are the important consequences of iodine deficiency. Natural iodine deficiency in farm animals, e.g. cattle and sheep, causes failure in reproduction, retarded or arrested foetal development with consequent foetal resorption, early foetal deaths, spontaneous abortions, stillbirths, as well as prolonged gestation and parturition, placental retention and low hormone levels. Maternal hypothyroidism before the onset of foetal thyroid secretion together with subsequent foetal hypothyroidism leads to reduced neuroblast multiplication. Maternal hypothyroidism in early pregnancy in the rat causes reduced pup weight and number of embryos, reduced brain weight and reduced transfer of maternal T₄.

Sheep on experimental iodine deficient feed of 5-8 µg I/day/40 kg bw showed more abortions, stillbirths and lower foetal weight, reduced or even complete absence of wool growth, retarded bone development, skull deformities, reduced brain weight, reduced brain cell numbers and brain DNA content. The same deficiency effects were seen in marmosets on 0.3 µg I/day/340 g bw (WHO, 1996).

2.6.6 Control of IDD

In Europe about 100 million and worldwide about 700 million individuals are affected by goitre. Of these some 1 million in Europe are also affected by impaired mental development compared to >11 million cases of cretinism worldwide (Vitti *et al.*, 1999). This constitutes a major public health problem. Combative measures are the introduction of iodised salt, iodised bread or iodised oil, the use of iodine supplements in the feed of cattle and pigs to raise the iodine level of milk and meat, and the preventive use of iodised oil by injection (1 mL contains 480 mg I) to all females in the human population in areas of severe IDD up to age 40 years and all males in the human population in areas of severe IDD up to age 20 years in areas

with poor control over iodine intakes of the population. If needed, injections should be repeated in 3-5 years. More recently iodised walnut or soya bean oil have been introduced as alternative oral treatment to supplementation of generally available dietary items with iodine.

2.6.7 Reported beneficial effects

Iodine supplements have been claimed to assist in the treatment of weight loss, rheumatism, ulcers, hair loss, maintenance of healthy arteries, nervous tissue and nails (EGVM, 2000). Iodine caseinate has been proposed as treatment for fibrocystic breast disease at doses of 70-90 µg I/kg bw (Murray and Pizzorno, 1998).

3. HAZARD IDENTIFICATION

3.1 Toxic effects in animals

Excess iodine intake in animals leads to acute inhibition of iodine uptake. Laboratory animals, poultry, pigs and cattle have a high tolerance to large iodine intakes. Animal data are of limited value because of species differences in basal metabolic rate and in iodine metabolism (US Food and Nutrition Board, 2001). The non-obese diabetic mouse (NOD)-42^{h4} develops spontaneously more frequent and severe autoimmune thyroiditis if iodine is added to the drinking water probably as a response to an increase in iodinated Tg (NNT, 2002).

3.1.1 Acute and subacute studies

The acute oral LD₅₀ in rats for NaI is 4340 mg/kg bw (3320 I), the oral LD₁₀₀ for KI in the mouse is 1862 mg/kg bw (1425 mg I) (Clayton and Clayton, 1981). Amounts of 200-500 mg/kg bw can cause death in experimental animals (SCOGS, 1975).

Two strains of chickens (CS and OS), genetically susceptible to autoimmune thyroiditis, were given either 20 or 200 mg KI/L in their drinking water for the first 10 weeks of their lives. At both levels the incidence of the disease was increased as shown histopathologically and also by measurements of T3, T4 and thyroglobulin antibody titres (Bagchi *et al.*, 1985).

Groups, each of 20 rats, were fed diets containing 0 or 1000 mg KI/kg diet (39 mg I/kg bw) for 19 weeks. No tumours of the thyroid were found either in controls or in treated animals. The exposure period in this inadequate study was too short for any carcinogenic effect to be detected (Hiasa *et al.*, 1987).

3.1.2 Reproduction and teratogenicity studies

Groups of female rats were given in their diet 0, 500, 1000, 1500 and 2000 mg KI/kg diet throughout gestation, lactation and weaning. Pup survival was reduced from 93% in controls to 16% in rats treated at the top dose and milk secretion was diminished. There were no adverse effects on ovulation rate, implantation rate and foetal development (Ammermann *et al.*, 1964).

Pregnant rats were given 11 mg KI/day in their drinking water (37 mg/kg bw/day) and the brain enzymes of pups investigated. Glutamate dehydrogenase was increased transiently, succinate dehydrogenase decreased transiently. Phosphofructokinase and malate enzymes

increased but hexokinases were unaffected. Serum T4 levels were unchanged compared to controls (Morales de Villalobos *et al.*, 1986).

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

3.1.3 Chronic studies

Metaplasia of the thyroid was reported in rats given potassium iodide in their drinking water for two years. This was thought to occur through a non-genotoxic proliferation dependent mechanism (EGVM, 2002).

3.1.4 Genotoxicity studies

The mutagenicity data for iodide are generally negative (EGVM, 2002)

3.2 Effects in humans

3.2.1 General observations on response to excess iodine

Disturbed thyroid gland activity as a result of excessive iodine intake may manifest itself either as a goitre, as hypothyroidism with/without goitre, or as hyperthyroidism (0.01-0.6% in populations on iodine prophylaxis, 0.25% in West Germany [JECFA, 1989]), the outcome depending on the initial and current iodine status and current thyroid dysfunction. Other effects may be sensitivity reactions (0.4-5%) (JECFA, 1989) and poisoning through ingestion of large quantities of iodine. Modest excessive iodine intake causes a temporary increase in iodide uptake by the thyroid with formation of more organic iodine and large hormone stores. Somewhat larger excessive intake inhibits the iodide release from thyrotoxic thyroids or from TSH stimulated glands and in 0.01-0.06% of exposed people leads to hypothyroidism. Greater excessive intake inhibits the formation of iodinated tyrosine, lowers the T4 and T3 plasma levels and raises the plasma TSH (Wolff-Charkoff iodide effect). These effects may be transient and in many individuals the thyroid can escape this Wolff-Charkoff effect. Individuals not escaping the Wolff-Charkoff effect develop goitre and become hypothyroid. The inhibiting effects of excess iodide occurs via unknown organic compounds, probably iodolipids (Cavalieri, 1997). TSH effects are blunted while the Wolff-Charkoff effect occurs. Other effects include the down-regulation of iodide transport, a raised ratio of iodotyrosines to iodothyronines in Tg, inhibition of pinocytosis and proteolysis with reduced hormone secretion (EGVM, 2000). The Wolff-Charkoff effect is the basis for the treatment of thyrotoxicosis with iodide. Very high intakes of iodide saturate the active transport system thereby preventing the uptake of radioactive iodine isotopes.

If excess intake occurs during pregnancy, the foetal thyroid is unable to escape the Wolff-Charkoff effect. The newborn therefore develops a goitre, is hypothyroid and may suffer possible tracheal compression. Alternatively, the condition may regress spontaneously postnatally after several months.

Some subpopulations such as those suffering from autoimmune thyroid disease, from IDD or nodular goitre with autonomous functioning nodules are sensitive to external iodine supply. They tend to respond adversely to levels of iodide which are without adverse effects in the general population. These persons may develop thyroiditis, goitre, hypothyroidism,

hyperthyroidism, sensitivity reactions, papillary thyroid cancer and acute effects following exposure to iodide. Iodine-induced hypothyroidism occurs particularly in underlying thyroid disease especially in women (Braverman, 1990).

There is much circumstantial evidence linking excess iodine intake with an increased risk of autoimmune thyroiditis. It is more prevalent in the US than in Europe because the US population has a higher iodine intake (250-500 µg I/day). It is also more prevalent in areas with adequate iodine intake. The existing homeostatic mechanisms control the tolerance to the widely changing dietary iodine levels except in a subsection of the population which develop thyroid dysfunction and autoimmunity on increased iodine intake. This occurs in IDD areas on introduction of iodine prophylaxis. T-cells from individuals with chronic Hashimoto's disease proliferate in the presence of iodinated Tg (NNT, 2002). Hashimoto's thyroiditis is associated with defective intrathyroidal organic binding of iodide leading to hypothyroidism at pharmacological iodide doses.

Hyperthyroidism can occur after an increase in iodine intake (iodine-induced thyrotoxicosis) usually in association with IDD but can also occur with non-toxic goitre. It is generally associated with nodular goitre and thyroid autonomy especially in elderly persons with IDD. Autonomy arises from mutation with activation of the TSH receptor or Gsα protein. The condition lasts about 1-6 months. It occurs also in euthyroid individuals from the use of iodinated compounds rather than from iodide, with 50% developing goitre but no exophthalmos. The mechanism is unclear (EGVM, 2000).

3.2.2 Excessive intake from food

In the normal human thyroid there is no real evidence that moderate acute excess iodine intake decreases thyroidal uptake of iodine largely because the variable dietary intakes do not appear to affect the serum levels of the thyroid hormones, the TSH level or the size of the thyroid gland. The normal amounts of iodine occurring in food do not cause goitre, thyrotoxicosis or iodine acne, only if intakes rise beyond the 10-fold normal value. Acute iodine excess increases thyroid hormone synthesis 10-20 fold while chronic iodine excess increases synthesis only 2-4 fold. Chronic intake of moderate or large doses of iodine decreases the serum level of thyroid hormones, increases TSH serum levels, increases the TSH response to TRH, and increases the size of the thyroid gland. In a random trial in Wales some participants received 500 µg iodide in addition to their normal daily intake of 250 µg. Some of those receiving the additional iodine showed significantly elevated TSH levels compared to the placebo controls (Chow *et al.*, 1991).

Excessive intakes can cause an increase in thyrotoxicosis and Hashimoto's disease (with autoantibodies against thyroid proteins), but can also reduce the incidence of toxic nodular goitre and diffuse non-toxic goitre. It can also induce hypothyroidism in autoimmune glands. These changes are not seen in Japanese people despite an average intake of 50-80 mg I/day. In these circumstances urinary iodide excretion would increase to 20 mg/day or more.

3.2.3 Excessive intake from anthropogenic sources

In iodine-induced hyperthyroidism excess hormone is produced. This occurs especially in areas with endemic goitre or IDD, when iodine supplementation of the diet is introduced. In normal circumstances or at intakes <5 mg/day by populations which had no previous experience of iodine deficiency the incidence of hyperthyroidism or toxic nodular goitre is rare (Nagataki, 1987). In populations with preexisting IDD 5-8% may get transient

hyperthyroidism and thyrotoxic goitre even at normal levels of iodine intake (150-200 µg/day) but always in response to dietary iodine supplementation. These effects occur usually in individuals aged 40-50 with nodular goitre or autonomous thyroid tissue (hormone production not controlled by TSH) or in individuals under 40 with undiagnosed Graves' disease. If the introduction of iodised salt to combat IDD is accompanied by poor monitoring of the quality of the iodised salt and of the iodine intake of the affected population cases of iodine-induced hyperthyroidism will occur. This was noted in Zimbabwe and the Democratic Republic of Congo (Delange *et al.*, 1999). Intake of water containing 1 mg I/L caused impaired iodotyrosine formation in 13% of individuals. In asthmatics and bronchitics treated with KI some 0.5% developed myxoedema and 0.2% showed slight thyroid enlargement. In cystic fibrosis patients treated with saturated KI solution some 15% developed goitre, 5% hypothyroidism and 5% goitre plus hypothyroidism.

3.2.4 The effect of pregnancy

Pregnancy is goitrogenic therefore intakes of >100-200 µg I/day are required to prevent the development of goitre and to keep the serum levels of free T4 and T3 stable. Intakes of <50 µg I/day during pregnancy lead to hypothyroidism and the development of goitre in the mother and the newborn (Glinioer *et al.*, 1995). Pregnant and breastfeeding women need a higher iodine intake because of increased urinary loss of iodine.

Excessive prenatal maternal iodine exposure of the order of 12-1650 mg iodide/day (0.2-27 mg/kg bw/day) from expectorant mixtures consumed during pregnancy was associated with 8 congenital goitres and hypothyroidism in infants but a clear causal relationship could not be demonstrated (Carswell *et al.*, 1970). Maternal multiple topical applications of povidone-iodine (1% free I) have produced hypothyroid infants (Danziger *et al.*, 1987). Similarly, maternal rectal irrigation with povidone-containing solutions have produced hypothyroid infants (US Food and Nutrition Board, 2001).

Pregnant women with concomitant excessive thyroid stimulation due to iodine deficiency, diagnosed by reduced free serum T4, reduced urinary I excretion, increased serum Tg, T3/T4, TSH and increased thyroid volume, if untreated, developed goitre in 18% of cases and the neonates had larger thyroids. When treated with either 100 µg KI/day or 100 µg KI + 100 µg L-T4/day TSH levels returned to normal, Tg decreased, and no goitre developed, while in the newborn Tg was also lowered and thyroid volume remained normal (Glinioer *et al.*, 1995).

3.2.5 Goitre and thyroid cancer

Some 70% of the epithelial tumours of the thyroid are papillary carcinomas, 15% are follicular carcinomas, >5% are anaplastic carcinomas, while some 5-10% arise from medullary calcitonin-producing C-cells. The papillary carcinomas are less aggressive while the follicular carcinomas have a worse prognosis. Carcinomas are more frequent in females than males, occur especially in the aged and the mortality ranges from 0.2-0.7/100,000 females. Thyroid cancer incidence is increasing in many countries, particularly Norway and Denmark, but mortality rates are decreasing (NNT, 2002). The incidence shows great geographical variation between and within countries indicating an influence of exogenous factors. In man the only well established cause of thyroid cancer is external radiation to the thyroid (NNT, 2002). Goitre predisposes to thyroid papillary cancer as diffuse hyperplasia may be followed by nodular hyperplasia, benign tumour formation and eventual follicular papillary cancer, the risk being related to the presence of goitre and not the functional state of the thyroid. There is no animal evidence for this cancerogenic effect of goitre. The effect of

iodine prophylaxis on the incidence of thyroid cancer in an IDD area of Argentina was examined by comparing the incidence in the 15 years before introduction of iodised salt with the incidence in the next 16 years. The incidence of papillary carcinoma increased but there was no effect on the incidence of follicular or medullary cancer. The papillary carcinomas were associated with a higher occurrence of lymphocytic thyroiditis (Harach and Williams, 1995).

Low dietary iodine intake may produce an increased gonadotrophic stimulation possibly leading to a hyperoestrogenic state with greater production of oestrogens and oestradiol. This may increase the risk of breast, endometrial and ovarian cancer (Stadel, 1976).

3.2.6 *Acute exposure*

Suicides have occurred with Lugol's solution, causing burning of mouth, gastrointestinal irritation, abdominal pain, ulceration, hyperthyroidism, haemolytic anaemia, acute renal failure with tubular necrosis, delirium, stupor and collapse. Tincture of iodine ingestion can cause vomiting, abdominal cramps, diarrhoea, anuria, fever, weak pulse, cardiac irritability, cyanosis, coma and death. Ingestion of 1184-9472 mg I causes death within 48 hours.

Doses of 2000-3000 mg iodine (30-40 mg I/kg bw) are probably lethal to humans but survival has been reported after ingestion of 10-15 g. Exposure to iodine vapour causes lung, eyes and skin irritation. Iodide in expectorant mixtures has been used at doses of 3.3 mg/kg bw mostly without adverse reactions. Iodine intakes >10 mg/day from drugs or accidental poisoning is toxic for some individuals (WHO, 1988).

The intake of foods or seasonings made from algae or seaweed containing more than 20 mg iodine/kg dry mass could damage health (BGVV, 2001)

Thirty two individuals, of which 22 had Hashimoto's thyroiditis and 10 normal controls were given a single dose of 2.0 mg iodide and the effect on the uptake of ¹³¹I was measured and compared with the uptake before treatment. Patients with thyroiditis had their I uptake reduced by 54%-99%, normal persons had a reduction of 8-54%. Thus iodide aggravated some thyroid disease (Paris *et al.*, 1961).

3.2.6.1 *Sensitivity reactions to iodine*

Iodide can also give rise to sensitivity reactions such as urticaria, angiooedema, polymyalgia, conjunctivitis, coryza, iodide fever, headache, salivary gland enlargement, cerebral symptoms and hypotension. Iododerma, eosinophilia, pruritic rashes, vesicular eruptions and fungoid eruptions may also occur (WHO, 1988). Some 3.2% of individuals treated with ¹³¹I-labelled protein developed sensitivity reactions. Following amiodarone treatment about 0.4% developed erythema nodosum. In individuals with hyperthyroidism treated with iodide some 1.75% developed fever. In asthmatics/bronchitics treated with KI about 5% showed swollen salivary glands, 3% had runny noses, 2% headaches and 15% gastrointestinal complaints. In individuals treated with contrast media for urography (I content 4935-5150 mg/dose) some 1.7% experienced acute allergic reactions and 1.5% suffered from hives, sneezing, nasal congestion, pruritus and facial oedema, diffuse rash, hypotension, collapse, asthma, laryngeal oedema, grand mal seizures and parotid swelling.

3.2.7 Subchronic exposure

For persons with autonomous thyroid tissue intakes of 100 µg/day posed no risk (Joseph *et al.*, 1980) but 200 µg/day caused thyrotoxicosis in some people resident in an IDD region (Stewart, 1975). Iodide supplementation of 1500 µg/day had a significant inhibitory effect on thyroid function in normal men (Meyers *et al.*, 1985). An evaluation of the oral doses at which adverse effects were reported showed 21 cases out of 1256 (1.7%) reported in the literature at doses <1.0 mg/day, while 49 cases out of 1256 (3.9%) occurred at doses of =10 mg/day. Of these some had underlying thyroid disease which may have affected their response to the extra iodine supplied (Pennington, 1990).

Normal subjects receiving 50-250 mg iodide/day for 10-14 days were reported to show subtle changes in thyroid function. These consisted of small but significant decreases in serum levels of T4, T3 and concurrent small compensatory increases in basal serum TSH concentrations and exaggerated serum TSH responses to i.v. TRH (Vagenakis *et al.*, 1973; Saberi and Utiger, 1975). The dietary intakes of iodine were not recorded in these studies.

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

Pharmacological doses of iodide of 1000 mg/person/day administered to 4 normal euthyroid volunteers for 11 weeks caused small but significant decreases in serum levels of T4 and T3 and compensatory increases in basal serum TSH levels and the responses elicited by TRH (Jubiz *et al.*, 1977).

The ingestion of about 3 mg iodine/day for 6 months during daily mouth-rinsing with an iodine-containing mouthwash had no effect on thyroid function (Ader *et al.*, 1988).

The ingestion of 200 mg/day of erythrosine (I-rich food colour) for 2 weeks caused a small increase in basal and TRH-stimulated TSH secretion. The urinary iodine excretion was about 1200 µg/day (Gardner *et al.*, 1987).

A study was designed to determine the effectiveness of oral doses of iodide (199, 300, 600, 1000 µg/day) in suppressing ¹³¹I uptake in groups of 4-10 children of different ages (1-3, 4-6 and 9-11 years) with clinically normal thyroid function as protection in the event of radio-iodine fall-out following a nuclear incident. In the group 1-3 years old, a decrease in uptake occurred with 300 µg/day within 2 weeks, and a further fall occurred when the intake was subsequently increased to 600 µg/day. Suppression of uptake was also analysed in relation to the iodide dose expressed as µg/m² body surface area/day. The maximum suppression of uptake occurred within 2 weeks with 1500-2000 µg/m². Doses of 100 µg/m² slightly increased uptake. The NOEL for any effect on the uptake of ¹³¹I by children aged 1-11 years was 100 µg/m²/day. No toxic effects were noted at any of the doses used, however the study used only small groups, exposure was short and the groups may not have included susceptible individuals. No indication of the iodine intake from the children's daily diet was given, and therefore it is not possible to calculate the total intake. A dose of 100 µg/m² is equivalent to about 170 µg/day (in addition to intake from food) for an adult (assuming 1.7 m² body surface area) (Saxena *et al.*, 1962).

The studies of Paul *et al.* (1988), Gardner *et al.* (1988), and Chow *et al.* (1991) are also subchronic studies and these are described in detail in Section 4 (Dose-response assessment).

3.2.8 Chronic exposure

Chronic exposure to iodine causes iodism. The symptoms resemble coryza as well as salivary gland swelling, gastrointestinal irritation, acneform dermatitis, metallic taste, gingivitis, increased salivation, conjunctivitis and oedema of eye lids (Goodman and Gilman, 1970). Some consider 2 mg iodide/day (0.03 mg/kg bw) excessive but the Japanese appear to consume 50-80 mg/day (0.8-1.3 mg/kg bw) without adverse effects (Mertz, 1986).

In a study on 37 patients with chronic lung disease, treated with 1000-2000 mg iodine/day for a mean 2.2 years, some 13 became clinically hypothyroid but in 7 of these patients normal thyroid function returned on withdrawal of iodine medication (Jubiz *et al.*, 1977).

The introduction of iodised bread in The Netherlands raised the daily intake by 120-160 µg iodine resulting in an increase in hyperthyroidism (Van Leeuwen, 1954). The use of winter milk in the UK raised the iodine intake of women to 236 µg/day and of men to 306 µg/day and was associated with a peak incidence of hyperthyroidism (Nelson and Phillips, 1985). In 32 young adult Swiss with simple goitre (and urinary I excretion of 32 µg/day) given 200 µg I/day only one case of transient hyperthyroidism appeared which showed a serum T4 of 14 µg/100 mL, a serum T3 of 293 ng/100 mL, suppressed TSH, tachycardia and weight loss (Baltisberger *et al.*, 1995).

When iodine intake was increased by iodide tablets, iodised bread and iodophors in Tasmania to 200 µg/day the incidence of hyperthyroidism rose from 24 to 125/100,000 in subjects >40 years suffering from multinodular goitre and preexisting heart disease over a period of 10-12 years (Connolly *et al.*, 1970). In Tasmania the incidence of nodular goitre and toxic nodular goitre was eliminated in persons with normal thyroids. Those which developed hyperthyroidism also had autoimmune antibodies (Adams *et al.*, 1974). A clinical survey of 30 hyperthyroid patients observed in Tasmania after the introduction of bread fortified with iodate detected 8 patients with autonomous thyroid nodules but no thyroid stimulating antibodies, 16 patients without localised autonomy but with antibodies and 6 patients without either localised autonomy or antibodies. Serum TSH was 0.15 mU/mL or less in all cases. Hence this crop of hyperthyroidism cases was due to the latent hyperthyroidism associated with the presence of toxic nodules or thyroid stimulating antibodies (Adams *et al.*, 1975).

The introduction of iodised salt (30-90 mg I/kg) in Zimbabwe, an area of moderate to severe IDD, led to an increase in cases of hyperthyroidism, normally rare among African populations, as shown by a review of local hospital records of relevant laboratory tests for free T3, T4 and serum TSH levels. The annual incidence of hyperthyroidism rose from about 90 to about 163 during two years after the introduction of iodised salt (30-90 mg/kg). A review of some 235 patients diagnosed as thyrotoxicosis showed an incidence of Graves' disease of 27% and of toxic nodular goitre of 58%. Patients were mostly females with a mean age of 50 years. Some 14 deaths occurred from heart failure with atrial fibrillation and some embolic episodes. Urinary iodine levels had risen from a median 20 µg/L to 238 µg/L. The problem of iodine-induced hyperthyroidism appeared to have lasted for about 2 years (Todd *et al.*, 1995).

Similar reports of iodine-induced biochemical and overt clinical hyperthyroidism in IDD areas have come from the Democratic Republic of Congo and 7 other African countries after the introduction of iodised salt. These measures reduced considerably the goitre prevalence in

school children and urinary iodine levels indicated the elimination of IDD (Delange *et al.*, 1999).

In a 5-year study using iodinated drinking water (1 mg/L) supplied to 750 male and female prison inmates no hyper- or hypothyroidism, no sensitisation reactions and no iodism were noted. The average dose was 30 µg/kg bw. There was a statistically significant decrease in ¹³¹I uptake and an increase in protein-bound iodine (PBI) of the thyroid. One-hundred and seventy seven women inmates delivered 181 infants showing no thyroid-related adverse effects. Four hyperthyroid women became more hyperthyroid. The difficulties with this study were the imprecise estimates of intakes from the diet and fluid consumption of the participating individuals as well as the variable exposure time but the group size and duration of exposure were adequate (Stockton and Thomas, 1978).

4. DOSE/RESPONSE ASSESSMENT

A study on the effects of doses of 250, 500 or 1500 µg iodide/day for 14 days on thyroid function was carried out in 9 euthyroid men (mean age 34 years) and 23 euthyroid women (mean age 32 years) with 5 age-matched controls. The parameters examined were PBI, total serum iodine, T4, T3, TSH, integrated 1-hour serum TSH response to an intravenous dose of 500 µg TRH, and 24-hour urinary iodine excretion. The dietary intake of iodine was estimated from the urinary iodine excretion to be approximately 200 µg/person/day making the total ingested doses approximately 450, 700 or 1700 µg iodide/day. The estimated dose of 1700 µg/day increased the total serum iodine without affecting the PBI, significantly decreased serum T4 and T3 and increased TSH levels, whilst 700 and 450 µg/day did not affect significantly these values. Only 1700 µg/day increased the TSH response to TRH (in women more than in men). The TSH response to TRH was also increased, though not significantly, in the individuals receiving 700 µg iodide/day. No biochemical effects were detected with 450 µg of iodide/day; however this study used only small groups, extended over only 2 weeks and the dietary iodine intake was not determined analytically but was estimated (Paul *et al.*, 1988).

In another study groups of 10 males (mean age 27 years) were treated for 2 weeks with either 500, 1500 or 4500 µg iodide/day. The dietary intake was estimated from urine iodine excretion to have been approximately 300 µg/person/day making the total ingested doses approximately 800, 1800 or 4800 µg iodide/day. Serum levels of T3, T4, TSH, PBI, and total iodide, the TSH response to intravenous TRH and 24-hour urinary excretion of iodide were measured before treatment and again on day 15. Serum T4 levels decreased significantly after ingestion of 1800 µg and 4800 µg/day but did not change after 800 µg/day. Serum T3 levels did not change at any dose. Serum TSH levels remained unchanged in those receiving 800 µg/day but increased in those receiving 1800 µg and 4800 µg/day. The TSH response to TRH was significantly enhanced with all iodide doses administered. No adverse effects were reported and no significant symptoms of thyroid dysfunction were noted. Again only small groups of subjects were studied, only males were examined, exposure was rather short and the actual dietary intake of iodine was not determined analytically but estimated (Gardner *et al.*, 1988).

A study on the effect of supplementation of normal dietary intakes (about 250 µg I/day) with 500 µg/day iodide, giving a total iodide intake of approximately 750 µg iodide/day, or a placebo for a period of 28 days, on the serum levels of free T4 and TSH was carried out in women selected from a general practice in Cardiff. The groups studied were aged 25-54 years and thyroid antibody positive (subclinical Hashimoto's thyroiditis) (n=20) or antibody

negative (n=30), or aged 60-75 years and from an area with adequate dietary iodine supply (n=29) or from an area that was previously iodine deficient (n=35). The study was described as a randomised placebo-controlled trial, but it is not clear whether the study was of crossover or parallel group design. Small decreases in T4 levels and small increases in TSH levels, indicating mild biochemical hypothyroidism, occurred in all iodide-supplemented subjects of all groups. None of the groups on supplemental iodide showed any incidence of hyperthyroidism. Following iodide supplementation TSH levels increased above the normal level of 5 mU/L in 3 of the 60-75 year old subjects, while the raised TSH levels increased even further in 2 antibody-positive subjects (Chow *et al.*, 1991).

5. DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

The parameters altered in these dose-response studies included an elevation of serum TSH levels in response to iodine intake and the enhanced response in TSH levels to TRH stimulation. They were all of a biochemical nature and not associated with any clinical adverse effects. However, elevated serum levels of TSH are not necessarily clinically adverse, but could be regarded as indicators of an existing risk of induced hypothyroidism. There is uncertainty whether the subtle changes observed, such as an enhanced response to TRH, would have significant adverse biological consequences even if sustained over longer periods, because all observed values remained within the normal ranges for the parameters determined. It remains uncertain whether chronic exposure to these small doses would have any relevant clinical consequences in normal euthyroid individuals.

An UL can be established on the basis that the noted biochemical changes in TSH levels and the TSH response to TRH administration were marginal and unassociated with any clinical adverse effects at estimated intakes of 1700 and 1800 µg/day.

Although the studies on which these UL estimates are based were all only of short duration, involved only a small number of individuals, and lacked precision of the actual total dietary intakes, their results were supported by the study covering a 5-year exposure at approximately similar iodide intake levels of 30 µg/kg bw/day (equivalent to approximately 1800 µg iodide/day) in which no clinical thyroid pathology occurred. An UF of 3 is thus considered adequate and provides an UL for adults of 600 µg/day.

The UL of 600 µg is also considered to be acceptable for pregnant and lactating women based on evidence of lack of adverse effects at exposures significantly in excess of this level.

Since there is no evidence of increased susceptibility in children, the ULs for children were derived by adjustment of the adult UL on the basis of body surface area (body weight^{0.75}).

Age (years)	Tolerable Upper Intake Level (UL) for Iodine (mg per day)
1-3	200
4-6	250
7-10	300
11-14	450
15-17	500

In the US the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board together with Health Canada are pursuing a joint project

which proposes a tolerable upper level of intake for iodine for adults of 1100 µg/day (US Food and Nutrition Board, 2001). WHO has suggested a provisional maximal tolerable daily intake of 1 mg/day from all sources, equivalent to 17 µg/kg bw (WHO, 1988). In countries with long-standing IDD the intake should not exceed 500 µg/day to avoid the occurrence of hyperthyroidism. In France the Expert Committee on Human Nutrition has suggested an UL of 500 µg I/day in countries with long-standing IDD to avoid the occurrence of hyperthyroidism (AFSSA, 2001).

6. CHARACTERISATION OF RISK

Data from European populations indicate that the intakes of iodine from all sources in adults are unlikely to exceed the UL. For example, in the UK where iodine intake is considered to be high relative to other European countries, the 97.5 percentile intake in men is 434 µg/day.

In the UK survey data in young children aged 1½-4½ years have shown that iodine intakes may vary from 87-309 µg/day, with almost all iodine deriving from the consumption of milk. High winter milk consumers may ingest up to 247-309 µg/day. The UK COT considered that the intake of iodine at the concentrations that have been found in cow's milk is unlikely to pose a risk to health even in those children who are high level consumers (COT, 2000). The SCF agrees with this and notes that an UL is not a threshold of toxicity but may be exceeded for short periods without an appreciable risk to the health of the individuals concerned.

Ingestion of iodine-rich algal products, particularly dried products, can result in dangerously excessive iodine intakes.

These ULs do not apply to IDD populations, as these are more sensitive to iodine exposure.

The UL is not meant to apply to individuals who are being treated with iodine under medical supervision.

7. RECOMMENDATIONS FOR FUTURE WORK

1. More precise definition of the safety levels for iodine-sensitive individuals relative to those with normal thyroid function.
2. Better data on the iodine intake and thyroid status of children aged 1-3 years.

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