

EXPERT GROUP ON VITAMINS AND MINERALS

REVISED REVIEW OF IODINE

The attached review of iodine is a revised version of the paper first presented to the Expert Group on Vitamins and Minerals at the meeting on 29 March 2000. It has been amended to take account of some of the comments made by members and to correct a number of minor inaccuracies. Revised versions were presented to the Group at the meetings in October 2001 and December 2001.

The following annexes are attached to this paper:

- Annex 1 Tables referred to throughout the review
- Annex 2 Intakes of Iodine from food and supplements in the UK
- Annex 3 Summary table of selected nutrition related information and existing guidance on intakes

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IODINE

Chemistry and Geochemistry

1. Iodine is a group VII element, that is, a halogen. It has an atomic weight of 126.9. Elemental iodine occurs as a blue-black solid, which sublimes into gaseous form at room temperature.
2. Although less reactive than the other halogens it readily forms compounds with many elements, common compounds include iodides (e.g. KI) and iodates (e.g. KIO₃). The main oxidation state for iodine is -1 but it can exist in oxidation states ranging from 0 to VII. The naturally occurring isotope of iodine is ¹²⁷I; radioisotopes of iodine range from ¹²⁰I to ¹³⁵I.

Natural Occurrence

3. Iodine is present in seawater at low levels (approximately 0.05 ppm) where it is taken up by seaweed, marine algae, fish etc. Iodine is also present in igneous rocks and soils.

Occurrence in food, food supplements and medicines.

Food

4. Iodine in the diet is present in inorganic forms such as iodate or iodide. Rich sources of iodine include marine fish (up to 0.25 mg/100 g), shellfish (up to 0.16 mg/100 g) and sea-salt (up to 0.14 mg/100 g). In the UK, cows' milk is also a source of iodine (average level, 0.015 mg/100 g) as the element is included as a supplement in cattle feed and is present in the iodophors used for sterilising milking equipment and as teat washes. Iodine levels in grains and cereals vary depending on the iodine content of the soil. In certain countries, table salt has to be iodized. The red food colour erythrosine is also rich in iodine (Braverman, 1987).
5. The iodine content of raw food is reduced by cooking (WHO, 1996). For example, the iodine loss on boiling or grilling/frying fish was 50-82 and 20% respectively (Harrison *et al.*, 1965).

Food Supplements

6. Iodine is present in a variety of food supplements, both in multi-mineral and/or vitamin products (providing doses of up to 0.1 mg/day) (OTC, 2001) and in products derived from seaweed (kelp).

Licensed medicinal products for oral use

7. Iodine (as iodine, sodium iodide or potassium iodide) may be included in products sold in supermarkets and other retail outlets without the supervision of a pharmacist. The maximum permitted daily dose is 10 mg elemental iodine. Four authorised medicinal products containing iodine (in addition to other nutrients) may be sold in supermarkets and other retail outlets, whilst nine may only be sold under the supervision of a pharmacist. Their licensed uses include the prevention and treatment of nutrient deficiencies, debility, supplementation of special diets and malabsorption. The maximum daily doses specified in the licences for most products are up to 150 micrograms elemental iodine.
8. Of particular interest in relation to the effects of excess iodine is the anti-arrhythmia drug, amiodarone.

Other sources

9. Iodine solutions are widely used as topical medicines, antiseptics such as povidone-iodine (povidone being a polymer, which binds iodine) and radiographic contrast solutions.

Intake and Exposure

10. Iodine, derived from seawater, is present in air at levels of 10-20 ng/m³. It has been estimated that an individual inhales an average of 0.5 µg/day (Nordic Project Group, 1995).
11. Iodine concentrations in unpolluted surface waters have largely been reported to be less than 3 µg/l. Drinking water generally contains less than 15 µg/l, though much higher concentrations occur in some instances. Assuming consumption of 1.5 to 2 litres/day, iodine intake from drinking water would normally be less than 30 µg (discussed JECFA, 1989).
12. Iodine intake is very dependent on the composition of the diet, but average daily intakes of 1 mg/person (increasing to several mg/person where seaweed is consumed) are not uncommon (JECFA, 1989). In the UK, mean intake from food has been estimated to be 0.219 mg/day. In high level (97.5%ile) adult consumers, iodine intake from food has been estimated to be 0.434 mg/day. The details are provided in Annex 1. When calculated on a body weight basis, iodine intakes in infants and children are significantly higher than those in adults as a result of the larger proportion of milk consumed by children. Figures on consumption data from the survey of 1½-4½ year olds shows that mean total iodine intake for high level consumers of milk during the winter ranged from 247 µg/day in 3½ year olds and 309 µg/day in 1½ -2½ year olds. This data suggests that some high level consumers of milk in the pre-school children age group are likely to have intakes above the JECFA Provisional Maximum Tolerable Daily Intake (PMTDI) of 1 mg.

13. The drug amiodarone contains 37.2% iodine by weight and the daily dose ranges from 0.2 to 1.2 g (BNF, 1999). A substantial proportion of the drug is thought to be deiodinated following consumption (Fradkin and Wolff, 1983). The half-life of amiodarone is variable, ranging from 5 to 100 days. The iodine content per dose of radiographic contrast agents is 1-4 g for cholecystography and over 10 g for urography; up to 5 mg free iodide per dose may be present as a contaminant (Fradkin and Wolff, 1983).

Recommended Amounts

14. The Lower Reference Nutrient Intake for iodine in adults is 70 µg/day and the Reference Nutrient Intake 140 µg/day (COMA, 1991). No increments were added for pregnancy or lactation. The Population Mean Intake recommended by WHO (1996) is 100 to 150 µg/day. However this is increased to 200-300 µg/day where there are goitrogens present on the diet. Intakes of 200 µg/day were recommended for pregnancy and lactation.

Analysis of Iodine status

15. Iodine status can be measured by assessing the goitre rate in the population, by measuring urinary iodine excretion (deficiency is indicated by iodine levels <390 nmol (50 µg)/g creatinine), or by measuring blood thyroxine (T₄) Thyroid Stimulating Hormone (TSH) levels (WHO, 1996) or measurement of thyroid volume by ultrasonography (Delange *et al.*, 2000). Normal circulating levels of T₄ are 100 nmol (equivalent to 80 µg/ and T₃ (triiodothyronine) concentrations are 1.8 nmol (equivalent to 1.2 µg/l). However, in regions of endemic goitre (see paragraphs 42-47) these techniques are not feasible so the extent of the problem can be assessed by the prevalence of goitre in the area. There are 3 levels of severity:
- 1) Mild iodine deficiency – the prevalence of goitre in school children is between 5 and 20%, and the mean urine excretion of iodine is >50 µg/g creatinine.
 - 2) Moderate iodine deficiency – prevalence of goitre up to 30%, some hypothyroidism and median iodine excretion between 25 and 50 µg/g creatinine.
 - 3) Severe iodine deficiency – prevalence of goitre > 30% and endemic cretinism between 1-10%; median iodine excretion is < 25 µg/g creatinine.

Bioavailability

16. Little information is available on the bioavailability of iodine (Nordic Project Group, 1995). Where data exist, bioavailability appears to be high. Over 80 % of radiolabelled iodine injected into fish, two days prior to cooking and consumption, was excreted by volunteers over a 5 day period (Harrison *et al.*, 1965). However, it is known that goitre (probably of the iodine deficiency type) can occur in infants given soy-based formulae. This is thought to be due to interference with the enterohepatic recirculation of thyroxine. Soya formula is thus enriched with

iodine; in the UK, the *Infant formula and follow-on formula regulations* specify a minimum iodine content of 1.2 µg/kJ (5 µg/100kcal).

Interactions

Cations and anions in drinking water

17. Certain cations and anions present in drinking water (nitrate, fluoride, calcium, magnesium and iron) may be goitrogenic in iodine deficiency areas (Ubom, 1991).

Cyanogenic glycosides and other natural goitrogens in foods.

18. Degradation of the cyanogenic glycosides present in foods such as corn, maize, cassava, potato, cauliflower and broccoli can lead to the production of thiocyanate, which is a natural goitrogen (i.e. a substance that impairs thyroid hormone synthesis). Soybeans, peanuts and walnuts may also contain natural goitrogens.

Selenium

19. This interaction is considered in detail in the review of selenium (EVM/99/17). Where deficiency of both iodine and selenium has occurred, it has been suggested that supplementation with selenium alone may exacerbate the iodine deficiency since selenium is a component of the enzyme tetraiodothyronine 5-1'-deiodinase I, which increases urinary excretion of iodine (Nordic Project Group, 1995). However this effect is apparent only in situations of extreme deficiency of both elements and is not relevant to the UK.

Vanadium

20. Absolute and relative thyroid weights were increased in Wistar rats deprived of vanadium (Uthus and Nielsen, 1990). As iodine intake increased, plasma glucose increased in the vanadium deficient animals and decreased in the vanadium supplemented animals. As dietary iodine increased, thyroid peroxidase activity decreased. This was more marked in the vanadium supplemented rats. The authors concluded that vanadium could have a role in iodine metabolism and thyroid function.

Coal-Derived pollutants

21. Endemic goitre in iodide sufficient areas of the US and Columbia has been linked to water-soluble goitrogens (Lindsay *et al.*, 1997). Some of the water-soluble compounds derived from coal, such as 2 and 5-methyl resorcinol were found to be substantially more potent goitrogens than the anti-thyroid drug 6-propylthiouracil. Other compounds with less potent activity included thiocyanate, disulphides and hydroxypyridines. When tested in combination, the net effect of these compounds was both additive and synergistic.

Absorption

22. Inorganic iodine is readily absorbed from the gut, generally as iodide (Nordic Project Group, 1995). However, probably only 50% of iodine present in organic compounds in foods is absorbed (Bender and Bender 1997). Though 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).
23. Iodine can be absorbed dermally via topically applied preparations such as povidone iodine particularly when applied to broken or damaged skin (for example after burns) or mucosal membranes (Fradkin and Wolff, 1983).

Distribution

24. Once iodide enters the circulation, it is distributed throughout the extracellular fluid (Cavalieri, 1980). Iodide levels are low in plasma; small amounts are present in the salivary glands, mammary glands and ventricular epithelial cells. Iodide is able to cross red blood cell membranes, with plasma and red blood cell iodide rapidly reaching equilibrium (Riggs, 1951). The iodide secreted into saliva or gastric juices enters the small intestine where it is reabsorbed (Cavalieri, 1997). The mean iodine content of human milk in 19 US subjects was 142 $\mu\text{g}/\text{kg}$ (range 21-281 $\mu\text{g}/\text{kg}$) (Bruhn and Franke, 1983). In the milk of 10 Italian women, the mean iodide concentration was 0.27 mg/l (270 $\mu\text{g}/\text{kg}$) on day 3 after birth declining to 0.11 mg/l 90 days after birth (Chierici *et al.*, 1999). In 11 women given daily supplements of 116 μg potassium iodide, milk iodine levels were not significantly different being 0.32 and 0.08 mg/l respectively. Flynn (1992) quotes mean levels of 70-90 $\mu\text{g}/\text{l}$ milk in European women (range 20-330 $\mu\text{g}/\text{l}$). Iodide is also able to cross the placenta.
25. The only significant store of iodine in the body is in the thyroid gland. For example, six human volunteers were given a 70 μg dose of radiolabelled iodine in a sodium iodate carrier (described Murray, 1953). After three days, an average of 38% of the ingested iodine remained in the thyroid glands. The mean thyroid iodide level in adults from the USSR aged 26-65 was 345 ± 21 mg/kg (range 35-1207 mg/kg) (Zaichick and Zaichick, 1997). Mean levels were higher in both younger adults aged 16-25 (494 ± 65 mg/kg) and adults aged > 65 (668 ± 60 mg/kg). This was calculated on a dry weight basis in a non-endemic goitre region. The findings were stated to be comparable with those of authors looking at thyroid iodine levels in subjects from other European countries. Approximately 80% of iodine in the thyroid is stored as iodinated tyrosines (mono-iodo-tyrosine and di-iodo-tyrosine), 20% as thyronines and 1% as iodide (Nordic Project Group, 1995).
26. Uptake of iodide by the thyroid is dependent on need; this process is largely mediated by thyroid stimulating hormone (TSH) a thyrotrophic hormone secreted by the anterior pituitary gland. TSH activity increases in iodine deficiency. Uptake of iodide by the thyroid occurs via a carrier mechanism linked to a sodium-potassium ATPase, operating against an electrochemical gradient (Cavalieri, 1997). The iodide pump is a co-transporter, two sodium ions being transported for each iodide ion. A similar mechanism operates in other organs, but it is only

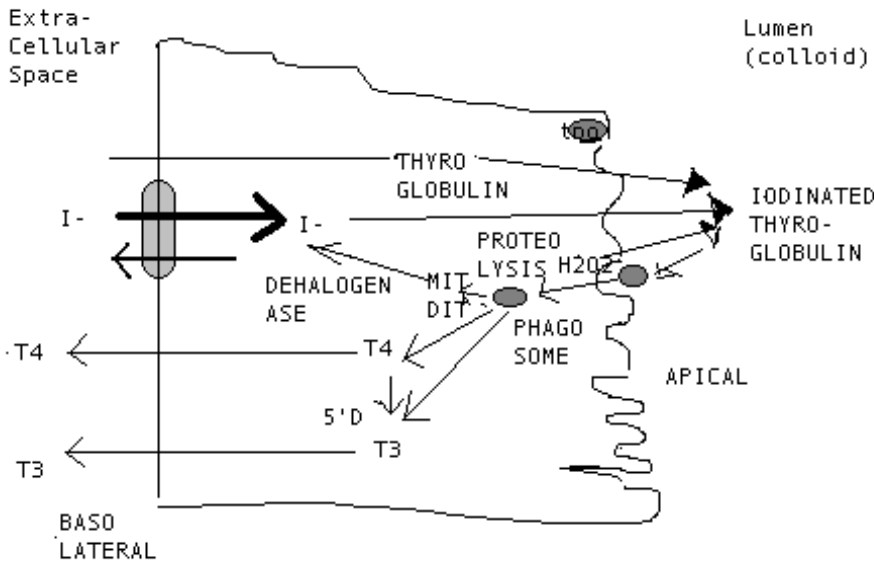
regulated by TSH in the thyroid. TSH stimulation of iodide transport was thought to involve gene expression (Cavalieri, 1997) but recent work suggests that it may involve translocation of the iodide pump from the interior of the cell to the plasma membrane or the activation of the pump within the plasma membrane. Once requirements for thyroid hormone synthesis have been met, the thyroid does not accumulate more iodine and any excess is excreted in the urine (Bender and Bender, 1997).

27. Thyroxine does not readily enter red cells, but protein-bound iodine (thyroxine or a derivative has been found in the liver, and is likely to occur within the cells of most body tissues (Riggs, 1951). Thyroxine iodine in the tissues is then broken down, releasing iodide. Thus there are two sources of iodide within the body - absorption from the gastrointestinal tract or from the breakdown of thyroid hormones.

Metabolism and Excretion

28. Circulating iodide is concentrated by the cells of the thyroid, where it is then oxidised to elemental iodine by the enzyme thyroid peroxidase (Saller *et al.*, 1998). The reaction requires aerobic energy and a source of hydrogen peroxide; this is largely generated by thyroid NADPH-oxidase, and has been shown to be a rate-limiting factor for protein iodination and hormone synthesis. Elemental iodine is highly reactive and immediately reacts with tyrosine to form thyronines (Nordic Project Group, 1995).
29. The metabolism of iodine is given in Fig 1.
30. Iodine taken up by the thyroid is converted to organic iodide, and is incorporated into tyrosine in intrafollicular thyroglobulin within the colloid at the basal cell surface of the thyroid follicular cell. The tyrosines are iodinated at one (monoiodotyrosine) or two (diiodotyrosine) sites and then coupled to form the active hormones (diiodotyrosine + diiodotyrosine = thyroxine [T₄]; diiodotyrosine + monoiodotyrosine = triiodothyronine [T₃]). Another source of T₃ within the thyroid gland is the result of the outer ring deiodination of T₄ by the selenoenzyme type I 5'-deiodinase (5'-D-I) (Merck, 2001). Thyroglobulin contains 120 tyrosine residues, two thirds of which are available for iodination (Cavalieri, 1980). All of the intra-thyroidal processes are regulated by TSH. Under normal conditions, the amount of iodinated thyroglobulin in the colloid of the gland is sufficient to meet hormone secretion for approximately 100 days (Bender and Bender, 1997).

FIG 1. IODINE METABOLISM (adapted from Cavalieri,1997)



Iodine metabolism and hormone biosynthesis in a thyroid follicular cell. The shaded oval is the iodide transporter.

tpo= thyroid peroxidase
5'D Type I iodothyronine 5'deiodinase

31. Deiodination of thyronines is carried out by a family of selenoproteins. Iodotyrosine dehalogenase regenerates iodide from monoiodotyrosine (MIT) and diiodotyrosine (DIT) for reuse 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). Cells of the liver contain a considerable amount of T₄, some of which is converted into T₃ and some excreted into the bile and ultimately reabsorbed or excreted (Cavalieri, 1980). Brown adipose tissue also contains a deiodinase enzyme and this is responsible for the local formation of T₃ within target tissues. This deiodinase enzyme is not selenium dependent (Bender and Bender, 1997).
32. Iodide is largely excreted in the urine; all circulating iodine is cleared, regardless of the circulating plasma levels (Riggs, 1951, Nordic Project Group, 1995). The majority of urinary iodine is in the form of iodide with only a small proportion being organically bound. Impairment of renal function, if severe, causes plasma iodide levels to increase, conversely, diuresis causes plasma levels to decline (Cavalieri, 1980).
33. Iodide is also secreted into the large bowel and excreted, but this accounts for only 1% of total body iodide clearance (Cavalieri, 1997). However, higher levels of faecal excretion (15-20% of the ingested dose of 100 µg iodine/day) have been reported in earlier balance studies (Harrison *et al.*, 1965). Compared to the

euthyroid subjects in the study, the proportion of iodine excreted in the faeces was increased in subjects with thyrotoxicosis and reduced, though not abolished, in hypothyroid patients (Harrison *et al.*, 1965).

34. Trace quantities of iodide can be excreted in sweat and, as noted above, 10-15% of daily iodine intake is excreted in breast milk by lactating women (Saller *et al.*, 1998). Very small quantities of iodide may also be excreted in exhaled air (Riggs, 1951).

Function

35. As noted above, iodine forms part of the hormones thyroxine (T4) and triiodothyronine (T3) which are necessary for the maintenance of metabolic rate, cellular metabolism and integrity of connective tissue (COMA, 1991). It is uncertain whether the multiple effects of thyroid hormones are mediated by a single mechanism. Receptors binding T3 and T4 have been found in the nucleus where they are involved in protein synthesis and in the mitochondria, suggesting that there are many sites of action (Cavalieri, 1980) for thyroid hormones. In the developing foetus and infant, iodine is necessary for the development of the nervous system.
36. Hormone secretion involves firstly, pinocytosis of colloid-containing iodinated thyroglobulin, then fusion of colloid droplets with lysozymes, followed by proteolysis which liberates MIT, DIT, T3 and T4. The supply of iodine regulates thyroid hormonogenesis and alters thyroid sensitivity to TSH. The release of T4 and T3 into the blood takes place by passive diffusion, though this may be facilitated by thyroid hormone binding protein in the plasma. Approximately 20 molecules of T4 are released for every T3 but the precise ratio varies with conditions (Cavalieri, 1980). The iodotyrosines (monoiodotyrosine and diiodotyrosine) are also released from thyroglobulin, but only very small amounts reach the bloodstream.
37. Within the plasma, T4 and T3 exist in free (0.03% and 0.3% respectively are free) and bound forms. Although the free forms are in rapid and reversible equilibrium with the protein bound forms, only free T3 and T4 are available to the tissues (Cavalieri, 1980). The primary binding protein for both T3 and T4 is thyroxine-binding globulin (TBG), which has a high binding affinity but low binding capacity for the thyroid hormones, accounting for 75% of the circulating bound hormones. The binding of T4 to TBG is stronger than that of T3. Other low affinity, high capacity binding proteins i.e. transthyretin and albumin, account for the remaining 25% (Merck, 2001). It is believed that circulating T4 is the form available for entry into most tissues (particularly the liver) and which ultimately exerts the multiple effects of the hormone (Cavalieri, 1980). In contrast, the majority of the extrathyroidal pool of T3 is in the tissues, predominantly skeletal muscle with relatively little in the circulation (Cavalieri, 1980).
38. T3 is approximately three times as biologically potent as T4. About one third of the T4 turned over daily is converted into T3 in extrathyroidal sites (primarily the liver) by mono-deiodination of the outer ring of T4 by 5'D-I accounting for 80% of T3 production (Cavalieri, 1980) the remainder being secreted by the thyroid.

Mono-deiodination of the inner ring of T₄ by 5'D-III also occurs in extrathyroidal sites to generate reverse T₃ (rT₃) which has minimal biological activity – see footnote 3, paragraph 98 for definition of rT₃.

39. TSH stimulates every step in the biosynthesis of thyroid hormones, from the concentration of iodide to the proteolysis of thyroglobulin (Cavalieri, 1980). There is a sensitive negative feedback mechanism between the thyroid and the pituitary gland to maintain the levels of thyroid hormones. This axis is influenced by the hypothalamus, which secretes thyrotrophin-releasing hormone (TRH) which in turn mediates the secretion of TSH from the pituitary.

Deficiency

40. It has been reported that vegans and vegetarians can consume inadequate intakes of dietary iodine. A controlled experimental diet (performed in Germany, a classical iodine deficient country until the mid 1990s) used a repeated measure method (Remer *et al.*, 1999). It exposed six adult volunteers to a 5 day dietary intervention in which isoenergetic lactovegetarian and non vegetarian diets were consumed. The strict vegetarian diet produced both an extremely low iodine intake (<20 µg/d) and urinary output (36.6 (SD 8.8) µg/d). The authors concluded that strict vegetarians are possibly at risk of developing iodine deficiency disorders.
41. A variety of mechanisms exist to compensate for low dietary intakes of iodine. It is only when these mechanisms are insufficient that the clinical symptoms of iodine deficiency become apparent. If iodine intake is low, iodide uptake from the plasma is increased via the action of TSH. The thyroid epithelial cells increase in size and become more efficient. The production of T₃ (containing 3 iodine atoms) is increased and the production of T₄ (containing 4 iodine atoms) is decreased. Iodine deficiency is therefore partly compensated for by the larger epithelial cells and the enlarged thyroid gland. This enlargement is known as a goitre. A statistically significant negative correlation has been reported for thyroid weight and iodine content in adults (Zaichick and Zaichick, 1997).

Endemic goitre

42. A detailed review of the incidence of endemic goitre around the world and the remedial action being taken is given in Matovinovic (1983). Endemic goitre due to iodine deficiency is generally more common in the developing world and typically occurs in mountainous areas. However, iodine deficiency is still apparent in certain parts of Europe (Delange and Bürgi, 1989). Goitre was once widespread in the UK, but has declined notably since the 1960s (Phillips, 1997). This is thought to be due to changes in farming practice, particularly supplementation of dairy herds with iodine, resulting in higher iodine concentrations in milk.
43. Goitre occurs when in response to low circulating concentrations of T₄, thyrotrophin (TSH) secretion by the pituitary is increased stimulating both iodide uptake into the thyroid and enlargement of the gland itself. In mild cases the thyroid may not be visibly enlarged.

44. Three grades of visible enlargement can be defined:
- i) palpably enlarged (grade 1a) and visible when the neck is extended and the head is thrown back (grade 1b);
 - ii) visible when the head is in a normal position;
 - iii) so grossly enlarged as to be clearly visible at a distance of 10 m.
45. In some cases the enlargement of the thyroid is sufficient to permit normal production of T4 from a marginal iodine intake, resulting in normal circulating concentrations of the hormone – euthyroid goitre. However, it is more usual that the iodine supply is inadequate to meet the requirements for T4 synthesis resulting in hypothyroidism i.e. low circulating concentrations of T4 and T3. The clinical symptoms of hypothyroidism (myxoedema) include lethargy, weakness, cold intolerance, increased weight, poor mental concentration, somnolence, paraesthesia, angina pectoris, dyspnoea, oedema, constipation, irregular menstruation and muscle ache. Other clinical findings include hoarseness, dry skin, pallor, reduced sweating, loss of body hair, delayed return of tendon reflexes, puffy eyelids and slow cardiac rhythm. Recurrent cycles of TSH mediated stimulation and involution may result in the formation of non-toxic nodular goitres (Merck, 2001), which may develop into hyperfunctioning autonomous nodules (Delange and Hetzel, 2000).
46. Large goitres may cause obstructive complications of the trachea, oesophagus and blood vessels of the neck. Goitres may also be associated with an increased risk of other thyroid disease and malignant growth (Matovinovic, 1983). Iodine intakes consistently lower than 0.05 mg/day are associated with the development of goitre (JECFA, 1989) with women and adolescent girls being particularly susceptible.
47. Treatment of endemic goitre has involved dietary supplementation with iodate tablets or iodised oil. Fortification of foodstuffs such as salt and bread has also been undertaken to reduce the incidence of endemic goitre in vulnerable populations. In certain situations this has resulted in subsequent increases in thyrotoxicosis (hyperthyroidism) or other disturbance of thyroid function (see paragraph 52 below). This will be discussed in detail later in this review.

2) *Endemic (goitrous) cretinism*

48. The effects of iodine deficiency in pregnancy can have a major detrimental impact on the developing foetus, particularly the developing nervous system, which may result in endemic cretinism. Symptoms include deafness, mutism, motor spasticity, squint and intellectual impairment. This is known as the “nervous” or neurological type of cretinism. Studies in laboratory animals suggest that iodine deficiency has an early effect on neuroblast multiplication, which could be important in the pathogenesis of the neurological form of endemic cretinism (Hetzel and Mano, 1989). When the infant’s iodine intake post-natally is not severely deficient it may show euthyroid goitre and suffer only the neurological and intellectual signs of the condition. It has been suggested (Matovinovic, 1983) that the maternal thyroid becomes progressively more depleted with each successive pregnancy, such that subsequent children become more retarded. It is estimated that 6% of American women compared to 1% of men suffer from thyroid disorders with the difference attributed to iodine deficiency during

pregnancy. A report of general practitioners in the UK suggested that thyroid disorders are 4-10 times higher in prevalence amongst women than men (Wynn and Wynn, 2000).

49. Post-natally, the persistence of hypothyroidism due to iodine deficiency will result in myxoedematous cretinism, which entails the neurological impairments of neurological cretinism as well as severe growth retardation, incomplete maturation of features, and delayed sexual maturation. In addition to frank cretinism, a larger proportion of the population (estimated to be 3-5 times as great) will suffer from some degree of mental retardation and coordination defect (Delange and Hetzel, 2000)
50. It has been suggested that it is not possible to separate out the effects of intra uterine deficiency from those continuing throughout childhood (Grantham-McGregor *et al.*, 2000). The thyroxine status of the mother during pregnancy affects later behavioural development of the child. In two maternal iodine supplementation trials, the children were followed up between the ages of 8 and 16 years. The results indicated that those born to women who received supplements during pregnancy had higher IQ scores and increased motor skills compared to those whose mothers had no supplement.
51. Iodine deficiency in pregnancy is also associated with an increased incidence of spontaneous abortion, stillbirth and congenital abnormalities (WHO, 1996).

3) *Hyperthyroidism*

52. Hyperthyroidism (or thyrotoxicosis) is defined as an increased synthesis and release of excess thyroid hormones. The most common cause in the UK is Graves disease (diffuse toxic goiter) due to antibodies against the TSH receptor, which results in continuous stimulation of the thyroid to synthesise and secrete excess quantities of thyroid hormones. However, iodine ingestion can also cause iodine induced hyperthyroidism (IIH). In the UK it is most often seen in patients with underlying nontoxic nodular goiter (see above), especially the elderly, who are given drugs that contain iodine or whose radiological and cardiac investigations use iodine rich contrast agents. It is far more common in areas of the world with historically low iodine intake following iodine supplementation. The aetiology of iodine induced hyperthyroidism is unclear but may be due to supplying excess iodine to hyperfunctioning autonomous nodules (Merck, 2001), which as noted above may result from iodine deficiency – hence IIH is considered an iodine deficiency disorder (IDD). Most signs and symptoms of hyperthyroidism are the same for all types with some exceptions e.g. infiltrative ophthalmopathy which is only seen in Graves disease. The clinical presentations of hyperthyroidism may be dramatic or subtle. Common signs and symptoms include goitre, tachycardia, tremor, sweating, weight loss, nervousness, fatigue, increased appetite, weight loss, and eye signs e.g. lid lag. Thyroid storm, which results from untreated hyperthyroidism, is characterised by the abrupt onset of hyperthyroid symptoms and is considered a life threatening emergency (Merck, 2001).

Natural Goitrogens

53. As noted previously, certain foodstuffs contain thioglycosides, these are natural goitrogens which impair iodine uptake by the thyroid or impair incorporation of iodine into thyroxine (JECFA, 1989). These are found in vegetables of the genus Brassica and family Crucifera (cabbage, broccoli, sprouts, turnips etc) as well as in nuts, cassava, maize and bamboo shoots. Drugs such as thiouracil and related compounds are also goitrogens. The effect of goitrogens in food, but not in drugs, can be overcome by adequate intakes of dietary iodine.

Iodine deficiency in animals

54. In animals, iodine deficiency has also been associated with reproductive failure and thyroid insufficiency. Foetal development is frequently delayed resulting in early death or resorption, spontaneous abortion, stillbirth, or the birth of weak, hairless offspring associated with prolonged gestation, parturition and retention of placental membranes (Hetzl and Mano, 1989).

Overview of reported beneficial effects

55. In addition to the treatment of hypothyroidism, marketing information obtained on the internet indicates that iodine supplements (including in the form of seaweeds such as bladderwrack or kelp) have been claimed to assist in weight loss, rheumatism, ulcers, hair loss and maintenance of arteries, nervous tissue and nails.

56. Iodine, specifically iodine caseinate, may be an effective treatment for fibrocystic breast disease (FBD) (Ghent *et al.*, 1993). It is suggested that iodine deficiency makes the breast cells more sensitive to oestrogen stimulation which in turn leads to small cysts being produced by the breast ducts with subsequent fibrosis. Three clinical trials of iodine/iodide supplementation have been conducted on women with FBD (Ghent *et al.*, 1993, Murray and Pizzorno 1998). The results indicated that treatment with iodides was effective in 70% of subjects but there was an associated high rate of side effects (see paragraph 135). A dosage of 70-90 µg iodine/kg bodyweight appears to be a safe and effective treatment for FBD (Murray and Pizzorno, 1998).

Human Toxicity

57. JECFA (1989) divides the human response to excess iodine into three types. These are:

- 1) Disturbance of thyroid activity resulting in goitre, hypothyroidism with or without goitre, or hyperthyroidism (thyrotoxicosis) – alterations to the pattern of thyroid malignancy may also occur;
- 2) Sensitivity reactions, and;
- 3) Iodine poisoning following ingestion of large quantities of iodine.

This review uses the same divisions.

58. Not all members of a population react adversely to excess iodine. The incidence of such reactions was reviewed by JECFA (1989). With regard to the

development of hypothyroidism or goitre, 2.8 to 9.3% of US participants with high levels of iodine excretion developed goitre. In a Chinese village where there were high levels of iodine in well water, the incidence of iodine-induced goitre and enlarged thyroid was 7.3% and 28.3% respectively. The incidence of these conditions was much lower in a nearby village with lower iodine levels in the water. Two out of 15 prison inmates (13%) showed impaired organification of iodide following disinfection of water with iodine at 1 mg/l (Freund *et al.*, 1966).

59. Following iodine prophylaxis in Serbia, Tasmania, Holland and Austria, the incidence of hyperthyroidism ranged from 0.01 to 0.6% of the population (discussed JECFA, 1989). The incidence of iodine-induced thyrotoxicosis in West Germany has been reported to be 0.25%. In-patients with thyroid disease, the incidence of iodine-induced hyperthyroidism is generally higher (up to 10%).
60. The incidence of sensitivity reactions to iodine compounds reported in the literature varied from 0.4 to 5% (JECFA, 1989). However, the incidence of gastrointestinal symptoms in subjects treated with potassium iodide for bronchial asthma was higher.

Disturbance of thyroid function

61. The effect of excess iodine on the thyroid may have a variety of effects, depending on the current and previous iodine status of the individual and their current and previous thyroid dysfunction (JECFA, 1989). For example, subjects exposed to low levels of iodine early in life may be particularly prone to the development of iodine-induced hyperthyroidism if iodine exposure increases at a later date.
62. Wolff (1969) has defined four degrees of iodide excess:
- 1) A relatively modest excess promoting temporary increases in the uptake of iodine and the formation of organic iodine, but without inhibiting the capacity to release iodine in response to physiological demand. This may lead to a considerable increase in hormone stores.
 - 2) A larger increase, which can inhibit iodine release from the thyrotoxic human thyroid or from thyroids in which iodine release has been accelerated by TSH.
 - 3) A slightly greater intake, which inhibits organic iodine formation and probably causes iodide goitre. This is known as the Wolff-Chaikoff effect.
 - 4) Very high levels of iodide, which saturate the active transport system. The acute pharmacological effects of iodine can usually be demonstrated before saturation becomes significant.
63. Excess iodine generally has inhibitory effects occurring via unknown organic compounds, possibly iodolipids (Cavalieri, 1997). There is a blunting of all TSH-mediated effects produced via second messenger cascades. The Wolff-Chaikoff effect, the acute iodine-induced inhibition of iodine organification appears to occur via hydrogen peroxide production. The Wolff-Chaikoff effect is transient and disappears if the high iodide levels are maintained, thus increasing iodide organification. Other effects of iodine excess include down-regulation of iodide transport, increase in the ratio of iodotyrosines to iodothyronines in thyroglobulin

and acute inhibition of pinocytosis and proteolysis resulting in reduced hormone secretion. In normal subjects, chronic exposure to excess iodine does not significantly affect thyroid function as a result of these regulatory mechanisms.

64. It has been suggested that in the presence of high iodine intakes, T4 is produced at lower than normal levels of TSH, so that the thyroid is small, with relatively flattened epithelium and abundant rich colloid (Williams *et al.*, 1977). Pharmacological doses of stable iodine can block uptake of radioiodine by the thyroid, as prophylactic measure in the event of nuclear accidents (Wolff, 1980). If enough iodide is administered with or before exposure to ¹³¹I, uptake can be reduced to virtually zero. Zanzonico and Becker (2000) noted that 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, or inhibition of hormone release.
65. It has been observed that in areas with relatively high iodine intakes, the incidence rate of hypothyroidism is several fold higher than that of hyperthyroidism. For example, in Whickham, UK (an area with a relatively high iodine intake) the prevalence of overt hypothyroidism was approximately 5 times that of hyperthyroidism (Vanderpump *et al.*, 1995 cited in Laurberg *et al.*, 1999). Conversely, in areas with moderately low iodine intakes, hyperthyroidism is reported to predominate. Laurberg *et al.*, (1999) concluded that the iodine intake of an area seems to be of major importance for the pattern of thyroid disorders observed. In agreement with this observation, Garcia-Major *et al.*, (1999) reported that iodine supplementation of children residing in an area with mild iodine deficiency significantly reduced the prevalence of sub-clinical hyperthyroidism (as measured by suppressed serum TSH concentrations).

Goitre/hypothyroidism

66. Excess iodine may induce thyroid dysfunction in susceptible patients (Saller *et al.*, 1998). Iodine-induced hypothyroidism is generally seen in areas with high dietary iodine intake. Possible mechanisms for this dysfunction include a failure to escape from the Wolff-Chaikoff effect or a decreased thyroid reserve. Although, iodine-induced hypothyroidism has occasionally been reported in normal subjects, patients with previous or underlying thyroid disease are particularly prone to iodine-induced thyroid dysfunction (Braverman, 1990). Iodine-induced hypothyroidism is more common in women. Generally the individuals have received iodine for long periods of time, but occasionally goitre or hypothyroidism may occur within a few weeks following the administration of small quantities of iodine (Braverman, 1990).
67. In areas of the world where iodine intake is adequate, autoimmune lymphocytic thyroiditis is the most common cause of hypothyroidism (Weatherall *et al.*, 1996). It is more common in women and typically occurs at around 30-50 years of age. There are two major types, distinguished by the presence or absence of goitre. Patients with chronic lymphocytic (Hashimoto's) thyroiditis, have an enlarged thyroid, whereas those with idiopathic or primary myxoedema (atrophic thyroiditis) do not. Where the biochemical parameters indicate hypothyroidism, the presence of circulating autoantibodies to thyroglobulin and thyroperoxidase make autoimmune lymphocytic thyroiditis the likely cause. The interplay of genetic and environmental factors initiates autoimmune thyroiditis with factors such as age and sex hormones acting as modifying influences (Many *et al.*, 1995). Among the environmental factors, dietary iodine plays a significant role both in man and laboratory animals. Several mechanisms have been proposed to explain how iodide provokes thyroiditis (Many *et al.*, 1995). Thyroglobulin is more immunogenic in normal animals if it is highly iodinated and the response of murine hybridoma to thyroglobulin is also directly related to its iodine content. Iodine may also enhance the IgG synthesis of peripheral lymphocytes. However it has also been suggested that iodine-induced cell necrosis is the initial event in autoimmune prone subjects.
68. Patients with Hashimoto's thyroiditis, often have a defect in the intrathyroidal organic binding of iodide and can develop iodine-induced hypothyroidism at pharmacological doses of iodine, possibly as a result of the failure to escape the Wolff-Chaikoff effect. Euthyroid subjects previously treated for Graves' disease by radiation, subjects that have undergone hemithyroidectomy for benign nodules or individuals with post sub-acute thyroiditis may also be prone to iodine-induced hypothyroidism (Braverman, 1990).
69. Wolff (1969) divides patients with iodide induced goitre into 4 groups: adult iodide goitre, iodide goitre of the newborn resulting from placental transfer, "coastal goitre" as observed in Hokkaido, Japan and hypothyroidism in patients with Graves' disease treated with potassium iodide or Lugol's solution (which contains 5% I₂ and 10% potassium iodide).
70. The majority of the patients with adult iodide goitre as described by Wolff (1969) suffered from chronic lung disease, the goitre being attributed to treatment with

iodine containing compounds. Females were more likely to be affected than males and iodide goitre could occur at any age. Most patients had received large quantities of iodine, ranging from 18 mg to >1g/day for prolonged periods before the goitre appeared. Myxoedema might then appear some months after the goitre. A spectrum of goitre and/or any degree of hypothyroidism may occur. Withdrawal of the source of iodine generally resulted in reduction of the goitre and restoration of euthyroid status. It was noted that “rebound hyperactivity” could occur following withdrawal of treatment but it was uncertain whether this was a true rebound effect or the persistence of pre-existing stimulation. Iodide goitres will shrink if treated with T3 or T4 even if iodide was still being given, suggesting that the goitre resulted from TSH stimulation. Organic iodide formation is blocked in iodide goitre, although accumulation may be markedly increased.

71. Since iodides are able to cross the placenta, goitre may be induced in the offspring of pregnant women administered large quantities of iodine (Wolff, 1969, Braverman, 1990). These cases tend to occur in geographical areas where mild to moderate iodine deficiency is present. The infant goitres may regress spontaneously after several months but deaths due to compression of the trachea have been reported (Wolff, 1969, JECFA, 1989). Goitre need not be present in the mother (Wolff, 1969). Iodide is readily secreted into breast milk, which may also be a factor in neonatal goitre.
72. Infants may also be affected when mothers are treated with topical iodine preparations. In a case described by Danziger *et al.*, (1987) Transient hypothyroidism was observed in a 6 week old infant whose mother had regularly washed in a solution of povidine-iodine during pregnancy and lactation and who had also used povidine-iodine ointment due to spreading furunculosis. Laboratory tests indicated that the baby had elevated serum TSH and reduced T4 levels. Elevated levels of iodine were found in cord blood of infants whose mothers were exposed to povidone –iodine antiseptics during routine preparation for delivery (Bachrach, *et al.*, 1984). A study by Chanoine *et al.*, (1988) investigated thyroid function in children born to mothers who had become overloaded with iodine as a result of povidine-iodine as an antiseptic in obstetric procedures. Compared with a control group, the infants had a shift of neonatal TSH levels to high values. This was particularly marked in breast-fed infants and resulted in a 25-30-fold increase in the recall rate at screening for congenital hypothyroidism in this group (subsequent investigations did not reveal any thyroid problems).
73. The most common form of iodide goitre is that seen in Hokkaido, Japan known as coastal goitre (Wolff, 1969). A survey of goitre was made in the goitrous regions of Hokkaido, the northern island of Japan (Suzuki *et al.*, 1965). Goitre was confirmed in several areas where the usual diet of the inhabitants consisted of large quantities of iodine-rich seaweed. In five patients, urinary iodine excretion exceeded 20 mg/day compared with 0.175 mg/day in-patients on an iodine-restricted diet and 1.565 mg/day in-patients on the normal hospital diet. Withdrawal of seaweed from the diet tended to reduce the size of the goitres, suggesting that high iodine intakes were associated with the occurrence of goitre. Protein-bound iodine, T3 uptake and plasma thyronine iodine levels were normal. Administration of thiocyanate to the goitrous patients consuming the seaweed diet

resulted in a discharge of iodine, this was taken to suggest that the thyroid was able to trap iodine without converting it to organic iodide.

74. The prevalence of thyroid dysfunction in relation to iodine intake was studied in adults in five coastal areas of Japan that produced kelp and where kelp-induced endemic goitre had occurred 30 years previously. (Konno *et al.*, 1994). The prevalence of hyperthyroidism was similar in all 5 areas, but that of hypothyroidism varied from 0 to 9.7 %. Urinary iodine was found to be at higher than normal levels in 3.7 to 30.3% of subjects. The frequency of high urinary iodine correlated significantly with that of hypothyroidism with negative thyroid autoantibody but not with positive thyroid autoantibody or hyperthyroidism. It was reported that earlier work by the same authors had determined that restriction of dietary iodine restored thyroid function, mainly in thyroid autoantibody negative subjects. This suggested that the aetiology of thyroid autoantibody positive hypothyroidism was different and explained the lack of correlation found in this study. Overall, the authors concluded that the prevalence of hypothyroidism in iodine-sufficient areas could be associated with iodine intake, that hypothyroidism is more prevalent and marked in subjects consuming further excessive amounts of iodine and that excessive intake should be considered an aetiology of hypothyroidism in addition to the chronic thyroiditis found in these areas.
75. The first examples of induction of hypothyroidism by iodide or Lugol's solution were reported in-patients with Graves' disease (Wolff, 1969). The induction period is generally shorter than that necessary to induce hypothyroidism in previously euthyroid patients. It is uncertain whether the same mechanism applies in both cases.
76. A number of literature reports are available describing hypothyroidism resulting from iodination programmes, medical treatment or increased iodine exposure. These are considered below (paragraphs 77-80).
77. Hypothyroidism was diagnosed in a subject that had taken a proprietary "blood mixture" for three months (Dimitriadou and Fraser, 1960). The dose of iodine was estimated to be 300-400 µg/day. The goitre reduced in size on withdrawal of the treatment. A biopsy suggested high uptake of radioactive iodine as well as inefficient synthesis of thyronines. The authors note that the latter was the possible underlying defect that resulted in susceptibility to goitre.
78. Thyroid abnormalities were detected in Peace Corps volunteers exposed to iodine through water purification units (Khan *et al.*, 1998). Of 96 volunteers tested, 33 had thyroid dysfunction (as assessed by thyrotrophin concentrations) and 44 had enlarged thyroids; of these 30 had normal thyroid function tests. There was no evidence of iodine contamination of food or medication. It was determined that water filters involving iodine were in use, resulting in water containing approximately 10 mg/l iodine. Volunteers reported drinking 5-9 l of water, leading to total iodine consumption of at least 50 mg iodine.

79. Since iodine is largely excreted via the kidneys, serum iodine levels can rise in patients with uraemia, and some dialysis patients have goitres with high intrathyroidal iodine levels. However in patients undergoing regular dialysis treatment, TSH and free T3 and T4 levels are generally normal, despite abnormal serum total T3 and T4 levels. Hypothyroidism accompanied by elevated TSH levels was found in 3/93 patients undergoing dialysis treatment (Takeda *et al.*, 1993). The three patients had no underlying history of thyroid disease and were not taking medicines thought to influence thyroid function. However, the patients had consumed iodine-rich foods such as seaweed; serum iodine levels rapidly returned to normal when iodine intake was reduced.
80. Subclinical hypothyroidism occurred in a 15 year old male, whose ulcerated leg was treated with potassium iodide solution (Leshner *et al.*, 1994). The patient was given 5 drops of a saturated (1 g/ml) solution three times a day. Thyroid function tests, indicated normal T3 and T4 but slightly elevated TSH levels. After further treatment, TSH levels were further elevated and the response to thyrotrophin releasing hormone was also increased. The clinical parameters returned to normal once treatment was completed. The thyroid function of very-low-birthweight infants in the first 4 weeks of life was investigated in two different hospitals (Smerdely *et al.*, 1989). One of the hospitals used a topical iodinated antiseptic agent whilst the other used chlorhexidine-containing agents. Urinary iodine excretion rose rapidly in the iodine exposed infants and was 50 times higher than in the non-exposed ones. Within 14 days, 25% (9/36) of the exposed infants had elevated serum thyrotrophin levels compared with none of the non-exposed infants. In the same 9 infants, serum thyroxine levels were lower than in the non-exposed infants or the exposed infants with normal thyrotrophin levels. The disturbances in thyroid function correlated strongly with urinary iodine excretion and thus with iodine absorption. Thyroid function had returned to normal by the time of discharge from hospital. The authors concluded that topical antiseptics containing iodine should not be used in very-low-birthweight infants because of the potential risk of hypothyroidism during a critical period of brain development.
81. The technique of amniocentesis (AFG) uses radio-opaque dyes containing iodide to provide a clear outline of foetal soft tissue and thus allow the diagnosis of foetal abnormalities (Rodesh *et al.*, 1976). The thyroid function of 7 newborns that had undergone AFG was assessed by serial determination of T4 and thyrotrophin levels. The mothers were confirmed to be euthyroid in status. It was reported that AFG had an adverse effect on the thyroid function of six of the seven infants, two being diagnosed as having hypothyroidism and with goitre being apparent in one of them.
82. In a study in 6 euthyroid patients, that had undergone a thyroid resection 2 months to 10 years beforehand (Clark, 1990) the subjects were given iodide for 1-3 months. Thyroid parameters were normal at the start of the experiment. Serum TSH rapidly reached abnormal levels within 2-4 weeks in 5 of the 6 patients. A correlation was found between baseline TSH levels and the increase in TSH following iodide treatment. The author suggests that baseline TSH levels may therefore be used to predict which patients will develop hypothyroidism when exposed to iodine and that abnormal thyroid tissue was not necessary for this iodine-induced hypothyroidism to occur.

Hyperthyroidism

83. The occurrence of hyperthyroidism following an increase in iodine intake (also known as Jodbasedow) has been known since 1900 (Vagenakis *et al.*, 1972). This is not thought to be a single aetiological entity (Fradkin and Wolff, 1983). Although this has generally been considered to be confined to patients in areas of endemic iodine deficiency, iodine-induced hyperthyroidism (thyrotoxicosis) may also occur in areas of iodine sufficiency (Braverman, 1990). For example, thyrotoxicosis has also been induced experimentally in subjects with both pre-existing toxic¹ (eg Graves' disease) and non-toxic goitre². In the latter group of patients, there was no evidence of high dietary intakes, elevated iodine uptake or increased serum TSH levels. The dose of iodine necessary to induce thyrotoxicosis is uncertain, but above a certain threshold there does not appear to be a dose response relationship (Fradkin and Wolff, 1983).
84. The clinical features of iodine-induced hyperthyroidism are similar to that of Graves' disease, however there are certain distinguishing features (Fradkin and Wolff, 1983). The ratio of men to women is often higher than in Graves' disease and exophthalmos is usually absent; it has been suggested that where this has occurred, it may be due to the appearance of classical Graves' disease previously masked by iodine deficiency. Stewart, (1975) noted that the small increase in the incidence of thyrotoxicosis in patients aged less than 40 which occurred following an iodization programme in Tasmania was largely due to Graves' disease.
85. In contrast to the diffuse toxic goitres found in Graves' disease, iodine-induced thyrotoxicosis is generally associated with non-toxic nodular goitres. The incidence of iodine-induced hyperthyroidism parallels the prevalence of thyroid autonomy (Stanbury *et al.*, 1998). Autonomous function of the thyroid is a result of long standing iodine deficiency and is particularly common in elderly subjects with non-toxic nodular goitres (Corvilain *et al.*, 1998). However, nodular is not necessarily synonymous with autonomous (Fradkin and Wolff, 1983). It is thought that autonomy arises from mutational events, conferring activation to the TSH receptor or the Gs α protein. Autonomous cells are characterised by the lack of efficient autoregulatory mechanisms leading to increased thyroid hormone secretion and eventually hyperthyroidism when iodide supply increases. (Corvilain *et al.*, 1998).
86. The pathogenesis of iodine-induced hyperthyroidism is unclear, but it may relate to prior intrathyroid iodine content. In particular, it is uncertain whether the condition arises *de novo* or whether some degree of pre-existing sub-clinical hyperthyroid state, requiring some degree of autonomy is necessary (Livadas *et al.*, 1977). In patients with toxic adenoma of the thyroid, supplementation with small amounts of iodine increased serum T4 levels, but without the corresponding decrease in T3 observed in patients with endemic iodine deficiency goitre (Livadas *et al.*, 1977). The authors suggest that increased iodine supply can

¹ Toxic goitre is enlargement of the thyroid gland accompanied by hyperthyroidism.

² Nontoxic goitre is enlargement of thyroid gland without evidence of thyroid dysfunction unless the aetiology is iodine deficiency.

trigger thyrotoxicosis in the proportion of older people in endemic areas that have autonomous nodules.

87. Denham and Himsforth (1974) proposed a mechanism by which iodine deficient subjects may develop IHH following administration of large doses of iodine. They proposed that the combination of autonomously secreting thyroid tissue with a poor ability to concentrate iodine resulting in sparsely iodinated thyroglobulin, and increased iodide influx due to the increased iodine intakes could result in the production of more heavily iodinated thyroglobulin and thus an increased rate of synthesis and release of thyroid hormones from functionally abnormal tissue. The excessive release of thyroid hormone would be expected to continue until once more the abnormal parts of the gland became depleted of iodine. Stanbury *et al* (1998) suggest that the biological basis for IHH most often is a mutational event in the thyroid cells that lead to autonomy of function.
88. Although concern has been expressed regarding the possible induction of hyperthyroidism in subjects with pre-existing non-endemic goitre, few cases have actually been reported given the widespread exposure to iodine compounds (reviewed Fradkin and Wolff, 1983). Some of the case reports originate from areas of marginal iodine intake. The majority of cases involved multi-nodular goitres. The duration of the hyperthyroidism lasted from 1-6 months, and where specifically noted, exophthalmia was not present.
89. Iodine-induced thyrotoxicosis has also been reported in subjects without pre-existing thyroid disease (reviewed Fradkin and Wolff, 1983). The condition is equally common in men and women, in contrast to Graves' disease. The majority of cases resulted from the use of iodinated compounds rather than exposure to iodide. The onset of thyrotoxicosis varied from days to years after commencement of iodine treatment often resolving within a few months of discontinuing the drug. Transient hypothyroidism following the resolution of the hyperthyroidism was sometimes reported. Goitres were present in around half the cases, but exophthalmia was not present. As discussed previously, excess iodine generally causes inhibitory effects, however, the mechanism of iodine-induced hyperthyroidism in such subjects without pre-existing thyroid disease is uncertain but it has been suggested that defective autoregulation of hormone biosynthesis may be involved (Fradkin and Wolff, 1983). It has also been suggested that while the thyroids of euthyroid subjects in non-endemic areas are apparently normal, it is impossible to exclude small areas of autonomy within or outside nodules or small nodules that are clinically undetectable (Stanbury *et al.*, 1998).
90. There are numerous reports of iodine-induced thyrotoxicosis occurring in endemic areas following the introduction of iodination programs. In a restricted area of Holland (discussed Fradkin and Wolff, 1983) mandatory iodination of bread resulted in an average iodine intake of 100 µg/day. An average yearly incidence of iodine-induced hyperthyroidism of 0.02% was calculated compared to 0.001% previously. Thyrotoxicosis was also reported to increase from 0.0025% to 0.01% in Serbia and to 0.06% from 0.03% in the Austrian Tyrol (reviewed Fradkin and Wolff, 1983). Generally, following the introduction of iodination supplementation programmes, the increased incidence of thyrotoxicosis begins to rise around 6 months after initial exposure, peaking at 1 to 3 years. During continuing exposure,

the increase then returned to baseline in 3-10 years. Although ITH has not been reported following all iodination programs, this may be due to poor follow up and inexperience in detecting thyrotoxicosis situations where other wasting conditions such as malaria, malnutrition, parasitism and AIDS are also prevalent (Stanbury *et al.*, 1998).

91. Potassium iodate was added to bread in Tasmania as a prophylaxis against endemic goitre (Connolly *et al.*, 1970). Following this intervention, the incidence of thyrotoxicosis at the two thyroid clinics on the island doubled to 0.04%. The majority of the patients were in the older age groups and had toxic nodular goitre. The mean daily iodine intake from bread was estimated to be 80-270 µg depending on age and sex.
92. In a prospective study, the annual incidence of thyrotoxicosis in 12 towns in England and Wales was found to range from 9.7-49.2 per 100,000 (Barker and Phillips, 1984). The incidence of thyrotoxicosis was strongly correlated with the previous prevalence of goitre. The authors suggest that high intakes of iodine as a result of contamination of milk could result in toxic nodular goitre in people made susceptible by iodine deficiency early in life. They could also contribute to the occurrence of Graves' disease. A spring –summer peak in thyrotoxicosis was attributed to higher levels of iodine in winter milk, resulting in substantially higher dietary intakes in the winter months (Nelson and Phillips, 1985).
93. Biochemical signs and overt clinical hyperthyroidism were reported in 2 severely iodine deficient African countries soon after the introduction of iodized salt (Delange *et al.*, 1999). A multi-centre study was then set up in seven countries to determine whether this was a generalised phenomenon or corresponded to specific local situations. It was determined that iodine deficiency had been eliminated in all the areas investigated. However, as a result of poor quality control of the salt and insufficient monitoring of the iodine intakes, some areas were being exposed to iodine excess. This was demonstrated by elevated urinary iodine concentrations (the median level exceeding 200 µg/l, the upper limit of the normal range) in two of the seven countries studied. Samples taken from the salt factory common to the centres had iodine concentration of 0-200 ppm (mean 90 ±54). Following this study the recommendations made by WHO-UNICEF-ICCIDD (International Council for Control of Iodine Deficiency Disorders) were revised with a reduction in the level of iodination and strict monitoring procedures being recommended.
94. The incidence of thyrotoxicosis was determined before and after dietary iodine supplementation in an iodine sufficient area of Spain (Galofré *et al.*, 1994). A mandatory programme of salt iodization began in Galicia in 1985, an iodine-deficient area. However within Galicia, the city of Vigo was an iodine-sufficient area (urinary iodine excretion being 130 µg/g creatine). All newly diagnosed cases of thyrotoxicosis in Vigo city (population 267,330) were included in the study. Prior to the iodination programme (1977-84) the average incidence rate was significantly lower (3.10 per 100,000) compared to the period of supplementation (1985 –1989) (7.68 per 100,000). The confidence interval for the difference was –20.4 to 30.1, p=0.05. The increased incidence of thyrotoxicosis was comprised of both nodular and diffuse goitres. The salt was iodized to a level of 60 mg/kg but was not analysed. The increased level of exposure was not

estimated and data on biochemical and clinical parameters (including any increase in urinary excretion) are not provided.

95. Hyperthyroidism has been reported following treatment with drugs such as amiodarone, clioquinol and benziodarone, radiographic contrast agents and food supplements. A number of these cases are considered below.
96. A female patient with a slight enlargement of the thyroid (aetiology unknown) consumed a multivitamin preparation during pregnancy (Block and DeFrancesco, 1979). Seven months later, symptoms of hyperthyroidism developed; these resolved when consumption of the supplements ceased. The patient was subsequently found to have underlying Hashimoto's thyroiditis. The supplement preparation was stated to contain 150 µg iodine/dose, however, it was noted by the authors that a survey of supplements detected 375 µg iodine/dose in the same brand. Dietary iodine intake in the local area was considered to be high.
97. Thyrotoxicosis was diagnosed in a male consuming kelp tablets in the UK. The iodine intake was estimated to be 900 mg/day and symptoms resolved when the subject stopped taking the supplements (Shaw *et al.*, 1996).
98. A 22-day old infant developed hyperthyroidism following medistinal lavage with povidone iodine (povidone is a polymer which binds iodine) (Bryant and Zimmerman, 1995). The total dose of iodine was approximately 29 g (3 ml/hour povidone iodine for 4 days, followed by 1 in 20 dilution for a further 24 hours). Total and free T4 was elevated, with T3 being normal indicating T4 toxicosis. Iodine excretion and reverse T3³ were also elevated Thyroglobulin levels were not elevated; this was stated to be compatible with previously reported cases of iodine induced hyperthyroidism where there was no underlying thyroid disease. The hyperthyroidism was driven by increased iodine and T4 concentration. Increased efficiency of iodination was sufficient to lead to hyperthyroxinaemia without increased production or turnover of thyroglobulins. It is noted that in adults, histologic evaluation of the thyroids of two individuals showed a rise in iodine and T4 content, with the presence of slightly overiodinated thyroglobulin. No palpable goitre was found. The hyperthyroidism resolved during the month following treatment.
99. Hyperthyroidism was induced in 3/31 geriatric patients given potassium iodide as part of a ¹²⁵I-fibrinogen test (the compound being given to minimise the effects of radiation on the gland) (Denham and Himsworth, 1974). Significant depression of thyroid activity was observed in a further 10 of the 31 patients; this subsequently reverted to normal. A loading dose of 120 mg potassium iodide (equivalent to 91 mg iodine) was given followed by twice daily doses of 60 mg (equivalent to 46 mg iodine) for 2-3 weeks. Though not iodine deficient, two of the three patients that developed hyperthyroidism had preceding thyroid disease with abnormal thyroid biochemistry being apparent prior to treatment. The authors suggested that

³ Reverse T3 (3:3':5' triiodothyronine) is a mono-deiodinated derivative of T4 which has no hormonal activity and may be apparent in patients with no evidence of thyroid disease but normal T4 and low T3 levels. This is reported to occur after surgery, acute infection and in obese patients on energy restricted diets. These conditions appear to alter the mono-deiodination of T4 in the periphery resulting in decreased T3 formation and increased reverse T3 formation (Whitby *et al.*, 1984).

potassium iodide should not be given to elderly subjects undergoing the tests and that reduced doses should be given to younger subjects.

100. The potential of computed tomography (CT) contrast agents to cause iodide induced hyperthyroidism was studied over a three year period (DeBruin, 1994). A total of 24, 600 scans were conducted and 7 patients required admitting to hospital as a result of clinically severe iodide induced hyperthyroidism. The condition developed following a total dose of 3-12 mg intra-venous iodine in the contrast medium.

Thyroid malignancy

101. Hyperthyroidism is often the result of diffuse hyperplasia of the thyroid acinar cells most commonly in Graves' disease (Wheater *et al.*, 1990). However, sometimes the hyperplasia is confined to benign thyroid adenomas, or, to one or two nodules in an otherwise inactive multinodular goitre. There are three main types of thyroid carcinoma; papillary (70% in affluent countries), follicular (20%) or anaplastic (5-15%) (Franchesi, 1998). Medullary carcinoma of the thyroid is an uncommon malignant tumour of the calcitonin-producing cells and is considered to have a completely different aetiology than the other types of thyroid cancer. Radiation is the best defined risk factor, but experimental evidence from animals suggests that situations resulting in prolonged TSH exposure lead to the development of thyroid neoplasia (Franchesi, 1998).
102. It has been suggested (discussed Pendergrast *et al.*, 1961) that iodine deficiency goitre may predispose to cancer of the thyroid, with changes in thyroid cells progressing from diffuse hyperplasia to nodular hyperplasia to benign tumours to cancer. Thyroid cancers are higher in goitrous than non-goitrous areas (Pendergrast *et al.*, 1961) and rates of follicular and anaplastic thyroid cancer have declined in goitrous areas following prophylaxis. Animal studies suggest that iodine deficiency and goitrogens are potent tumour promoters. However, Pendergrast (1961) concluded that there was insufficient evidence for an association between goitre and thyroid cancer, although such an association clearly existed between goitre and thyrotoxicosis. Later authors suggest that sub-optimal iodine intake, dietary goitrogens and factors such as alcohol consumption can result in increased TSH stimulation increasing the risk of thyroid carcinoma (Franchesi, 1998).
103. Thyroid cancer is high in the Andean region of Ecuador where endemic goitre occurs (Fierro-Benitez, 1973). The incidence of thyroid cancer was assessed on the basis of pathological samples from 844 thyroidectomies. Thyroid cancer was found in 9.71% of the samples, the most common type being papillary carcinoma, followed by anaplastic carcinoma. The proportions of follicular and medullary carcinomas were noted to be less than reported elsewhere.
104. Other studies have reported higher rates of thyroid cancers in populations where iodine exposure is high. This appears to be related to the differences in previous exposure to iodine. For example, iodine-rich food decreases the risk of thyroid cancer in iodine-deficient areas of Japan but increases the risk in the iodine-rich coastal areas (Takezaki *et al.*, 1996). The proportion of malignant nodules was

higher in patients in iodine-sufficient areas of Italy compared to iodine-deficient areas (Belfiore *et al.*, 1992).

105. In a study of 191 cases and 441 matched controls in Hawaii, Kolonel *et al* (1990) reported that miscarriage particularly as an outcome of first pregnancy, and the use of fertility drugs was associated with an increased risk of thyroid cancer with other non-dietary factors being obesity, work as a farm labourer and a family history of thyroid disease being involved. High dietary intake of iodine increased risk, whereas consumption of goitrogenic vegetables was associated with a decrease in risk. In women, hormonal factors were also apparent since the Odds Ratio for the combined effect of high iodine intake and first-pregnancy miscarriage was 4.8 (95% CI = 1.2-19.2) and for high iodine intake and use of fertility drugs was 7.3 (95% CI = 1.5-34.5). Comparable results were obtained from a case-control study of 207 pairs of women in Shanghai (Preston-Martin *et al.*, 1993), though the association with fish and shellfish (and thus iodine) intake was less marked. The major risk factor for thyroid cancer was previous history of goitre or benign nodules (O.R =7.0, 95% CI= 2.5-27.5) and miscarriage as an outcome of first pregnancy (OR = 9.9, 95% CI = 2.0-48.4). Weaker associations were seen for women who were ever-pregnant (OR=2.1, 95% CI=1.1-4.2) or who had an induced abortion (OR=1.6, 95% CI=0.9-2.9) or used oral contraceptives (OR=1.7, 95% CI=1.0-3.1). Cases also gained significantly more weight from menarche to highest non-pregnant weight. The same reproductive factors were seen in a case-control study of 94 female patients compared to 22, 666 female outpatients conducted by Takezaki *et al.*, (1996) suggested that the major risk factor for thyroid cancer was previous history of thyroid disease (benign thyroid mass or goitre, OR=13.9, 95% CI= 5.0-38.7, hyperthyroidism, O.R. = 5.0, 95% CI= 1.2-20.6) but that hormonal factors could also be involved since, patients had experienced more child birth. Older age at first menarche was associated with a small increase in risk but age at first delivery did not have any effect.
106. The incidence of different histological types of thyroid cancer were compared in Iceland (an area of high iodide intake) and North East Scotland (an area of low iodide intake) (Williams *et al.*, 1977). In both areas, the population served by each hospital was clearly defined with few alternative sources of treatment being available. All thyroid carcinomas resected over a 20 year period were examined by the same two pathologists, the incidence of carcinoma and the relative incidence of the two histological types were then calculated in the two areas. The age-specific incidence rates for papillary carcinoma rose with age in both areas, but were 5 times higher in Iceland. The number of follicular carcinomas was smaller but the incidence was lower in Iceland compared to North East Scotland. These findings along with the known low rates of follicular carcinoma and high rates of papillary carcinoma in areas of endemic goitre were taken to indicate that the incidence of the two conditions are influenced separately by iodine levels. No evidence was found to suggest that lymphocytic thyroiditis, radiation or genetic factors were involved. Undifferentiated thyroid carcinoma was found to be three times higher in Iceland, whereas malignant lymphoma was common in Scotland, this was possibly related the high frequency of thyroiditis found in the region.

107. The ratio of papillary to follicular carcinoma in a goitrous area of Argentina increased from 1.7:1 in a period 5 years pre-iodine prophylaxis of salt to 10 years after prophylaxis to 3.1:1 in the period 11 to 27 years post-prophylaxis (Harach and Williams, 1995). The authors also noted that non-Hodgkin's lymphoma was only seen in the post-prophylaxis period suggesting that this might be a result of the increased incidence of thyroiditis. A similar increase in the frequency of papillary carcinoma was determined by analysis of the records of an Italian General hospital (Deandrea *et al.*, 1997). This was attributed to a gradual, silent, increase in iodine intake, but it was also noted that improvements in diagnostic tools have also occurred.
108. Thyroid cancer (multinodular or solitary adenoma) was lower in an area of Denmark with low levels of iodine intake compared to other Nordic countries with higher intakes (Kristensen *et al.*, 1995). In Sweden, 5,838 incident cases of thyroid cancer were diagnosed in the period 1958-1981 (Pettersson *et al.*, 1996). Residence in an iodine deficient area was associated with a 2-fold increased risk of follicular cancer in men and a 17% increase in risk in women. The regional differences in iodine intake which began in 1936 and was enhanced in 1966. However, the incidence of both papillary and follicular cancer increased during the study period with similar trends being apparent in iodine-sufficient and iodine-deficient areas. The incidence of thyroid cancer differed only marginally between 6 different health care regions, suggesting that the observations defined by iodine intake were unlikely to be artefactual. Overall, the authors concluded that iodination of the food supply was not associated with trends in the occurrence of thyroid cancer.
109. It is suggested by Franchesi (1998) that the conflicting effects of iodine are not surprising if both iodine excess and iodine deficiency result in prolonged exposure to TSH.
110. Geographical studies suggest that dietary iodine levels are inversely associated with cancer of the breast, ovary and endometrium (Stadel, 1976). The author hypothesised that low dietary iodine intake producing borderline hypothyroidism may produce a state of increased effective gonadotrophin stimulation (via increased prolactin production), which in turn may lead to a hyperoestrogenic state, characterised by relatively high production of oestrogen. A relatively high rate of oestrogen production by the ovaries would result in a relatively low oestriol proportion for oestrone, oestradiol and oestriol excreted in the urine. This relatively high rate of oestrogen production with a relatively low oestriol proportion would be expected to result in growth stimulation for the glandular tissue of the breast and endometrium, thus increasing the risk of cancer at these sites. However, the Committee on Medical Aspects of Food and Nutrition Policy (COMA) in its report *Nutritional Aspects of the Development of Cancer* did not report on a link with these cancers and iodine (COMA, 1998).

Sensitivity Reactions

111. Iodine can cause various allergic reactions, such as polyarteritis nodosa-like syndrome, oedema, eosinophilia and iodide fever, and reactions which indicate unusual sensitivity to iodide, such as dermatitis herpetiformis and hypocomplementemic vasculitis (Fradkin and Wolff, 1983). Iodide fever mimics bacterial infection and presents approximately 3 days after treatment (Wolff, 1980).

1. *Iododerma*

112. Oral or intravenous exposure to iodine-containing drugs, contrast media or radiographic protection agents can result in iododerma, skin eruptions which may occur in the presence or absence of systemic symptoms some days after the drug has been withdrawn (Champion *et al.*, 1992). The following lesions may occur: urticaria, acneform rash, papulopustular lesions, nodules, anthracoid or carbuncular lesions, or clear or haemorrhagic bullae on the face, forearms, neck and flexures, or buccal mucosae. If iodine exposure is maintained, the bullae may be replaced by vegetating masses, which simulate pemphigus vegetans or granulomatous infections. Iododerma is more frequent in patients with renal failure and may be accompanied by leucocytoclastic vasculitis. The eruptions can re-occur within days of a sensitised individual being exposed to further iodine. The mechanism is uncertain but cell-mediated and hyperinflammatory mechanisms have been proposed. Vegetating iododerma may be an idiosyncratic response, which is more common in patients with polyarteritis nodosa or paraproteinaemia.

2. *Iodine Mumps*

113. "Iodine mumps" (swelling of the submandibular, sublingual and/or parotid glands) is a unusual complication of intravascular administration of iodine-containing contrast media (Christensen, 1995). The aetiology of iodide mumps is uncertain, but the reaction appears to be related to the toxic accumulation of iodide in the ductal systems of the salivary glands (which are able to trap and concentrate free iodide in the contrast media). This leads to swelling and partial obstruction of the glands. However, there is a strong idiosyncratic component to the reaction. Other reported reactions include facial paralysis, localised erythema, enlarged thyroid and lacrimal glands, conjunctivitis, photophobia, puffiness of the face, choking sensations and abdominal pain. In many of the reported cases, recovery occurs without treatment; anti-histamines and steroid treatments have been used but the efficacy is uncertain.

3. *Other sensitivity Reactions*

114. A number of case reports of sensitivity reactions to iodine are given below:

115. Of 1,726 patients given contrast media containing iodine, hives, sneezing and facial oedema were experienced by 13, 9 and 1 subjects respectively (Tucker and Di Bagno, 1956).

116. In a study by Witten *et al.*, (1973) it was reported that 568 out of 30,713 patients (1.72%) given intravenous doses of urographic contrast media containing iodine, experienced acute reactions. The reactions were divided into 3 types; 1.44% of subjects experienced dermal symptoms (hives, cutaneous oedema, diffuse erythematous rash, peri-orbital oedema); 0.12% experienced nasal and mucosal symptoms (nasal congestion, sneezing, rhinitis, angioneurotic oedema). Cardiovascular symptoms (syncope with transient hypotension, hypotension (shock) with diffuse erythematous rash, cardiovascular collapse) were observed in 0.07% patients and respiratory symptoms (bronchospasm, bronchial asthma, laryngeal oedema with airway obstruction) in 0.05% subjects. Neurological (grand mal seizures) and "other" symptoms (parotid swelling) were experienced by 0.01% and 0.025% of patients respectively. Reactions classified as severe occurred in 30 of the 30, 713 patients, one of these, a patient who suffered cardiovascular collapse died of cardiac arrest. The first 9,934 patients were examined with specific reference to their allergy history. It was found that a higher percentage of patients with a history of allergy (3%) reacted to the contrast media compared to those without (1.2%). The severity of the reaction was not related to allergy history.
117. Allergic reactions (itching, angioedema, erythema) have been reported in a subject taking iodine as a part of a cough syrup (Munoz *et al.*, 1997). The authors note that iodine has been implicated in many dermatological reactions following local application. The mechanism involved is one of delayed hypersensitivity.
118. During metabolism studies of radiolabelled proteins in human volunteers, 4/126 patients repeatedly developed urticaria and other symptoms following administration of potassium iodide and were suspected of being sensitive to the compound (Curd *et al.*, 1979). Two of the 4 patients and 10 controls were then orally challenged with 1g potassium iodide (equivalent to 0.76 g iodide). In the sensitive patients, the challenges precipitated urticaria, angioedema, polymyalgias, conjunctivitis and coryza. One of the patients also developed a severe systemic illness characterised by fever, headache, peritonitis, episcleritis and pneumonitis (it is not stated whether this is iodide fever). The four sensitive patients were similar in that they exhibited hypocomplementemia and dermal vasculitis associated with chronic urticaria or systemic lupus erythematosus. The authors propose that subjects with such conditions may be sensitive to potassium iodide administration and could potentially develop severe systemic illness. The reaction was not apparent in the control subjects (whose diagnoses included chronic idiopathic urticaria, hereditary angioedema, non- hereditary angioedema, Sjogrens's syndrome and hypergammaglobulinaemia).

Iodine Poisoning

119. Symptoms of acute iodine ingestion can include, brownish coloured vomit, diarrhoea, weak pulse and urinary retention followed by delirium, stupor and collapse (Clark, 1981). Death has occurred from 30 minutes to 52 days after ingestion. A review of cases of suicide by iodine poisoning suggested (cited JECFA, 1989) that death generally occurred within 48 hours of ingestion. Where the dose was known, this ranged from 1.1 to 9g of iodine (18 to 150 mg/kg for a

60 kg adult). However Tresch, *et al.*, (1974) reported a case where a 54 year old male survived the accidental ingestion of 15 g iodine in the form of saturated potassium iodide solution.

120. A 9 week old infant died following treatment with povidone-iodine (Kurt *et al.*, 1996). A 50 ml enema of a 1/5 dilution of povidone-iodine in bowel irrigant was given initially, followed 16 days later by three, hourly, 50 ml doses of the same solution given by nasogastric tube. The infant was found lifeless three hours after the last dose and could not be resuscitated. The total dose of iodine was estimated to be 15,000 mg. At autopsy, a corroded and necrotic gastrointestinal tract and serous fluid in the body cavities was apparent. Life threatening toxicity has also been reported following rectal irrigation of a 3 month old infant with povidone-iodine solution (Means *et al.*, 1990).
121. Fatal iodine toxicity occurred in a 74 year old adult, who had undergone povidone iodine irrigation of a surgical hip wound (D'auria, 1990). The patient had previously suffered from hypothyroidism. Death was due to cardiovascular collapse and appeared to be due to the toxic manifestations of systemic iodine absorption. The serum iodine level at necropsy was 7 mg/100 ml (normal value 0.005-0.008 mg/100 ml), a concentration which can produce refractory high anion gap, metabolic acidosis, cardiogenic shock and death. Metabolic acidosis was also observed in a patient who had ingested a large quantity of Lugol's iodine solution (5% iodine, 10% potassium iodide) (Dyck *et al.*, 1979). The authors concluded that the metabolic acidosis was largely due to lactic acidosis, possibly due to the iodine/iodate interfering with adenosine triphosphate generation by oxidative metabolism.
122. Renal failure and seizures were reported in a 62 year old male who had undergone mediastinal drainage of an infected sternal wound with povidone-iodine (Zec *et al.*, 1992). Serum iodine was 1200 µg/dl compared to the normal range 5.3-7.6 µg/dl. Renal function improved when the drainage solution was changed.

Amiodarone

123. As previously noted, amiodarone is a widely used anti-arrhythmia drug which can induce thyrotoxicosis in 1-23% of patients (Guyétant *et al.*, 1995). In a few cases this may be refractory to conventional pharmacological therapy, leading to thyroidectomy. Histological examination of tissue obtained from 4 such thyroidectomies demonstrated colloid transformation of the parenchyma, areas of follicular disruption with foamy macrophages being present in the colloid, regenerative areas, and moderate T lymphocytic invasion. *In vitro* studies have suggested that the thyroid cytotoxicity produced by amiodarone may be largely due to direct cytotoxicity, but that the excess iodide released by the drug may also contribute (Chiovato *et al.*, 1994).

Sperm counts

124. Neonatal hypothyroidism is reported to retard Sertoli cell maturation, prolonging the period of proliferation and ultimately increasing the number of Sertoli cells.

Thus it is postulated that the improved iodine status of the population (for example due to salt iodisation in the US) has led to a decrease in the number of reproductive-age men who experienced neonatal hypothyroidism which, Crissman *et al* (2000) hypothesised, may partly explain the apparent decline in sperm counts in the developed world.

Human Supplementation studies (see Table 1)

Single Doses

125. In a series of experiments designed to identify a dose of iodine able to block thyroid uptake of iodine, volunteers were given varying doses of stable iodine (Ramsden *et al.*, 1967). Based on a mathematical model, the minimum dose necessary to completely block thyroid uptake of iodine was estimated to be 30 mg. Thyroid uptake was blocked within half an hour of taking the blocking dose and returned to normal approximately 8 days after treatment. Dietary iodine levels were uncertain but the volunteers were asked to refrain from foods containing high levels of stable iodine.
126. Single doses of 5-1000 mg potassium iodide (equivalent to 3.8-764 mg iodine) were given to adult volunteers (Blum and Eisenbud, 1967). The 24 hour uptake of ¹³¹I was measured prior to, and 1-2 days after, dosing by measuring radioactivity in the neck. Iodine uptake was blocked such that none of the volunteers given more than 50 mg potassium iodide concentrated more than 1.3% of the dose of ¹³¹I (compared to a mean of 27.1% prior to treatment). No adverse effects were reported by the volunteers with the exception that two of the 4 subjects taking 1000 mg potassium iodide reported uncomfortable sensations in the angles of the jaw and headaches some hours after dosing.
127. Single doses of 10-100 mg iodide (as sodium iodide), were given to adult volunteers; subsequent experiments used 12 daily doses of 10-100 mg iodide (also as sodium iodide), (Sternthal *et al.*, 1980). All single doses greater than 10 mg suppressed 24-hour uptake of ¹²³I to 0.7 to 1.5%. Continued daily administration of 15 mg iodide or more resulted in 24-hour uptake values of less than 2% (compared to baseline values of 17.2-22.6%). When the values of the subjects taking 30-100 mg iodide were pooled, a significant increase in serum TSH and significant decreases in T3 and T4 levels were apparent. These returned to normal following the withdrawal of treatment. No adverse effects were reported. The authors stated that the stable iodide rapidly blocks the thyroid uptake of radioactive iodine because of rapid inhibition of intrathyroid organification (acute Wolff-Chaikoff effect) and saturation of the iodide-transport mechanism.

Repeat doses

128. The minimal effective dose necessary to suppress radioactive iodine uptake was investigated by Saxena *et al.*, (1962). Increasing doses of stable iodine (as an aqueous solution of sodium iodide) were given to children with normal thyroid function. Doses of 100, 300, 600 or 1000 µg I/day were given to children aged 1-

3, 4-6 or 9-11 years of age. The 24 hour uptake of ^{131}I was measured every two weeks until uptake declined to 5% or until there was no change between successive uptakes. The iodide was then discontinued. No adverse 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 ^{131}I being achieved with an estimated dose of 1.5-2 mg iodide per square meter of body surface. This was equivalent to a daily dose of 1-2 mg iodide in children and 3-4 mg in adults. ^{131}I uptake rapidly returned to normal once the iodide dose was discontinued.

129. In the study by Ramsden *et al.*, (1967) it was calculated that repeat doses of 35 mg stable iodine every 12 hours to 250 mg every 48 hours were necessary to maintain effective blocking of thyroid uptake in human volunteers.
130. Doses of 150 mg iodine given to normal individuals in iodine sufficient areas for periods of 1 to 3 weeks decreased serum T3 and T4 levels, with a small, compensatory increase in serum TSH also occurring (Braverman, 1987). The values for all 3 parameters remained within the normal range. Similar changes were reported in male volunteers given 200 mg/day of the iodine-rich colour erythrosine for 14 days. The dose was 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 200 mg dose of erythrosine was estimated to be equivalent to 1.5 mg iodine, a dose which produced comparable changes in thyroid parameters when given to volunteers for 14 days. The author considered that these subtle changes represented physiological adaptation to iodine excess.
131. Normal, euthyroid subjects (9 men and 23 women) were given doses of 250, 500 or 1500 μg supplemental iodine/day for 14 days (Paul *et al.*, 1988). Following the administration of 1500 $\mu\text{g}/\text{day}$ there were small but significant decreases in serum T3 and T4 concentrations and a small compensatory increase in serum TSH levels and TSH response to TRH. No effects were observed in the subjects given the lower levels of iodine.
132. Thirty normal men were randomly assigned to receive 500, 1500 or 4500 μg iodide/day for 2 weeks (Gardner *et al.*, 1988). A range of thyroid parameters were measured on day 1 and day 15. Mean serum T4 levels and free T4 index values were decreased at the 1500 and 4500 $\mu\text{g}/\text{day}$ dose. No changes in T3 charcoal uptake or serum T3 concentrations were observed at any dose. Doses of 500 $\mu\text{g}/\text{day}$ resulted in a significant increase in the serum TSH response to TRH and the two larger doses resulted in increases in basal and TRH-stimulated serum TSH concentrations.
133. A randomized controlled trial was performed in healthy women and in women with underlying thyroid abnormalities due to sub-clinical Hashimoto's thyroiditis (Chow *et al.*, 1991) to investigate the effects of low levels of iodine supplementation. A group of 225 women were 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 500 µg/day iodide or placebo. Dietary iodine intake was estimated to be approximately 250 µg/day. Free thyroxine (T4) and thyrotrophin levels were measured after 14 and 28 days treatment. 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. No changes in thyroid function were seen in the placebo group. The authors noted that the changes would not be of clinical significance in the general population but that a small shift in the mean of a population tended to result in greater effects at the extremes of the distribution. They further concluded that dietary intakes in the UK should be monitored since levels of 750 µg/day could adversely affect thyroid function.

134. Potassium iodide supplements of 0.1, 0.2 or 0.8 mg/day (equivalent to 0.077, 0.154 and 0.616 mg iodine) were given to normal subjects (9, 6 or 7/group respectively) for a 12 week period (Koutras *et al.*, 1964). With all 3 doses, plasma inorganic iodide (PII) concentrations increased, though this was only outside the normal range in the top dose group. The authors reported that thyroidal iodide clearance (presumably this refers to iodide clearance from the plasma by the thyroid though details are not provided) decreased in the top two groups though absolute iodine uptake (AIU) by the thyroid increased in both groups by approximately an additional 6 mg over the 12 week supplementation period. The levels of thyroid hormone secreted (as determined by protein-bound iodine levels) did not rise, suggesting that utilisation of iodine by the thyroid became less complete.
135. Iodine, specifically iodine caseinate, has been tested as a possible treatment for fibrocystic breast disease (FBD) (Ghent *et al.*, 1993 – abstract only available (see paragraph 56). Three clinical trials of iodine/iodide supplementation have been conducted on women with FBD (Ghent *et al.*, 1993, discussed Murray and Pizzorno 1998). The results indicated that treatment with iodides was effective in 70% of subjects but there was an associated high rate of side effects. These included; altered thyroid function, iodism (characterised by watery nose, weakness, excessive salivation and bad breath) and acne. Results with elemental iodine were similar but without significant side effects. A dosage of 70-90 µg iodine/kg bodyweight appears to be a safe and effective treatment for FBD (Murray and Pizzorno 1998). This is equivalent to a total dose of 420-540 µg iodine in a 60 kg adult.
136. The health and thyroid function of representative subjects of a prison population (initially 133 euthyroid prisoners though due to discharge this number was gradually reduced to 70) was assessed before and during usage of iodinated water for 9 months (Freund *et al.*, 1966). Water containing 1 mg/l iodine induced a marked decrease in the uptake of radioactive iodine to 7% but protein bound iodine levels did not change significantly until the iodine concentration was increased to 5 mg/l for 2 months (following 7 months exposure at the lower level), resulting in a decrease of radioactive iodine to 2%. Serum thyroxine concentration did not change regardless of the iodine concentration. No information on actual intake is provided but it can be assumed that water

consumption would be approximately 2 litres/day. The authors noted that prisoners continued to receive iodine from the diet including the use of iodised salt. It was also noted that no effects on thyroid function were found 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 who had had consumed water containing 1 mg I/l for at least 3 months, had impaired iodine organification (as measured by the change in thyroidal ¹³¹I concentration following administration of perchlorate). The clinical significance of this effect is unclear as individual T4 concentrations remained unchanged throughout the study i.e. no patients demonstrated iodine-induced hypothyroidism.

137. As a continuation of the study discussed above, 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 years did not result in any change to serum thyroxine level (Thomas, *et al.*, 1978). During the same period, 177 women in the prison gave birth to 181 full term infants without any enlargement of the thyroid being noted in the infants (Stockton and Thomas, 1978). The mothers of 101 infants had been in prison for ≥ 122 days, whilst 80 mothers had been incarcerated for < 118 days (10-118). However, the symptoms of 4 women who were hyperthyroid before entering, worsened. Of 15 women tested, impaired organification of iodide was found in two.
138. Serum T3 and T4 concentrations and free T4 index were unchanged in normal subjects who rinsed their mouths with iodine-containing mouthwash once a day for 6 months (Braverman, 1987). A small but significant increase in TSH levels was measured; this was within the normal range and was considered a normal physiological adaptive response to the increased iodine intake. The amount of iodine absorbed was equivalent to 2- 4 mg/day (based on increased urinary excretion)
139. In a study by Garber *et al* (1993) 104 healthy hyperlipidaemic subjects were placed on a low fat diet for 12 weeks. Between weeks 4 and 12, the group were randomised into a control group (n=53) or were given an iodine enriched egg/day (iodine enriched eggs are produced by hens fed a diet containing kelp and contain an average of 711 μg 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 and 21 subjects respectively in the test and control group by week 16. No significant adverse clinical effects were reported with the exception of one subject that reported an allergic-type response shortly after beginning egg consumption. There were no differences in clinical chemistry values between the two groups. It is noted that three subjects (2 test and 1 control) had elevated TSH levels but thyroid function tests (T3, T4, T3 uptake, TSH, thyroid binding globulin and free T4 index) were normal in the remaining subjects. However, details are provided on only one of these subjects. The individual concerned also had a high level of urinary iodine excretion and may have been exposed to other sources of iodine. Unfortunately, the subject was lost to follow up and it was unknown whether he developed clinically significant hypothyroidism. Plasma and urinary iodine levels were significantly higher in the test subjects compared to the controls.

Other Studies

140. The iodine intake of 184 patients with thyroid diseases (simple goitre, hyperthyroidism, hypothyroidism, thyroiditis, benign thyroid nodules and thyroid cancer) was compared to that of 207 normal subjects (Kim and Kim, 2000). Intake was assessed via a semi-quantitative food frequency questionnaire and was reported to be 673.8 ± 794.9 $\mu\text{g/day}$ in patients with thyroid diseases compared to 468.9 ± 481.9 $\mu\text{g/day}$ in the controls. Higher intakes were found in subjects with cancer $1460.6 \mu\text{g/day} \pm 1044.8$ compared to 443.5 ± 470.4 $\mu\text{g/day}$. The higher intakes were generally due to the consumption of seaweed or seaweed-containing dietary supplements. Urinary iodine excretion was also significantly higher in patients with hyperthyroidism, hypothyroidism, sub-acute thyroiditis, Hashimoto's thyroiditis and thyroid cancer compared to normal subjects, being generally approximately 2-fold higher; the highest levels of excretion (3-fold higher than control) being found in the individuals with thyroid cancer.

Adverse drug reactions

141. Suspected adverse reactions to medicinal products are reported to the Committee on Safety of Medicines/Medicines Control Agency. Many factors influence the number of reports received, and in most situations there is considerable "under-reporting" of reactions. A small number of reactions to oral iodide have been reported but there is no pattern suggesting an association with treatment.

Vulnerable Groups

142. Pregnant women and neonates can be considered to be vulnerable groups. Elderly subjects previously exposed to low iodine levels may also be susceptible to subsequent increases in iodine levels.

Children

143. Children may be vulnerable to the effects of iodine whilst the brain is developing.

Genetic Variants

144. Some genetic defects in thyroid hormone production have been identified (Cavalieri, 1980). The most common involve a defect in the process by which iodide is oxidised and incorporated into tyrosyl residues, possibly as the result of deficient thyroidal iodide peroxidase activity. Other defects include the lack of the iodotyrosine deiodinase enzyme. No data have been identified regarding variants in the handling of excess iodine.

Toxicity in Laboratory Animals*Acute Toxicity*

145. No symptoms were apparent in mice given a single oral dose of 250 mg/kg bw sodium iodate (equivalent to 160 mg iodine) (described Murray, 1953). However, 7/10 mice treated with 750 mg/kg bw (480 mg) died within 3 weeks of treatment. A single dose of 2,500 mg/kg (equivalent to 1,600 mg iodine) was lethal within 12 hours. Few other details are provided.
146. Swiss mice were given single oral doses of potassium or sodium iodide or iodate (Webster *et al.*, 1957). Some of the mice were fasted prior to treatment. Symptoms of iodate intoxication included diarrhoea, alternate hyperactivity and lassitude followed by weakness, prostration and dyspnoea. At the higher doses, excitability and convulsions frequently preceded death. Haemoglobinuria was observed but only in the fasted animals. Iodide intoxication produced similar symptoms but developed more slowly; haemoglobinuria was not observed. The LD50 values are as given below: Sodium iodate and iodide were tested only in mice fasted on screens and were slightly more toxic than the equivalent potassium compound. Weanling animals were no more susceptible to iodine toxicity than older animals.

Compound	LD50	Iodine equivalent
Potassium iodate (KIO ₃)	1177 mg/kg	697 mg/kg
KIO ₃ –mice fasted on sawdust	815 mg/kg	483 mg/kg
KIO ₃ –mice fasted on screens	531 mg/kg	314 mg/kg
Potassium iodide (KI)	2068 mg/kg	1581 mg/kg
KI–mice fasted on sawdust	1982 mg/kg	1516 mg/kg
KI–mice fasted on screens	1862 mg/kg	1424 mg/kg
NaI–mice fasted on screens	1650 mg/kg	1057 mg/kg
NaIO ₃ –mice fasted on screens	505 mg/kg	324 mg/kg

147. High intra-venous doses of iodine have been reported to have retinotoxic effects (Olsen *et al.*, 1979). However, this is thought to result from damage to biochemical mechanisms caused by the reduction of iodate to iodide rather than the specific accumulation of iodine in the tissues and fluids of the eye.

Sub-chronic Toxicity- see Table 2

148. Iodine (I₂) and iodide (I⁻) have been presumed to be equivalent in terms of toxicity, even though the oxidation state of iodine is higher; however, some data suggest that this may not be the case. Groups of 6 Sprague Dawley rats of each sex were given drinking water containing 0, 1, 3, 10 or 100 mg/l iodine or iodide (as sodium iodide) for 100 days (Sherer *et al.*, 1991). Treatment had no effects on body, brain, testes or heart weights. Although some increases in kidney and

liver weights were reported these did not appear to be treatment related. Thyroid weights were significantly increased in male rats treated with increasing concentrations of iodide but not iodine. Thyroid weight was significantly decreased in female rats treated with 100 mg/l iodate. After 10 days of iodine treatment, a dose-related increase in plasma T4 levels and an increase in the T4/T3 ratio was apparent; this was maintained for the duration of the study. In the iodide treated animals, no effect was apparent at 10 days and although the T4/T3 ratio increased after 100 days of treatment the magnitude of the increase was smaller. The authors concluded that iodine and iodide had different effects on thyroid hormone status. It was suggested that the mechanism for the increase could be due to either inhibition of the enzyme that converts T4 to T3 or, the reaction of iodine with deiodinated thyroxine metabolites in the intestine, regenerating thyroid hormones. No information is provided on water consumption in the treatment groups, making comparison of the received dose in the different treatment groups difficult. Serum T4 levels were also increased and T3 levels decreased following single oral doses of iodine but not by the equivalent dose of iodide (Thrall *et al.*, 1992).

149. In a second investigation by the same group (Thrall *et al.*, 1992) it was reported that incubation of diiodothyronine (T2), T3 or reverse T3 with iodine in phosphate-buffered saline *in vitro* resulted in the formation of T4. Addition of iodine to washes from the initial segments of rat intestine demonstrated that substances were present that could react with iodine to form thyroxine. In a further experiment, rats were treated with radiolabelled iodine or iodide; higher concentrations of a radioactive substance that bound a T4 specific antibody was found in the iodine treated group. The authors concluded that the data supported the hypothesis that iodine reacted with thyroid hormone metabolites to resynthesize T4 and elevate blood levels.
150. Excess iodide has been reported to have differing effects on the thyroids of growing and non-growing animals (Kanno *et al.*, 1994). Groups of male F344 rats aged 4 or 45 weeks were given drinking water containing 260 mg/l potassium iodide for six weeks. Control rats received untreated water. In the growing rats, the iodide treatment resulted in increased thyroid and pituitary weights, serum T4 and TSH levels. A slight, but not statistically significant, increase in labelling index was also apparent. Histologically, an increase in follicular cell height and colloid accumulation was observed; evidence of colloid absorption was also noted. The excess iodine also enhanced the effects of bovine TSH and protirelin tartrate on the labelling index of the thyroid cells. In the non-growing rats, the iodine treatment resulted in increased thyroid weights and T4 levels but not in pituitary weight, TSH level or labelling index. Histologically, an increase in colloid accumulation was observed. In the non-growing rats, iodine treatment did not enhance the proliferative effects of bovine TSH or protirelin tartrate. The authors concluded that growing rats were still susceptible to acute hypothyroidism, even after six weeks exposure to excess iodide, whereas the non-growing rats were refractory within the same treatment period. Data on water consumption are not provided, but if it is assumed that the 4 and 45 week old rats consumed 20 ml water/day, the dose of potassium iodide can be estimated to be approximately 84 and 12 mg/kg bw/day at the start of the study (equivalent to 64 and 9.2 mg/kg iodine), decreasing to 20 and 12 mg/kg bw/day

(equivalent to 15.3 or 9.2 mg/kg iodine) by the end of the study. It is uncertain to what extent the difference in achieved dose may have affected the observed differences between the two groups.

151. Groups of 6-10 Swiss mice were given drinking water containing 0.05, 0.1, 0.25, 0.5 or 0.75% potassium iodate for up to 16 weeks (Webster *et al.*, 1959). Control mice received untreated water and an additional group of mice received water containing 0.65% potassium iodide (equivalent to 0.84 % potassium iodate). Total potassium iodate intake/mouse over the first 104 days of the study was estimated to be 196, 358, 831, 1292, 1653 or 2228 mg respectively in the iodate and iodide treated groups (equivalent to 116, 212, 495, 766, 980 or 1702 mg/kg iodine). Water consumption was decreased by approximately one third in the 0.5 and 0.75% groups. Three mice in the top dose (0.75%) iodate group died within 7 days. After 12 weeks of treatment, haematologic studies were conducted. Haemoglobin and haematocrit levels were significantly reduced in the 0.25% mice and white cell counts tended to be elevated in treated animals. The red cell count was reduced in the mice receiving 0.25% or greater iodate; this was significant in the 0.5 and 0.75% groups. However, it should be noted that the haematological parameters of the two control groups also varied. Haemosiderin deposits were found in the renal tubules of the mice receiving 0.5% iodate, suggesting that haemolysis was occurring. No other significant toxicological changes were apparent. A sub group of mice received either water or the 0.25% solution for 6 weeks, and were then given a challenge dose by stomach tube of approximately the LD50 of potassium iodate. Pre-treatment with lower doses of iodate did not protect against the effects of the challenge dose.
152. Dietary iodine intake was found to affect the levels of epidermal growth factor (mEGF) in the thyroid and submaxillary glands of BALB/c mice following treatment with diet containing different levels of iodine for 21 days. (Dagogo-Jack, 1994). Compared to the controls, tissue mEGF was reduced by 30-40% in iodine deficient animals and increased by 60-150% following physiologic iodine replacement. In the submaxillary glands, mEGF levels showed a dose-related increase at physiologic (300 µg/day) and pharmacologic (3 mg/day) levels. However in the thyroid, the high iodine dose did not produce an additional increase in mEGF levels compared to the physiologic dose. Thyroid weights were increased in both the iodine deficient and high dose iodine treated animals. Serum thyroxine levels were comparable in all treatment groups except the high dose iodine group, where the levels were substantially increased, suggesting that the differences in mEGF levels were not associated with any of the known effects attributed to hypo or hyperthyroidism.
153. Non-obese diabetic (NOD) mice are a strain prone to autoimmune disease (Many *et al.*, 1995). When control NOD mice were fed standard (1µg/day iodide) or high (10 µg/day iodide) diet, they did not spontaneously develop thyroiditis. However, NOD mice previously made goitrous by initial treatment with a low iodide diet, developed thyroiditis similar to Hashimoto's disease following treatment with the high iodine diet for 96 days. Thyroid cell necrosis and diffuse inflammation was apparent in these mice after 4 days of treatment.

154. Groups of 6 guinea pigs were given drinking water treated with 0, 0.05 or 0.5% potassium iodate (the concentration in the top dose group was reduced to 0.25% within a few days due to drastically reduced water intake) for 4 weeks (Webster *et al.*, 1959). The estimated intake was 540-662 and 1525-1708 mg/ animal by day 28 of the study (equivalent to 320-393 and 904 –1013 mg/kg iodine). No treatment related clinical signs or haematological changes were apparent. Following post-mortem examination, no treatment-related gross pathological or histological changes were observed.
155. No symptoms were apparent in rabbits given twice weekly doses of 1 or 10 mg/kg bw sodium iodate (equivalent to 0.64 or 6.4 mg/kg iodine) (described Murray, 1953) for 6 weeks. However, following two doses of 100 mg/kg (equivalent to 64 mg/kg iodine), 2/3 treated animals died. Few other details are provided.
156. Dietary iodine in the form of iodide or iodate at concentrations of up to 150 ppm for 10 weeks did not have any adverse effects on the growth, viability, feed utilisation, haematology parameters or methaemoglobin levels of growing chicks (Brumbaugh *et al.*, 1959).
157. Supplementation of the diet of Large White Turkey breeder hens with 35 or 350 ppm (mg/kg) iodine during a 20 week laying cycle resulted in adverse effects on the hatchability of their eggs (Christensen and Ort, 1991). The 350 ppm supplement resulted in decreased egg weights, egg production and eggshell water vapour conduction. Embryonic mortality data indicated that the toxic effects of iodine on the embryos largely occurred during the first week of incubation, immediately prior to and during pipping. A supplement of 7 ppm iodine supported good hatchability. Direct injection of hens' eggs with iodide delayed hatching and reduced hatchability (Guo *et al.*, 1995). The body weights of the embryos were not affected by treatment, but thyroid weights were increased compared to the controls. Histological examination indicated that on the 12th day of incubation, iodide treatment had inhibited follicular formation. However on the 14th day of incubation, no differences were apparent. By the 18th day of incubation, the thyroid follicles of the iodide treated chicks were significantly larger than in the controls.

Lymphocytic thyroiditis

158. BB/W rats are a substrain of Wistar rats, which are susceptible to the development of lymphocytic thyroiditis (LT). The condition is accelerated by high dietary iodine, but it was uncertain whether this is due to a direct effect of iodine on immune effector cells, or is a secondary response to the toxic effects of iodine on thyroid tissue. In a study by Li and Boyages (1994) the mechanism of the iodine related effect was investigated by treating groups of Wistar or BB/W rats with either non or high iodide supplemented diets. When examined by Electron Microscopy, the thyroid glands of non-iodide-supplemented Wistar rats were morphologically normal while no overt symptoms were found in iodide treated Wistars. However, in the iodide treated BB/W rats, marked accumulation of secondary lysosomes and lipid droplets were observed, as were swollen and disrupted mitochondria and extremely dilated rough endoplasmic reticulum.

These were accompanied by nuclear changes indicating, necrosis. The effects observed were dose related and were accompanied by defects in iodine uptake and organification. In the non-iodide treated BB/W rats, only slight swelling of the mitochondria and endoplasmic reticulum were apparent. The authors concluded that iodide appeared to have a direct toxic effect on the thyroid of the BB/W rat, possibly via oxidative stress. Iodide could accelerate lymphocytic thyroiditis by damaging the subcellular structures of the thyrocytes, resulting in the formation of unknown factors that attract antigen presenting cells to the thyroid and accelerating the immunologic process.

159. However, when Wistar, LT-prone and non-LT prone BB/W rats were given iodine-containing (0.05%) drinking water overnight, intrathyroidal glutathione rose in all treated strains (Allen, 1993) regardless of LT-proneness. Hepatic glutathione levels were not affected by iodine treatment. In Wistar rats, given water with increasing concentrations of iodine (0.0125-0.075%), the increase in intrathyroidal glutathione was found to be dose-related, peaking at the 0.025% concentration. In Wistar rats given iodine (0.05%) in drinking water for 10 days, there were no differences in the glutathione levels in the thyroids of treated and control rats. Staining of samples from the thyroid and livers of Wistar rats given iodinated drinking water overnight did not provide any evidence of lipid peroxidation, though there was an apparent shift of glutathione staining from the apical border of the thyroid to the cytoplasm in the iodine treated rats. The authors concluded that the LT-prone rats did not have an inherent deficit in this response and there was no role for oxidative damage in iodine-induced LT. They suggest that iodine-induced LT is caused by the acceleration presentation of autoantigens to an intolerant immune system and additionally propose that glutathione has a role in intrathyroidal iodine metabolism and hormonogenesis. Earlier work by this author (Allen, 1992) showed that basal levels of lipid peroxidation (as assessed by malonyldialdehyde measurement) were higher in the LT prone BB/Wor substrain (before the onset of LT) than in the parent Wistar strain, but treatment with iodine did not influence lipid peroxidation levels.
160. Further work by the same group (Zhu *et al.*, 1995) suggested that the lymphocytic infiltration induced by excess iodine in the BB/W rat was accompanied by the development of thyroid cell proliferation evident as numerous microfollicles or cell masses. A high incidence of solid cell nest-like lesions was also apparent; these had either solid epidermoid or squamous structure or were cystic in nature. The incidence of the lesions was higher in the BB/W rats that were treated with iodine. It was suggested that these lesions could be a precursor to thyroid carcinoma.

Chronic Toxicity

161. Three male and 4 female rabbits were given a biweekly oral dose of 1 mg sodium iodate/kg (Murray, 1953). Two rabbits were killed after two months of treatment and the remaining 5 after 8 months. All animals gained weight and appeared healthy. A second group of animals, born and suckled by those in the initial treatment group were treated in the same way from 2 months of age. Three animals were killed after 5 ½ months and two after 7 months of treatment. The surviving rabbits were in good health after 14 months treatment. There was no

evidence of retinal degeneration following either ophthalmoscopic or histological examination. Histological examination of the liver, kidneys and thyroid glands of the treated animals did not reveal any abnormalities.

162. Groups of 40 F344/DuCrj rats of each sex were given drinking water containing 0, 10, 100, 1000 ppm iodine (as KI) for 2 years (Takegawa *et al.*, 1998). The intake was estimated to be 0, 0.6, 5.3 or 53 mg/kg bw/day. Squamous cell carcinomas were observed in the salivary glands of 4 males and 3 females in the top dose group only. This was not statistically significant, but it was noted that the tumours have not been reported in historical data for the strain. Ductular proliferation with lobular atrophy was frequently observed in the submandibular glands of these animals and squamous metaplasia was also evident in the proliferative ductules and larger interlobular ducts. A transitional state from metaplasia to squamous cell carcinoma was also observed. The authors concluded that metaplasia, secondary to lobular impairment caused by iodine may develop into carcinoma via a non-genotoxic, proliferation-dependent mechanism. Data for other tissues are not presented.

Reproductive and Developmental Toxicity

163. As previously noted, cretinism and goitre can occur in neonates as a result of maternal iodine deficiency. Neonatal goitre may also result from exposure to iodine in medical treatments or antiseptics. Few data are available from conventional reproductive toxicity studies in laboratory animals, in addition a number of the reports are not available in English. However, the available literature has been summarised on the REPROTEXT system database. Excess iodine is able to produce adverse effects in the offspring of treated animals. In minks, 100 ppm dietary iodine reduced the number of offspring produced, with 1000 ppm resulting in no offspring being born. Doses of 10 mg/kg potassium iodide in rabbits resulted in increased embryonic and neonatal mortality, runting and reduced birth weights.

164. Pregnant Sprague Dawley rats were given water containing 0.01% sodium iodide or tap water through pregnancy and lactation (Theodoropoulos *et al.*, 1979). Once weaned, the offspring were given the same until they were 60 days old when the experiment was terminated. The dose received by the rats was estimated to be 1-2 mg/day iodine. The treatment induced hypothyroidism (increased serum TSH, decreased serum T3 and T4) in the neonatal rats but this resolved by the time the animals were 18 days old despite the continuing treatment. The authors considered that synthesis rather than hormone release was impaired.

Carcinogenicity

165. Groups of F344 rats were given 1000 ppm potassium iodide in drinking water for 2 years (Takegawa *et al.*, 1998). Squamous cell carcinomas were found in the salivary glands of 4/40 and 3/40 treated males and females respectively and appear to have progressed through ductule proliferation and squamous metaplasia. The authors suggest that the lobular impairment induced by

potassium iodide could lead to metaplasia and subsequently, squamous cell carcinoma by a non-genotoxic proliferation dependent mechanism.

166. Both iodine excess and iodine deficiency can promote tumours in laboratory animals.
167. Male Wistar rats (44 divided between 3 groups) were fed iodine deficient, adequate or rich diets for up to 10 months (Yamashita *et al.*, 1990). The diets contained 0.5, 12 or 200 mg/kg iodine. The achieved dose is not given, but can be estimated to be approximately 0.05, 1.2 or 20 mg/kg bw/day (WHO, 1987). From the second experimental month, the rats were given a weekly injection of N-nitrosobis (2-hydroxypropyl)amine (BHP) for the following 10 weeks. In the iodine adequate and iodine rich groups, benign nodules were found in all treated animals. Papillary carcinomas were found in 33 and 29% respectively. The area of the thyroid gland occupied by the nodular lesions was much narrower in the iodine rich group. In the animals of the iodine deficient group, the thyroids were markedly enlarged, due to multiple nodular proliferation of follicle cells. All of the treated animals had carcinomas, both papillary and follicular. A pulmonary metastasis was found in one animal. As the dietary iodine content decreased, the number and size of the nodular lesions increased and the incidence of carcinomas increased. The authors suggest that the effect is due to the goitrogenic and/or promoting effect of TSH.
168. Groups of 30 male F344 rats were given a single intravenous dose of vehicle or N-nitrosomethylurea (MNU) and were then placed on an iodine-deficient, iodine-adequate or a commercial diet for up to 77 weeks (Ohshima and Ward, 1986). The iodine adequate diet contained 10 ppm iodine; other concentrations are not given). Following 52 weeks of treatment, MNU treated rats on the iodine-deficient diet had increased thyroid weights and a higher (90%) incidence of both thyroid follicular cell carcinoma and diffuse pituitary thyrotroph hyperplasia. The majority of the tumours were invasive when transplanted into weanling rats of the same strain. Rats on the iodine-deficient diet without MNU treatment had a 40% incidence of thyroid adenomas at week 52, which increased to 60% by week 77. A 10% incidence of thyroid carcinomas was apparent by week 77 in the same group. The authors concluded that iodine deficiency was a potent tumour promoter but was also carcinogenic alone.
169. Groups of 20 six- week old male F344 rats were given a single sub-cutaneous injection of 2,800 mg/kg bw N-bis (2-hydroxypropyl)-nitrosamine (DHPN) or the saline vehicle and maintained on an iodine deficient diet for 26 weeks (Kanno *et al.*, 1992). The animals were given drinking water supplemented with 0 to 260 mg/kg potassium iodide (approximately equivalent to iodine intakes of 0.25 to 3000 µg/day). In the DHPN treated animals, both iodine deficiency and excess increased thyroid follicular tumourigenesis. The iodine intakes that showed the least tumour promoting activity were 2.6 and 9.7 µg/day. No thyroid follicular lesions were found in the non-DHPN treated animals. In the non-DHPN treated rats, iodine deficiency produced diffuse thyroid hyperplasia, characterised by small follicles with tall epithelium and reduced colloid. In these animals, T4 was decreased and TSH increased. In the rats receiving excess iodine, a colloid goitre was produced, characterised by large follicles with flat epithelium and abundant

colloid mixed with normal or small sized follicles lined by epithelium of normal height, together with normal T4 levels and slightly reduced TSH. The authors propose that the mechanism for tumour promotion by iodine excess is related to the phenomenon of escape from the Wolff-Chaikoff Effect, (ie the restoration of the euthyroid state along with the normalisation of TSH levels, possibly achieved via reduction in thyroidal iodide transport capacity).

170. It has been suggested that the mechanism for the induction of thyroid cancer by inadequate iodine intakes is that iodine deficiency interferes with thyroid hormone synthesis, inducing sustained hyperthyrotropinaemia, leading to the formation of neoplasia (discussed, Kanno, 1994). The changes in the latent period include an increase in thyroid weight and the development of diffuse hyperplasia of the thyroid. In later phases the development of nodular hyperplasia (adenomatous nodular hyperplasia) also occurs. Iodine excess also promotes thyroid carcinogenesis in a two stage model, but the mechanism is not well understood

Genotoxicity

171. Iodine compounds are largely negative in genotoxicity assays. Methyl iodide has been reported to be weakly mutagenic, but this appears to be due to the methylating action of the compound forming DNA adducts (Gansewendt *et al.*, 1991).

In Vitro

172. Silver Iodide was negative in the Ames Salmonella microsome test (Eliopoulos and Mourelatos, 1998). Salmonella strains TA 102, TA1535, TA97 and TA98 were tested in both the presence and absence of metabolic activation. Povidone iodine, iodine and potassium iodide were negative in the L5178 Y mouse lymphoma assay in the absence of activation, however, iodine and povidone iodine showed marginal activity in the presence of activation (Kessler *et al.*, 1980). No significant transforming activity was shown by povidone iodine, iodine or potassium iodide in the Balb/c 3T3 transformation assay (Kessler *et al.*, 1980). The positive controls used were positive under the experimental conditions.

173. Silver iodide did not cause an increase in sister chromatid exchange in human lymphocytes (Eliopoulos and Mourelatos, 1998).

In Vivo

174. P388 lymphocytic leukaemia cells were maintained by serial passage through the peritoneal cavity of DBA mice (Eliopoulos and Mourelatos, 1998). Four after the tumour was transplanted, the mice were given an intra-peritoneal injection of silver iodide in suspension (the precise dose is unclear). This did not cause an increase in sister chromatid exchange in the P388 cells.

175. Doses of 72 mg/kg of povidone iodine (given by i.p. injection) were not mutagenic in the mouse dominant lethal assay (Merkle and Zeller, 1979). The drug was also tested in mouse micronucleus assay and was negative at doses of 35 mg/kg bw (i.p) and did not produce chromosome aberrations in the bone marrow of Chinese hamsters given i.p. doses of 38.3 and 82.5 mg/kg bw, one quarter and one half of the LD 50 respectively.

In Vitro Toxicity

176. High doses (1mM) of iodide induce necrosis in the epithelial cells of human thyroid follicles grown *in vitro* (Many *et al.*, 1992). The ultrastructural lesions observed (apical blebbing, cytoplasmic fragments desquamation, endoplasmic reticulum vesiculation and accumulation of lipofuscin in secondary lysosomes) were considered to be consistent with free radical damage and lipid peroxidation. The toxicity was prevented by inhibitors of iodine uptake or oxidation. In FRTL-5 thyroid cells, apoptosis as well as necrosis was observed following iodide treatment (Golstein and Dumont, 1996). However, dog thyrocytes in primary cell culture were not sensitive to iodide under the same conditions.

Mechanisms of Toxicity

177. 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.

Regulatory Considerations

178. The Food Labelling Regulations (1996) specify 150 µg iodine as the Recommended Daily Allowance used for food labelling purposes. The UK *Infant formula and follow-on formula regulations* specify a minimum iodine content of 1.2 µg/kJ (5 µg/100 kcal) for infant formula and follow-on formula. The maximum limit for iodine specified for processed cereal-based foods and baby foods intended for infants and young children is 35 µg/100 kcal (The Processed Cereal-based Foods and Baby Foods for Infants and Young Children (Amendment) Regulations 1999). Foods intended for use in energy restricted diets to replace the whole of the total daily diet should provide 130µg iodine and those intended as a meal replacement should provide 39µg per meal (The Foods Intended for User in Energy Restricted Diets for Weight Reduction Regulations 1997).

Recommendations on maximum intake levels

179. COMA (1991) noted that few cases of toxicity had been observed in people with intakes less than 5 mg/day, although transient mild effects had been demonstrated in previously deficient individuals receiving 0.15 to 0.2 mg/day. In normal subjects, an intake of 1-2 mg/day resulted in increased iodine levels in the thyroid

but no other changes. It was concluded that since there was a small number of elderly people in the UK that could be sensitive to high intakes, the safe upper limit of 1 mg/day or 0.017 mg/kg should be retained. The Nordic Project Group (1995) stated that whilst 1 mg iodine/day was acceptable, toxicity could occur at lower levels of intake in individually predisposed persons. They concluded that 0.3 mg/day could be considered an acceptable intake.

180. The Provisional Maximum Tolerable Daily Intake set by JECFA (1989) is 1 mg iodine/day from all sources. This was derived from the study by Saxena *et al* (1962).

Recommendations on maximum supplementation levels

181. A joint MAFF/Department of Health Working party (1991) identified 1 mg/day iodine as an undesirable chronic dose and recommended that a daily dose should not contain more than one tenth of this amount.

182. The Council for Responsible Nutrition (CRN, 1999) the UK trade association recommend a maximum of 500 µg/day iodine for long term supplementation and 700 µg/day iodine for short term supplementation (the latter is noted to be precautionary since an adverse effect has not been established).

Summary

183. Iodine is a halogen. At room temperature it is a blue-black solid which sublimes into a gaseous form. Iodine is present in seaweed, igneous rocks and some soils.

184. In the diet, iodine is naturally present in marine fish, shell fish and sea salt. Levels in cereals and grains vary depending on the soil content. The food colour erythrosine is also rich in iodine. In the UK, iodine is also present in cows' milk probably as a result of the use of supplemented cattle feeds and iodophors as sterilants. Iodine is present in food supplements both in its elemental form and as a component of kelp products. It is also present in licensed medicines, topical antiseptics and radiographic contrast agents.

185. In the UK, the mean adult intake of iodine from food is estimated to be 0.219 mg/day. High level (97.5th percentile) intake in adults is estimated to be 0.434 mg/day. On a body weight basis, iodine intakes in children are higher than those in adults as a result of the larger proportion of milk consumed. Iodine intake from water is estimated to be generally less than 30 µg/day. The LRNI and RNI for iodine is 70 and 140 µg/day respectively.

186. Iodine interacts with selenium and possibly vanadium. Natural goitrogens in the diet derived from plants such as cassava, maize, potato, cauliflower and broccoli as well as ions present in drinking water interfere with iodine metabolism.

187. Iodine is readily absorbed, largely from the small intestine. It can also be absorbed dermally, particularly when the skin is damaged. Once absorbed, iodine is distributed rapidly throughout the extracellular fluid. Iodine can be

secreted into saliva or gastric juices and reabsorbed. It can cross the placenta and is secreted into human milk.

188. The thyroid gland is the only significant store of iodine. Uptake of iodine by the thyroid is determined by need, a process mediated by thyroid stimulating hormone (TSH). It is then incorporated into thyroid hormones within a large protein, thyroglobulin; this protein is then stored in the colloid of the thyroid gland.
189. Iodine is largely excreted in the urine with all circulating iodine being cleared regardless of the circulating concentrations. Very small amounts may be excreted in sweat and in faeces.
190. Thyroid hormones are involved in the maintenance of metabolic rate, cellular metabolism and cellular integrity. In the developing foetus and infant, thyroid hormones are necessary for the development of the nervous system. A variety of mechanisms exist to compensate for low levels of iodine intake. These include enlargement of the thyroid gland a condition known as goitre. Only when these mechanisms fail do the clinical signs of hypothyroidism (also known as myxoedema) become apparent. Symptoms include lethargy, weakness, weight gain, poor concentration, oedema, muscle ache, dry skin, delayed reflexes and slow cardiac rhythm. In pregnancy, iodine deficiency is associated with an increased risk of miscarriage, still birth and congenital abnormalities. In the developing foetus, the major feature of deficiency is endemic cretinism, characterised by mental retardation, deaf mutism and spastic diplegia. A less common form of cretinism, due to hypothyroidism persisting post-natally, is the myxoedematous type, which is characterised by hypothyroidism and dwarfism.
191. As with iodine deficiency, a number of mechanisms exist to protect the thyroid against iodine excess. These include reduced iodide uptake by the thyroid, a switch towards the production of the iodine-richer hormones and reduced secretion of thyroid hormones. In humans, the effects of excess iodine can be divided into three types (though not all exposed subjects will react). These are 1) disturbance of thyroid function, resulting in the induction of hypothyroidism and/or goitre, or hyperthyroidism (thyrotoxicosis). These types of responses may occur where there is general high iodine intake or where intervention has taken place to correct iodine deficiency. The patterns of thyroid malignancy may also be altered. 2) Sensitivity reactions, such as iodide mumps, iododerma and iodide fever. These tend to occur following treatment with iodine-containing drugs, or radiographic contrast media. 3) Iodine poisoning. This may occur following accidental or deliberate ingestion, medical procedures such as wound irrigation.
192. In animals, symptoms of acute iodine toxicity include diarrhoea, alternating periods of hyperactivity, weakness, prostration, convulsions and death. In sub-chronic toxicity studies, reduced weight gain and haemolysis have been reported in addition to specific effects on the thyroid. BB/W rats are susceptible to the development of lymphocytic thyroiditis and have been used to investigate the mechanism for this condition. No data have been identified on the carcinogenicity of iodine in laboratory animals *per se*, however, both iodine deficiency and excess can promote tumour formation in animals pre-treated with

known carcinogens. Metaplasia has been identified in one chronic study. The available genotoxicity data are negative. Adverse effects on reproduction and development have been reported, but the data are sparse.

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ANNEX 1 TO EVM/00/06.REVISED SEPT 2001

TABLES REFERRED TO THROUGHOUT THE REVIEW

Table 1 – Human Supplementation studies with iodine

Exposure	Subjects	Dose	Effects reported	Dose-response data	Duration	Comment	Reference
Stable Iodine	9 adults	30 mg	Blockage of further iodine uptake	Effect at 30 mg (calculated from model)	Single dose	Dietary iodine levels uncertain, but subjects asked to abstain from high iodide foods	Ramsden <i>et al.</i> , 1967
KI	62 adults (1-18/dose group) used as own controls.	5-1000 mg (approx 3.8 to 760 mg iodine)	Significant reduction in radioactive iodine uptake	Effect at 50 mg (38 mg iodine)	Single dose	Dietary iodine levels uncertain. Neck and jaw ache at 1000 mg	Blum and Eisenbud, 1967
NaI	22 adults	10-100 mg	Significant reduction in radioactive iodine uptake. Increased TSH and decreased T3 and T4 at doses of 30-100 mg.	No effect at 10 mg iodide (single dose). Effect at 15 mg, followed by 15 mg/day to maintain continuous suppression	Single dose, followed by 12 daily doses.	Dietary iodine levels uncertain	Sternthal <i>et al.</i> , 1980
NaI	63 children aged 1-11 yrs	0.1 to 1 mg/day	Significant reduction in radioactive iodine uptake.	Effect at 1-5 to 2 mg iodide/square m body surface (1-2 mg in children 3-4 mg/adults) dose).	Up to 3 months.	Dietary iodine levels uncertain but institutional population	Saxena <i>et al.</i> , 1962
Stable Iodine		35 – 250 mg	Blockage of further iodine uptake	Effect at 35 mg/12 hours to 250 mg/48 hours to maintain continuous suppression	Repeat doses	Dietary iodine levels uncertain, but subjects asked to abstain from	Ramsden <i>et al.</i> , 1967

				(calculated from model)		high iodide foods	
Iodine	9 adults	150 mg	Increased TSH and decreased T3 and T4	Effect at 150 mg	1-3 weeks	Dietary iodine levels uncertain	Cited, Braverman <i>et al.</i> , 1987
Iodine	Adult volunteers	1.5 mg/day	Increased TSH and decreased T3 and T4 (but remained within normal range).	Effect at 1.5 mg/day	2 weeks	Dietary iodine levels uncertain	Braverman <i>et al.</i> , 1987
KI	22 adults	0.1-0.8 mg as iodide	Increased plasma I and decreased thyroid clearance resulting in a small increase in I uptake. No effect on thyroid hormones.	Effect apparent at all doses but only 0.8 mg/day outside normal range.	12 weeks	Dietary iodine levels uncertain, but iodized salt not used.	Koutras <i>et al.</i> , 1964
Iodine in drinking water	Prison population of 750, 133 evaluated long term.	1-5 mg/l (estimated dose up to 2-10 mg/day)	Decreased radioactive I uptake. No effect on T4 levels.	Effects at 2 – 10 mg	8 months at lower dose, 2 months at higher.	Dietary iodine levels uncertain. Control values taken during initial 2 months of untreated water	Freund <i>et al.</i> , 1966
Iodine in drinking water	Prison population of 177 mothers (having 181 infants)	0.5-0.75 mg/l (estimated dose up to 1-1.5 mg/day)	No effect on T4 levels or neonatal goitre observed. Worsening of symptoms in 4 previously hyperthyroid subjects	Effect at 1 – 1.5 mg	Up to 15 years for whole group.	Dietary iodine levels uncertain. Abstract only	Stockton and Thomas, 1978
Iodine in mouth-	Adult volunteers	2-4 mg/day	Small increase in TSH, no effect on serum T3 or	Effect at 2 – 4 mg/day	6 months	Dietary iodine levels uncertain.	Braverman <i>et al.</i> , 1987

wash			T4 (but remained within normal range).			Controls(?)	
Iodine in eggs	104 hyperlipidaemic adults	Approx 0.7 mg/day (1 egg)	Increase urinary iodine, no differences in thyroid parameters (2 treated and 1 control subject had elevated TSH levels).	No effect at 0.7 mg/day	12 - 16 weeks	Iodine levels in rest of diet uncertain.	Garber <i>et al.</i> , 1993
Erythrosine	Adult volunteers	60-200 mg (urinary excretion increased by 1.5 mg/day)	Increased TSH and decreased T3 and T4 (but remained within normal range).	No effect at 60 mg	2 weeks	Dietary iodine levels uncertain	Braverman <i>et al.</i> , 1987
Iodine	32 Adult volunteers	0.25, 0.5 or 1.5 mg	Decreased T3 and T4, increased TSH	No effect at 0.5 mg	2 weeks	Dietary iodine levels uncertain	Paul <i>et al.</i> , 1988
Iodide	30 Adult volunteers	0.5, 1.5 or 4.5 mg	Decreased T4, increase in TSH response to TRH	Effect at 0.5 mg	2 weeks	Dietary iodine levels uncertain	Gardner <i>et al.</i> , 1988
Iodide	Healthy volunteers and subjects with sub-clinical Hashimoto's thyroiditis	0.5 mg or placebo	Decreased T4, increased thyrotrophin levels.	Effect at 0.5 mg	4 weeks	Dietary iodine estimated to be 0.25 mg	Chow <i>et al.</i> , 1991

Table 2. Repeat Dose Animal Toxicity Studies

Species	Endpoint/findings	Dose	Duration	NOAEL/LOAEL	Comment	Reference
6 Sprague Dawley rats/group	Increased thyroid weights in iodide treated males. Dose related increase in T4/T3 ratio. Patterns different for iodine and iodide.	1-100 mg/l iodine or iodide in drinking water (approx 5 and 8 mg/kg for males and females) ⁴	100 days	100 mg/l iodine 30 mg/l iodide (based on increased thyroid weights)	No information on water consumption	Sherer <i>et al</i> (1991)
F344 rats aged 4 or 45 weeks	Increased thyroid and pituitary weights, serum T4 and TSH levels in growing rats	260 mg/l KI in drinking water (198 mg/l iodine). Approx 64 and 9 mg/kg iodine at start of study decreasing to 15 and 9 mg/kg at end ⁵ .	6 weeks	LOAEL in growing rats (non-growing rats refractory to effects of iodine)	No information on water consumption	Kanno <i>et al</i> (1994)
Swiss Mice 6-10/group	Deaths at top dose. Reduced haematocrit and haemoglobin levels.	0.05-0.75% potassium +iodate or iodide. Iodine dose per mouse over study approx 116-980 mg in iodate group or	16 weeks	NOAEL = 0.1% (212 mg iodine/mouse equivalent to 95 mg/kg bw/day)	Low level treatment did not protect against effects of subsequent higher doses.	Webster <i>et al</i> (1959)

⁴ Assuming water consumption of 20 ml/day and body weights of 400 and 250 g for male and female rats respectively.

⁵ Assuming water consumption of 20 ml/day and body weights of 60 g and 420 g at the start of the study and 250 and 420 g at the end for the 4 and 45 week old rats.

		1702 mg/kg in iodide group.				
BALB/C mice	Increased tissue mEGF levels, thyroid weights and T4 levels	0.3 or 3 mg iodine/day	21 days	LOAEL = 3 mg/day (equivalent to 100 mg/kg bw/day)		Dagogo-Jack, 1994
Non-Obese Diabetic (NOD) mice	Thyroiditis (thyroid cell necrosis and inflammation observed) in susceptible strain.	1 or 10 µg/day iodine	96 days	NOAEL = 1 µg/day	Mechanistic study	Many <i>et al</i> , 1995
Guinea pigs, 6/ group	No adverse clinical, haematological or histological changes apparent.	0.05-0.5% potassium iodate (decreased to 0.25%). Equivalent to 320-393 or 904-1013 mg/iodine over study.	4 weeks	NOAEL = 904-1013 mg iodine/guinea pig in male and females (equivalent to 107 and 103 mg/kg bw/day respectively)	Limited details.	Webster <i>et al</i> 1959
Rabbits	No symptoms at lower dose. Top dose lethal after 2 doses.	1, 10 or 100 mg/kg bw sodium iodate (equivalent to 0.64 to 6.4 iodine) twice a week	6 weeks	NOAEL = 10 mg/kg bw	Few details provided	Murray, 1953
Rabbits	No symptoms or adverse clinical, haematological or histological changes	1 mg/kg bw sodium iodate (equivalent to 0.64 mg iodine)	Up to 8 months. F1 generation treated for	NOAEL = 10 mg/kg bw	Few details provided	Murray, 1953

	apparent	twice a week	up to 14 months			
Chickens	No effects on growth, viability, feed utilization, methaemoglobin levels or haematology	Up to 150 ppm iodine in diet	10 weeks	NOAEL = 150 ppm		Brumbaugh <i>et al</i> , 1959
Hens Eggs	Foetal thyroid weights increased	4 mg/egg iodide injection				Guo <i>et al</i> , 1995
Turkeys	Decreased egg production, weights and eggshell water vapour conduction	35 or 350 ppm iodine in diet	20 weeks	NOAEL = 30 ppm		Christensen and Ort, 1991

ANNEX 2 TO EVM/00/06.REVISED SEPT2001

INTAKES OF IODINE FROM FOOD AND SUPPLEMENTS

The data presented on iodine intakes are obtained from two sources: i) the UK Total Diet Study which provides population average intakes; and ii) dietary surveys of specific population age groups in Britain carried out over the last 15 years⁶⁷⁸⁹¹⁰. In each survey food consumption data were collected by means of a dietary record (usually weighed) kept for 4 or 7 consecutive days. Nutrient intakes were calculated using a set of nutrient composition data contemporaneous with the time of the survey. Therefore some apparent differences in intakes between population age groups may be due to changes in the nutrient composition data and reflect changes in the nutrient composition of foods over time.

Population average intake of iodine from food sources

The 1995 Total Diet Study¹¹ showed that estimated population average intake of iodine in 1995 was in the range 151-209µg/day. Table 1 shows the concentration of iodine in each of the TDS food groups and the intake from each food group. This intake is comparable with intakes estimated from previous TDS and with intakes from dietary surveys of specific age groups as presented in Table 2. The highest concentrations of iodine were found in the fish group while the milk group provided the main contribution to dietary intake.

Intakes of iodine in specific age groups from food and supplements

Table 2 provides information on the median intake and the upper and lower end of the intake distribution (defined as the upper and lower 2.5 percentiles, respectively), of iodine by the British population, classified by age and sex.

Iodine intakes were generally higher for males than for females. There was a general trend for median absolute intakes to increase with age between pre-school children and adults. However, when adjusted for energy intake, iodine intakes decreased with age in pre-school children and between the 4-6 year age group and older children, reflecting the fall in milk consumption, which is the main source, with age. Intake for infants was particularly high due to the high consumption of cow's milk in this group and because the survey was carried out in November so composition data for winter milk, which has a higher iodine content than summer milk, was used. It should be noted that this survey may not reflect current consumption of milk in infants given COMA's current advice that cows milk should not be used as a main drink until the age of 12 months. There was also a trend towards a slight decrease in intakes in people aged 65 years and over. Iodine intakes adjusted for body weight also showed a trend to decrease with age. Median iodine intakes were above the RNI for all groups

⁶ Food and nutrient intakes of British infants. 1986

⁷ National Diet and Nutrition Survey of children aged 1½-4½ years. 1992/3

⁸ National Diet and Nutrition Survey of young people aged 4-18 years. 1997/8

⁹ Dietary and nutritional survey of British adults. 1986/7

¹⁰ National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

¹¹ MAFF (1997) Dietary intake of iodine and fatty acids. Food Surveillance Information Sheet No 127.

except for girls aged 11-18 years and women aged 65 and over living in the community and aged 85 years and over in institutions. Intakes were below the LRNI for 13% of girls aged 11-14, 10% of girls aged 15-18 and 6% of older women in the community. In other age groups 5% or fewer had intakes below the LRNI.

Sources of iodine in the diet

Table 3 indicates the percentage contribution made by different types of food to average intakes of iodine by young people aged 15-18 years. This dataset was collected in 1997 and so most closely reflects current eating habits and fortification practices. The main source of iodine in this group as in all age groups, was milk and milk products, which provided over 40% of intake, followed by cereals and cereal products. Other age groups had similar patterns of intake except that the contribution of milk and milk products was higher in infants and younger children and lower in adults and older people. The contribution of fish and fish products was higher in older people at around 18% of total intake. Iodine is not commonly used as a fortificant and fortificant iodine is therefore likely to make a negligible contribution to total intakes¹².

Iodine intake from milk

Analysis of the nutrient content of pasteurised milk in 1995/6 showed that levels of iodine in milk had increased considerably since the previous analysis in 1990/91. These new higher values were used to determine iodine intakes in the survey of young people aged 4-18 years as shown in Tables 2 and 3. The values have also been applied to consumption data from the earlier surveys of children aged 1½-4½ years, adults aged 16-64 years and older people aged 65 years and over to assess the effect of the higher levels in milk on intakes in these age groups. The results show that intakes for the population as a whole, adults (including older people) and most young children were well below the JECFA Provisional Maximum Tolerable Daily Intake (PMTDI) of 17µg/kg/bwt/day. For children aged 1½-4½ years, mean total iodine intake by consumers of milk over a whole year was 149µg/day (11µg/kg bwt/day). High level consumers of milk could obtain 302µg/day (23µg/kg bwt/day) from milk alone in winter (ranging from 247µg/day in 3½-4½ year olds to 309µg/day in 1½-2½ year olds). This suggests that some high level consumers of milk in the pre-school children age group are likely to have intakes above the PMTDI in the winter when iodine levels in milk are higher.

The levels of iodine in milk from the 1995/96 survey were considered by the COT and the FAC. The COT considered that the levels found were unlikely to pose a risk to health but recommended that monitoring of iodine levels in milk should continue. The FAC endorsed these recommendations. Results from the most recent survey of iodine in milk carried out in 1998/99 show that the levels are very similar to those found in the 1995/96 survey (Food Surveillance Sheet No 198). The COT considered these more recent results and restated its opinion.

¹² These surveys do not record consumption of table salt so any contribution of iodised salt to intakes will be excluded.

Iodine intake from supplements

Table 4 shows the number of consumers of iodine supplements for each age group, together with the median and range of intakes for each group. Only a very small proportion of participants took supplements containing iodine and the contribution of iodine supplements to average intakes of iodine for the total sample was negligible for children, young people and older adults and about 3% for adults aged 16-64 years. For consumers of iodine supplements median intakes were between 3 and 140 µg/day. The high intakes of iodine from supplements in adults was due to the use of kelp supplements. In particular the maximum intake of 1920µg /day for men aged 16-64 years was due to a subject recording consumption of 6 kelp and calcium tablets on each day of the dietary record.

Table 1 Concentrations of Iodine in 1995 Total Diet samples and estimated average intake¹³

Food Group	I content ($\mu\text{g}/\text{kg}$)	I intake ($\mu\text{g}/\text{day}$) ¹⁴		
		upper	middle	lower
Bread	<40	4	2	0
Misc. cereals	<40	4	2	0
Carcase meat	50	1	1	1
Offals	92	0	0	0
Meat products	202	9	9	9
Poultry	58	1	1	1
Fish	1430 -1440	19	19	19
Oils and fats	44	1	1	1
Eggs	505	8	8	8
Sugars and preserves	176	12	12	12
Green vegetables	<40	1	1	0
Potatoes	79	10	10	10
Other vegetables	<40	3	2	0
Canned vegetables	<40	1	1	0
Fruit	<40	3	1	0
Fruit products	54	2	2	2
Beverages	<40	34	17	0
Milk	279 -303	86	82	79
Dairy products	151	9	9	9
Nuts	<40	0	0	0
Total		209	180	151

¹³ The Total Diet Study is a model of the average domestic diet in the UK. A total of 119 categories of food and drink are specified for inclusion in the Total Diet. These are assigned to one of twenty broad food groups. The quantities and relative proportions of each food that make up the Total Diet are largely based on data from the National Food Survey (NFS) and are updated annually. Food samples are purchased fortnightly from different locations representative of the UK as a whole and prepared and cooked according to normal consumer practice. The constituents of each group are then homogenised and frozen. Samples can be analysed for a range of food constituents. The population average intake of a particular food constituent can be estimated from its concentration in each food group and consumption of each group as determined by the NFS.

¹⁴ Levels of intake have been calculated by assuming concentrations below the limit of detection are zero for lower level, mid-point between zero and limit of detection for middle level and at the limit of detection for upper level.

Table 2: Total intakes of iodine

Age/sex	Absolute iodine intake ($\mu\text{g}/\text{day}$)			Bodyweight adjusted iodine intake ($\mu\text{g}/\text{kg bwt}/\text{day}$) ¹⁵		
	<i>intakes from food and supplements</i> ¹⁶					
	2.5%ile	Median	97.5%ile	2.5%ile	Median	97.5%ile
Infants (1986) 6-12mths/M&F	69	196	395	7.270	17.950	41.070
Pre-school children (1992/3) 1½-2½ yrs/M&F	38	101	322	3.013	8.411	26.005
2½-3½ yrs/M&F	36	101	296	2.533	6.938	20.234
3½-4½ yrs/M	40	111	246	2.656	6.704	14.706
3½-4½ yrs/F	40	102	246	2.702	6.150	14.890
Young people (1997/8) ¹⁷ 4-6 yrs/M	61	144	336	2.344	6.841	16.390
4-6 yrs/F	54	133	318	2.381	6.738	13.816
7-10 yrs/M	65	142	309	2.168	4.746	11.838
7-10 yrs/F	51	123	258	1.768	3.933	9.318
11-14 yrs/M	59	153	341	0.966	3.270	69.010
11-14 yrs/F	48	119	268	0.903	2.577	6.523
15-18 yrs/M	78	168	348	1.029	2.535	5.311
15-18 yrs/F	41	126	279	0.750	2.046	4.570
Adults (1986/7) 16-24 yrs/M	95	218	419	1.341	3.298	7.164
16-24 yrs/F	61	146	330	1.028	2.752	6.202
25-34 yrs/M	103	235	449	1.351	3.170	6.270
25-34 yrs/F	53	158	398	0.856	2.713	6.397
35-49 yrs/M	93	236	453	1.496	3.252	6.208
35-49 yrs/F	75	172	401	1.019	2.915	6.685
50-64 yrs/M	102	217	418	1.462	3.092	6.514
50-64 yrs/F	67	171	356	0.916	2.929	6.250
Older people free-living in the community (1994/5) 65-74 yrs/M	75	184	347	1.020	2.357	5.199
65-74 yrs/F	53	137	287	0.808	2.211	4.635
75-84 yrs/M	74	172	318	0.909	2.329	5.081
75-84 yrs/F	54	136	257	0.829	2.082	4.501
85 and over/M	65	155	309	0.990	2.149	5.194
85 and over/F	50	132	317	0.757	2.164	5.548
Older people living in institutions (1994/5) 65-84 yrs/M	73	177	372	1.197	2.549	5.361
65-84 yrs/F	86	169	303	1.412	2.676	6.189
85 and over/M	83	175	341	1.220	2.409	5.146
85 and over/F	74	138	322	1.171	2.489	6.625

¹⁵ Body weights measured for each subject for all age groups except infants aged 6-12 months where reported body weights were used.

¹⁶ Absolute intakes presented for pre-school children, young people and older people are from food sources only as the contribution of supplements was negligible.

¹⁷ The survey of young people aged 4-18 years used new data for iodine in milk with higher levels for whole milk. This resulted in higher intakes of iodine in the 4-6 year group compared with the survey of pre-school children.

Table 3¹⁸: Sources of iodine in the diet

Food Type	Contribution of food types to average daily intake of iodine		
	ug/day	% of total	
Cereal and cereal products	25		16
Milk and milk products	66		42
- of which whole milk		17	11
- of which semi skimmed milk		31	20
Egg and egg dishes	5		3
Fat spreads	3		2
Meat and meat products	11		7
Fish and fish dishes	12		8
Vegetables, potatoes and savoury snacks	9		6
Fruits and nuts	2		1
Sugar, confectionery and preserves	5		3
Beverages	11		7
- of which beers and lagers		8	5
Miscellaneous	6		4
Total intake from food	156		100
<i>Intake from dietary supplements</i>	<i>negligible</i>		
Total intake from food and supplements	156		

Table 4: Iodine intake from supplements

Age/sex	Consumers of iodine supplements		Iodine intake from supplements (consumers only) (µg/day)	
	Number	%	Median	Range
Infants (1986)				
6-12 mths/M&F	0	0	0	0
Pre-school children (1992/3)				
1½-4½ yrs/M&F	9	<1	37.5	25.0 – 110.0
Young people (1997/8)				
4-10 yrs/M&F	15	2	67.5	10.7 – 150.0
11-18 yrs/M	5	1	63.6	15.7 – 107.1
11-18 yrs/F	4	<1	23.2	21.4 – 114.3
Adults (1986/7)				
16-64 yrs/M	26	2	99.0	9.2 – 1920.0
16-64 yrs/F	46	4	99.0	14.1 – 548.6
Older people free-living in the community (1994/5)				
65 and over/M	12	2	140.0	4.9 – 366.0
65 and over/F	12	2	24.6	0.1 – 140.0
Older people living in institutions (1994/5)				
65 and over/M	2	<1	3.0	3.0 - 22.1
65 and over/F	5	2	7.0	5.3 - 34.8

¹⁸ NDNS: young people aged 4-18 years. 1997/8. 15-18 year group

ANNEX 3 TO EVM/00/06.REVISED SEPT2001

IODINE: SUMMARY TABLE OF SELECTED NUTRITION RELATED INFORMATION AND EXISTING GUIDANCE

Unit of usage	Tg/day		Tg/100 kcal	Tg/kJ
	male	female		
<i>UK DRV¹⁹ for adults (19-50+)</i>				
LRNI	70	70		
EAR				
RNI	140	140		
<i>Mean adult UK dietary intake from food sources (all sources)</i>				
Adults (16-64) ²⁰	226 (225)	163 (161)		
65 years and over ²¹				
free living	177	137		
institutionalised	177	154		
EU labelling RDA ²²	150			
Supplemental doses	40-150			
Regulations				
Infant formula ²³			5	1.2
Cereal-based baby foods ²⁴			35	
Weight reduction ²⁵				
whole daily diet replacement	130 per meal			
meal replacement	39 per meal			
<i>Maximum total safe daily intake</i>				
COMA 1991 ¹⁸	1,000			
CRN 1999 ²⁶	700 (short term) 500 (long term)			

¹⁹ Committee on Medical Aspects of Food and Nutrition Policy (1991). Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report on Health and Social Subjects 41. London: HMSO.

²⁰ Dietary and nutritional survey of British adults. 1986/7

²¹ National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

²² The Food Labelling Regulations 1996

²³ The Infant Formula and Follow-on Formula Regulations 1995

²⁴ The Processed Cereal-based Foods and Baby Foods for Infants and Young Children Regulations 1997.

²⁵ The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations 1997.

²⁶ The Council for Responsible Nutrition leaflet, The Safe Use of Supplements Benefits Good Health 1999.

