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Scientific Advisory Committee on Nutrition

SACN STATEMENT ON IODINE AND HEALTH

February 2014

1. The Scientific Advisory Committee on Nutrition (SACN), following the publication of a paper in the Lancet in June 2011 by Vanderpump *et al*., who suggested that "the UK was iodine deficient", asked for an overview of the current evidence that some degree of iodine deficiency might affect some groups within the UK population.

2. Iodine, as iodide, is an essential constituent for the synthesis, in the thyroid gland follicles, of the hormones thyroxine T4 (3,5,3',5'-tetraiodothyronine), and T3 (3,5,3'-triiodothyronine). Iodide maintains the active conformation of the thyroid hormones T4, and T3 (Lingvay and Holt, 2012) which are necessary for optimum cellular metabolism, growth, psychomotor and physical development and function at all stages of life. Severe iodine deficiency causes growth and mental retardation. The manifestations and reversibility of iodine deficiency vary according to the life stage at which it is experienced, and the degree and duration of that deficiency (Hetzel, 1983).

3. Experience gained from iodine supplementation programmes suggests that at a population level, correction of even mild degrees of iodine deficiency is beneficial, both for health and the economy. Thus there are concerns that if in the UK current intakes of iodine in some sections of the population are inadequate, such groups (e.g. children, adolescents and women of childbearing age and their babies) are at risk of subtle, but nonetheless significant, effects of low degrees of iodine deficiency.

4. As this is a scoping exercise rather than a full risk assessment, it is not intended to be comprehensive but is a narrative review of the current literature on the assessment, characterisation and impact of iodine deficiency. This paper considers issues and experience elsewhere relevant to deciding the necessity to assess fully the amount and adequacy of dietary intakes of iodine in the UK. It will not include public health recommendations. This exercise will enable the formulation of any risk assessment questions and determination of appropriate adverse events and exposure measurements that would be needed for a reliable risk characterisation of iodine deficiency.

Background

5.   Iodine[i] is a reactive element with a variable stereochemistry and several oxidation states. In the environment it enters the food chain predominantly as iodate salts, and organo-iodide compounds which are synthesised by algae and bacteria. Only a small proportion exists as iodide, or elemental iodine. Iodide is the state in which iodine initially is biologically used.

6.   Inorganic iodine salts are water-soluble and are leached out of surface soils. Thus, geographical areas which have been or are subject to glaciation, high rain or snow fall, and floods have a low iodine content in the soil, and in produce grown or reared on these soils (Küpper *et al.,* 2011). As a result, populations in these regions are at risk of iodine deficiency unless they receive dietary or other sources of additional iodine. These areas include the central and mountainous areas of Europe, Asia, South America, Africa, and the Highlands of Papua New Guinea, and floodplains, such as those of Bangladesh. Goitre secondary to inadequate iodine intakes (see below) was once endemic in the UK, particularly in the Derbyshire Pennines (Saikat *et al.,* 2004).

7.   In contrast, the iodine content of the sea and marine produce is relatively high (Barkley and Thompson, 1960). Iodine evaporates from the sea and is redistributed in rain and snow, however this is insufficient to restitute the iodine content of depleted surface soils (Zimmermann, 2010).

8.   The prevalence of iodine deficiency has been reduced by the use of iodised salt and oral or parenteral iodised oil (World Health Organization (WHO), 2007). The former approach was used in Europe either as a mandatory or, as in the UK, a discretionary measure. However, little iodised salt is now consumed in the UK and some other European countries, and a resultant concern is that there is an increasing risk of iodine deficiency in Western Europe.

Iodine absorption, distribution, utilisation and excretion

9.   Dietary iodine compounds are absorbed predominantly in the proximal small intestine as iodide. Small amounts of organic iodide compounds such as thyroxine can be absorbed intact but these are of little dietary significance. Dietary iodate is reduced in the proximal gut lumen to iodide which is taken up into the gut mucosa by a sodium iodide symporter (NIS) (Dohán *et al*., 2003). Some iodide crosses the gut mucosa by diffusion (Zimmermann, 2012).

10.   The absorptive efficiency and bioavailability of iodine is related to dietary intake and systemic needs for iodine. Absorbed iodine enters the plasma and extracellular fluid pool of inorganic iodide. The size of this pool (250-350 µg) is influenced by tissue uptake and renal excretion of iodide (Lingvay and Holt, 2012). Most iodide in plasma is taken up by the thyroid gland via its own NIS. In well-nourished individuals the thyroid contains about 75% of the 15-20 mg of total iodine in the body (Zimmermann, 2012). Iodine is also concentrated by other tissues including mammary tissue, salivary glands and gastric mucosa all of which have NIS systems.

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i Iodine occurs in foods largely as inorganic iodides or iodates. For the purpose of this paper 'iodine' will be used as a general term for all forms when the precise nature of the chemical species of iodine is either not known/specified or not relevant.

11. Iodide is transported into the central lumen of the thyroid follicles where it is oxidised by a haem-iron dependent enzyme thyroid peroxidase (TPO) to iodate which binds to the tyrosine residues in thyroglobulin (Tg; a large molecular weight glycoprotein that is also produced by the thyroid follicles), to form a mixture of mono and di iodinated tyrosines which coalesce to form T3 and T4 (Zimmermann, 2012).

12. T4 and T3 are released into the blood by passive diffusion after proteolysis from thyroglobulin, and circulate in protein-bound and free forms (Zimmermann, 2012). The unbound 1% or free T4 and T3 (fT3 and fT4) are the active entities and it is assumed that the bound forms serve as a circulating reserve (Zimmerman, 2012). At the relevant tissue or cellular sites, selenium dependent deiodinases transform fT4 into the metabolically active fT3, or reverse T3 (the non-functioning form of T3) (Brent, 2012).

13. The thyroid is estimated to use 60-80 μg of iodide daily to produce its customary output of thyroid hormones (Zimmerman, 2012). About a quarter of this is acquired from recycling endogenous iodide and the rest is acquired from the diet (Zimmermann *et al*., 2008). At customary intakes of iodide the thyroid gland can take up 5-90% of absorbed iodide. Iodine that has not been taken up by the thyroid and other tissues is excreted rapidly in the urine (Nath *et al.,* 1992).

Regulation of iodine turnover homeostasis

14. The finer regulation of the above processes is not understood. At the gross level, the anterior pituitary gland produces thyroid stimulating hormone (TSH) which regulates NIS activity, Tg synthesis and storage, peroxidase activity and iodination of Tg, the re-entry of Tg into the follicular cells, as well as the subsequent release and secretion of thyroid hormones (Dohán *et al*., 2003; Zimmermann, 2012).

15. TSH is produced under the control of the hypothalamic secretion of thyroid releasing hormone (TRH) and somatostatin which respectively increase and inhibit the release of TSH (Becker, 2001). Additionally various growth factors suppress the function of the NIS (Dohán *et al.*, 2003), and gonadotrophins have weak stimulatory activity on TSH (Glinoer, 2001).

16. The hypothalamic production of TRH is sensitive to feedback from fT3 and fT4; lower levels of which stimulate production of TRH (Zimmermann and Andersson, 2012), and in turn increase the synthesis of T4, and T3 whereas relatively high levels of fT3 and fT4 induce the hypothalamus to secrete somatostatin which inhibits the release of TSH (Becker, 2001; Brook and Dattani, 2012).

17. The components of adaptation to inadequate intakes of iodine are understood only in the broadest sense and there are insufficient data with which to construct a precise dose (i.e. oral intake and body burden) response curve for the key events that control and effect homeostasis of iodine and thyroid function, particularly at iodine intakes that are thought to be marginal to deficiency and excess.

18. If iodine supply is adequate, the thyroid NIS pump acquires sufficient iodine for hormone synthesis, and the surplus iodine is excreted by the kidneys (Zimmermann, 2012). The driver for the acquisition and retention of iodine appears to be the degree of need for T3 and T4. If the combined resource of recycled endogenous iodine and absorbed dietary iodine do not meet the systemic need for thyroid hormone synthesis, insufficient feedback of fT3 and fT4 to the hypothalamus stimulates TRH production and this then increases TSH secretion (Crook, 2012; Chiamolera and Wondisford, 2009).

19. The sensitivity, integration and characterisation of the signals and mechanisms to acquire more iodine at times of increased hormonal synthesis or inadequate intakes of iodine are not clear. One reason for this is the existence of the Tg depot of iodine, which possibly compensates for periods of low dietary iodine intake and smooths out the supply of iodine for synthesis of hormones (Zimmermann, 2012). Thus, the size of the Tg pool of iodine is a significant and uncertain factor in the characterisation of the response to iodine intakes, particularly those which are potentially inadequate.

20. Adequate intakes of iodine enable a sufficient production of fT3 and fT4 which down regulates the TRH and TSH stimuli which, in turn, reduce the intestinal uptake and renal retention of iodine.

21. When the iodine content of the thyroid gland becomes depleted, invariably as the result of inadequate iodine supply, T3 and T4, and thus fT3 and fT4, fall and TRH and TSH production increase. This increases intestinal uptake and transfer of iodine via the enterocytic NIS, and increased activity of the thyroid NIS increases the gland's uptake of iodine from the plasma pool. Increased renal NIS activity increases the renal retention of iodine. Simultaneously the thyroid produces more Tg and the gland becomes more cellular and enlarged (simple early diffuse goitre). With sustained stimulation and inadequate iodine intake, the goitre may become persistent and nodular (Delange, 2000).

22. At high dietary intakes of iodine the intestinal uptake of iodine and thyroid utilisation of the element become blocked (Teng *et al.,* 2011). The mechanism for this is not clear, but, it may be the result of a local or autonomous downregulation of the NIS (Eng *et al*., 2001).

Dietary Sources of Iodine

23. Dietary sources of iodine relevant to the UK are shown in Table 1. UK food composition data for iodine, as for other anions, are uncertain, have not been systematically updated and are unlikely to provide a reliable contribution to assessments of iodine intake. Levels in cereals and grains vary depending on the characteristics and iodine content of the soil on which they were grown; levels in meat, chicken, eggs and dairy products reflect the iodine content of the animal feed used (see paragraph 88). Unsurprisingly, high levels of iodine are present in marine fish and shellfish (Food Standards Agency (FSA), 2002), however, although sea water and brine have high iodine contents, these are lost during evaporation to form salt, therefore "sea salt" and mined salt are not significant sources of iodine (Dasgupta *et al.,* 2008).

Factors which impair the bioavailability of iodine

24. The transport of iodide by the NIS is reduced by perchlorates and related compounds and is virtually totally blocked by thiocyanates (Wolff, 1964). Consequently, both groups of compounds can impair the enterocytic and thyroid follicular cell uptake of iodide, inducing iodine deficiency and the development of a goitre (see below). Such compounds are known as goitrogens; particular sources of goitrogens include cassava, millet, maize, and cruciferous vegetables (Gibson, 1991).

25. The thiocyanate in cassava is derived from linamarin, however soaking and/or thorough cooking reduces the linamarin content, and the associated risk of iodine inadequacy (Zimmermann, 2009a). The consumption of foods containing goitrogens is not a concern for most people who have adequate iodine intakes and consume a varied diet (Zimmermann *et al.,* 2008).

26. The inhibitory effect of high intakes of iodide on NIS has been noted above.

27. Thyroid hormone regulation may be compromised by other general and specific nutritional factors. As a general issue the broad effects of fT3 and fT4 on systemic metabolism, growth and development might be compromised by any degree of malnutrition involving nutrients such as iron, zinc, selenium and vitamin A for example, and other limiting nutrients (e.g. essential amino acids) impairing the peripheral systemic response to thyroid hormones (Hess, 2010).

28. Other deficiencies may interfere with iodide utilisation, e.g. possible reduced TPO activity with severe iron deficiency, and, with selenium deficiency, reduced deiodinase activation of fT3 and fT4, or impairment of their nuclear function by vitamin A deficiency (Hess, 2010).

29. Despite being noted in animal models, these phenomena have not been well characterised in humans; but randomised controlled trials (RCTs) show iodine deficient children with iron deficiency anaemia[ii] have a less beneficial response to iodine supplementation than those without anaemia, and including iron in iodine supplemented salt has been shown in several studies to be more effective in reducing goitre size (Hess, 2010). However, this effect may be the result of correcting a systemic iron deficiency as part of a more general inadequacy of essential nutrients impairing the peripheral response to thyroid hormones.

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ii Haemoglobin concentrations of: children 5-11 years, <115 g/L; children 12-14 years and females over 15 years, <120 g/L; males $\geq$ 15 years, <130 g/L defined anaemia in the studies. Serum ferritin concentrations of: children under 5 years, <12 μg/L; males and females over 5 years, <15 μg/L defined depleted storage iron.

Iodine deficiency disorders

30. 'Iodine Deficiency Disorders' (IDD) encompass a spectrum of effects (set out in Table 2) ranging from progressive thyroid enlargement (i.e. goitre), as an adaption to acquire more iodine and to sustain production of thyroid hormones, to a range of effects arising from deficiency of the thyroid hormones, including defective reproduction, growth impairment, and neurodevelopmental damage (cretinism), which represent the vulnerability of developmental and physiological stages to iodine deficiency (Hetzel, 1983). Pregnant and lactating women and the fetus are of particular interest because of the effects of severe iodine deficiency in pregnant women resulting in impaired fetal growth and psychomotor development (Haddow *et al.,* 1999; Pharoah *et al.,* 2012).

31. In the UK, and in Western Europe, the prevalence of severe manifestations of iodine deficiency has diminished appreciably in the past century, initially in part due to improved general nutrition and, subsequently specific interventions designed to increase iodine intake. Now, however, there is public health concern that iodine intakes have again become marginally adequate or actually inadequate for systemic needs, especially during adolescence, reproduction and gestation and development.

32. The severity and likelihood of IDD in populations has been ranked by the WHO by setting four strata on the basis of median values for the 24-hour urinary iodine excretion (UIE) within that population and relating this to the prevalence of goitres, and cretinism (Table 3). The subsequent adaptation of expressing UIE, and use of this categorisation is discussed in paragraphs 40-56.

Disorders due to excess iodine intakes

33. Iodine toxicity is unlikely to occur in individuals who are on normal western diets particularly if they have never been iodine deficient. However, in Japan some populations with a high intake of marine fish and seaweed providing daily iodine intakes of 50-80 mg have been studied. Their UIE was in general around half of these values and was therefore not quantitatively representative of their dietary intake of iodine; which is consistent with the concepts of iodine homeostasis outlined earlier (Miyai *et al*., 2008; Nagataki *et al*., 1967).

34. In contrast to the above observation, in a follow up of populations previously exposed to iodine deficiency, iodine supplementation carried a risk that some individuals might develop hyperthyroidism (thyrotoxicosis) in which the gland autonomously produces too much T4 and T3. This is associated with a previous experience of iodine deficiency and an induction of thyroid hyperplasia and goitre, in which the thyroid follicular cells had become autonomous. This phenomenon has been observed with iodised salt prophylaxis (Pearce, 2006). In the UK, a spring-summer outbreak of hyperthyroidism was ascribed to the increased iodine content of milk produced by cows being fed on high iodine content winter feeds; the average daily intakes involved were 240 and 320 μg for women and men respectively (Barker and Phillips, 1984; Phillips *et al.,* 1983).

35. Similar events have occurred at slightly lower intakes of iodine in Tasmania (Adams *et al.*, 1975) and Holland (Van Leewen, 1954) with the use of iodinated bread.

36. The prevalence of hypothyroidism has been reported to have increased since mandatory iodisation of salt was introduced to Denmark in 1998 (Pedersen *et al.*, 2007; Vejbjerg *et al.*, 2009b). The increase was observed in subjects aged 20-59 years with previous moderate iodine deficiency (Pedersen *et al.*, 2007).

37. At a population level in the UK there are no concerns about excessive dietary iodine intakes (see paragraph 98). However, some medicines, water purification tablets, topical antiseptics and iodinated radiocontrast agents are appreciable sources of exposure to iodine (Mann *et al.*, 1994) and might precipitate hyperthyroidism in some individuals.

Assessment of iodine adequacy and deficiency

38. The assessment of dietary iodine intakes has been approached using food composition data. However, as has been said, food composition data on iodine are uncertain and dietary assessments are correspondingly insecure. Furthermore, it is also difficult to relate estimated dietary intakes of iodine to any risk of inadequacy because of the variability of consuming good sources of iodine, and because of the reserve of iodine provided by the Tg iodide pool and homeostatic adaptations. These also make it difficult to assess the period over which dietary intakes of iodine should be monitored in order to get a reasonable idea of their adequacy or otherwise.

39. Measuring UIE is a widely used approach to assessing iodine status and the risk of iodine deficiency, and is discussed below. The occurrence and character of goitres are markers of adaptation to inadequate intakes of iodine. An indication of this early adaptation by the thyroid would be provided by elevated TSH levels as the mediation of that adaptation. However, apart from neonatal screening for inherited defects in thyroid function, TSH is not widely used for population surveys. T3 and T4 represent late outcomes of iodine deficiency at a point when thyroid adaptation and function has failed; therefore they are of limited value in assessing the immediate adequacy of iodine supply.

Urinary iodine excretion

40. The "cut off" values for 24-hour UIE (Table 3) were initially considered as the "reference standard" for assessing the likelihood of iodine deficiency in a population. These values were derived from studies in children aged six-12 years. Subsequently the impracticalities and poor compliance with 24-hour collections of urine in field studies led to the use of single non-fasting casual (i.e. spot, random or nonfasting) urine samples (Hollowell *et al.,* 1998; WHO, 2007; Bourdoux *et al.,* 1986; Soldin, 2002; Benmiloud *et al.,* 1994). The urinary iodine content was either expressed as a concentration (i.e. urinary iodine concentration (UIC) μg I/L) or in relation to urinary creatinine (i.e. UIC μg I/g creatinine). The latter was a device, based on the assumption that daily creatinine excretion was reasonably constant, to compensate for the variabilities in urine volume that affect urinary iodine concentration in casual samples (Konig *et al.,* 2011; Andersen *et al.,* 2008).

41.   Urinary creatinine excretion, however, varies with age, sex, body size, and other aspects of nutrition, which render it unreliable as a denominator for standardisation of iodine excretion (WHO, 1994; Furnée *et al.,* 1994; Greenblatt *et al.,* 1976; Bourdoux, 1998; Demers and Spencer, 2002; Thomson *et al.,* 1997; Kesteloot and Joossens, 1996; Barr *et al.,* 2005; Haddow *et al.,* 2007). On the basis of the 2003-06 United States (US) National Health and Nutrition Examination Survey (NHANES) data, the Centers for Disease Control and Prevention (CDC) concluded that UIC corrected for creatinine (µg I/g Cr) provided no more information than UIC (µg I/L) alone (CDC, 2012).

42.   UIE is influenced by gender, age, pubertal development, pregnancy, and lactation, as well as by the nature of the diet, ethnicity, drug interferences, geographical location, and time of year which might operate by affecting dietary choice as well as the diet itself. Whereas 24-hour collections eliminated or reduced the influence of some of these factors, data from spot samples are susceptible to their confounding effects (Als *et al.*, 1994; Als *et al.,* 2000; Rasmussen *et al.,* 1999).

43.   In particular, UIE varies according to recent iodine intakes (Als *et al.,* 2000; Rasmussen *et al.,* 1999; Rasmussen *et al.,* 2002) and although UIE has been presumed to reflect iodine intake, the quantitative relationship of UIE to iodine intake has not been fully characterised across the range of dietary exposure to iodine, and neither has the time dependency of the relationship been fully evaluated. The Japanese experience cited above (Miyai *et al.*, 2008; Nagataki *et al.*, 1967) illustrates a lack of correlation at particularly high intakes, and the assumption that 90% of dietary iodine is absorbed (Zimmerman, 2009a) probably only applies to a specific range of intakes and circumstances which need to be characterised.

44.   One investigation, in a Korean population, used food composition data and a food frequency questionnaire (FFQ) to assess UIE as a marker of intake (mean iodine intake 478 µg/day (range 61–4086)), and found a high correlation (γ^{iii}=0.60, p<0.01) between dietary iodine intake and UIE (Kim *et al.,* 1998). However, assuming that they are accurate, these exposures are higher than is customary in most populations and the mean intake exceeds the range in which physiological adaptation to acquire and conserve iodine probably occurs.

45.   At dietary intakes nearer those of relevance to potential iodine inadequacy, Rasmussen *et al.,* (1999), collected 24-hour urine samples (n=30) from ten healthy Danish adults whose iodine intakes were determined by weighed diets and food composition tables for the 24-hours corresponding to the urine collection. They found a weak correlation between iodine intake (mean 89 µg/day; SD ±6.5 µg/day) and UIE within the same day (r^{iii}=0.46, p=0.01). The range and distribution of the data were not provided. The study found no relation between iodine intake on one day and UIE on the following day, which is consistent with what is understood about the rapidity of iodine loss via the urine. The result may also reflect the uncertainties of the assessments of iodine intakes.

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iii The correlation coefficients obtained in the Kim *et al*., (1998) and Rasmussen *et al.,* (1999) studies cannot be compared due to the use of different analytical methods.

46.   The homeostatic adaptation to iodine intakes suggests that the relationship between iodine intake and its urinary excretion is not as simple as has been commonly assumed. At high intakes i.e. above systemic requirements, UIE may match intake, however as intakes increase, intestinal uptake and transfer of iodine would be down regulated and UIE underrepresents dietary exposure. At "low" intakes of iodine and resultant low circulating levels of fT3 and fT4, raised TSH activity increases the absorption, retention and utilisation of dietary iodine. Thus UIE may also be expected to underestimate dietary intake of iodine at low exposures.

47.   Nonetheless, even if it does not closely represent dietary intakes of iodine, UIE is a potentially valuable marker of a risk of iodine deficiency within a population, and as can be appreciated from Table 3, a population UIE median above 100 μg/day is an indicator of a low prevalence of iodine deficiency within that group.

48.   The use of casual spot urine samples and the use of UIC rather than 24-hour collections introduced uncertainties about how well UIC represented 24-hour UIE. The values used in Table 3 were based, as has been said, on samples collected from school age children aged six-12 years in large investigations of the association of goitre and UIE in areas of endemic goitre (WHO, 1992). It was assumed that these children passed a litre of urine daily; thus although the denominator for iodine excretion changed from 24-hour to a litre, it was possible to express the UIC of spot samples using the same numerator.

49.   A similar manipulation was used for the expression of iodine excretion in relation to creatinine; it was assumed that a gram of creatinine was excreted per day. Consequently, although the way in which UIE is expressed (μg/L, μg/day and μg/g Cr) has changed, the numerical values involved have been consistent and the original categorisation of values for the likelihood of IDD has been maintained.

50.   A study by Als *et al*., (2003) indicate these measures are not equivalent in adults and that μg/L and μg/g Cr underestimate the excretion of iodine in urine and therefore overestimate the likelihood of iodine deficiency, compared to values expressed as μg/day. The UIC is only interchangeable with the UIE if the daily volume of urine produced is about 1 L/day. Since older children and adults pass about 1.5 L/day (Manz *et al.,* 2011), the UIE categorisation values should be reassessed in interpreting the cut of values (i.e. 100 μg/day corresponds to a UIC of around 60-70 μg/L). Thus, a more suitable cut-off for iodine sufficiency in populations of older children and adults may be a median value in the order of 60-70 μg/L (Zimmermann and Andersson, 2012).

51.   There is a diurnal variation in the urinary excretion of iodine; for example in adult men with a median UIC of 110 μg/L, the UIC peaked about four-five hours after a meal and fell to a nadir eight-12 hours overnight after a meal; this, of course, would correspond to an early morning or "fasting" sample, (Als *et al.,* 2000).

52. Collecting fasting spot urine samples (i.e. early morning samples), reduces the variability of the UIC (Thomson *et al.,* 1996; Busnardo *et al.,* 2006). However the values represent a nadir and are approximately 25% lower than those from random or non-fasting "casual" samples (Als *et al*., 2000). Therefore data from studies using fasting (usually early morning) spot urine samples should not be compared or amalgamated with those from "casual" spot urines (Als *et al.,* 2000). Furthermore, it indicates that it is inappropriate and unreliable to use data from fasting spot urines, and possibly early morning samples, to assess the likelihood of IDD in groups of older children and adults according to the WHO classification of iodine deficiency (Table 3).

53. It has been emphasised that a single urine spot sample is not adequate for the assessment of an individual's iodine "status": multiple samples are needed (Konig *et al*., 2011). Similarly, particular attention has been paid to the number of individual spot and 24-hour urine samples that are needed to provide a 95% degree of confidence of being within a specified range for crude UIC and for estimated 24-hour UIE in a population (Andersen *et al*., 2008).

54. Another source of uncertainty in measuring urinary iodine content has been the analytical methodology used and its quality assurance. An interlaboratory comparison of six methods showed a variation in the median of around 20% (May *et al.,* 1997). Inductively coupled plasma-mass spectroscopy (ICP-MS) is currently regarded as the preferred analytical method (Soldin, 2002) and is used for NHANES. The US CDC has established the Ensuring the Quality of Iodine Procedures Programme, to enable standardisation and quality assurance of laboratory methods.

55. The WHO criteria for assessing the severity of IDD based on the prevalence of goitre is set out in Table 3 (WHO, 2007). The WHO criteria for iodine sufficiency/deficiency originally related to prevalence of goitre in a population, but have been modified to fit with urinary iodine.

56. WHO advises that median UICs of $\geq$300 µg/L are in excess of the amount required to prevent and control iodine deficiency and increase the risk of adverse health consequences in a population, such as iodine-induced hyperthyroidism and autoimmune thyroid diseases (WHO, 2007). This value was not intended as a threshold for toxicity (see paragraph 65 for upper limits of iodine intake).

Goitre

57. There are several causes of goitre but in the context of public health nutrition, iodine deficiency with or without other nutritional deficiencies is the most common. Goitres have been classified according to whether the thyroid is palpable, but not visible; visible with the neck extended; through to being clearly visible when the neck is in the normal position (WHO, 2007). Goitre size can also be assessed by thyroid ultrasonography.

58. The earliest manifestation of thyroid enlargement is a "simple diffuse goitre" (Carton *et al.,* 2007), with prolonged iodine deficiency the gland continues to enlarge and develop nodules of hyperplastic tissue. The significance of the simple diffuse goitre is unclear. This is a common phenomenon in young people, particularly at adolescence, and in pregnancy (Melish, 1990). It has been regarded as a normal physiological feature in clinical practice and may be partly attributable to the TSH activity of gonadotrophins (Gaberšček and Zaletel, 2011) but it is uncertain whether or not it might be the consequence of some degree of iodine deficiency.

59. It has been reported that endemic goitre appears in populations where daily iodine intakes are less than 50 µg/day (Stanbury and Hetzel, 1980; Hetzel, 1988).

60. In the UK, there are no recent data on the prevalence of goitre in the general population and the subgroups considered to be vulnerable to iodine deficiency.

Serum concentrations of TSH, Tg and thyroid hormones

61. As discussed earlier, increased TSH activity leads to increased production of Tg, T3 and T4, and increased plasma concentrations thereof. This adaptive phenomena will obscure any relationship between urinary iodine, goitre, and circulating levels of TSH, T4 and T3, other than when the adaptation fails with severe iodine deficiency. However, understanding the relationship between these measurements as indicators of the adaptation to iodine intakes arguably might enable a better assessment of the risk of iodine deficiency at low intakes than would be urinary iodine alone.

62. Tg could be used as a marker for iodine deficiency and excess in children (Vejbjerg *et al*., 2009a; Ristic-Medic *et al.,* 2009). TSH is used in newborn babies as a marker of inborn errors of iodine metabolism and thyroid function (Zimmermann, 2008). fT4 and fT3 can be measured as evidence of "functional iodine" (Zimmermann, 2012), but they lack sensitivity as markers of iodine deficiency (Ristic-Medic *et al*., 2009; WHO, 2007). Examination of the 1988-94 NHANES dataset concluded there was no relationship between UIC and serum T4 or TSH concentrations in the US general population (Soldin *et al.*, 2005).

Dietary Reference Values (DRVs)

63. Balance studies in the 1930s and 40s suggested that the basal human adult iodine requirement was in the range of 44-75 µg/day or approximately 1 µg/kg of body weight (Scheffer, 1933; Flickinger, 1941). Subsequent work showed that the mean turnover of iodine by the thyroid approximated 95 µg/day in healthy adults (Fisher and Oddie, 1969).

UK DRVs

64. The UK Lower Reference Nutrient Intake (LRNI[iv]) for iodine was set by the Committee on Medical Aspects of Food and Nutrition Policy (COMA)[v] at 70 µg/day for adults, as this approximated the minimum necessary to avoid goitre in a population (Stanbury *et al*., 1974), and because increasing iodine intake from 100 µg/day to 500 µg/day had been shown to make no difference to the incidence of goitre in a population (Department of Health (DH), 1991), although an earlier report had proposed that the optimal daily requirement would be just below 200 µg/day for a 70kg adult (Curtis and Fertman, 1943). In order to provide a margin of safety and to allow for the possible effects of different dietary patterns, the UK Reference Nutrient Intake (RNI[vi]) for iodine was set at 140 µg/day for adults and between 50 µg/day and 140 µg/day for children (Table 4).

65. COMA advised that the upper limit on iodine intakes was 1,000 µg/day (DH, 1991), and a subsequent review by the Expert Group on Vitamins and Minerals (EGVM) concluded that iodine intakes of 940 µg/day would not be expected to have any significant adverse effects in adults (who had not been iodine deficient) (EGVM, 2003).

International dietary reference ranges for iodine

66. The Estimated Average Requirement (EAR[vii]) for iodine (adults aged 14 years and older), recommended by the Institute of Medicine (IOM) in the US is 95mg/day (IOM, 2001). The WHO recommends an iodine intake of 150 µg/day for adults and adolescents above 12 years (WHO, 2007).

67. The WHO adopted a precautionary approach in setting recommendations for iodine intake for the general population (and for pregnant and lactating women – see paragraph 72). The recommendations are based on risk management principles rather than an evaluation of the evidence as would be used in a full risk assessment. The UK has not adopted the WHO recommendations due to the uncertainties surrounding them.

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iv The LRNI is the amount of a nutrient that is sufficient to meet the needs of 2.5% of the population.

v The Committee on Medical Aspects of Food and Nutrition Policy (COMA) was disbanded in March 2000. The Scientific Advisory Committee on Nutrition (SACN) was set up in its place.

vi The RNI is the amount of a nutrient that is sufficient to meet the needs of most (97.5%) of the population.

vii The EAR is the amount of a nutrient that is sufficient to meet the needs of 50% of the population.

Iodine requirements and recommendations in pregnancy and lactation

68.   Thyroid function and iodine economy are altered during pregnancy. In early gestation, maternal thyroid hormone production increases in response to TSH, a rise in serum thyroxine-binding globulin (TBG; resulting from increased oestrogen levels) and, possibly because of the weak TSH activity of human chorionic gonadotropin (Glinoer, 2001). It is possible that the increase in glomerular filtration rate (GFR) results in a decrease to the circulating pool of plasma iodine (Glinoer, 2007; Gaberšček and Zaletel, 2011); it is unclear if this might be mitigated by increased renal retention of iodine. Additionally, any fall in plasma iodine concentrations would also be attributable, in part at least, to expansion of the plasma volume. A proportion of maternal thyroid hormone is transferred to the fetus, as is iodine via a placental NIS (Glinoer, 2001; Zimmermann, 2009b).

69.   Some pregnant women develop a simple diffuse goitre; this may be a feature of physiological adaptation to meet hormonal production independent of iodine deficiency (Burrow, 1990; Delange, 2004; Glinoer, 1997; Zimmermann, 2009b). However, maternal iodine needs and metabolism during pregnancy and lactation have not been well characterised.

70.   UK DRVs do not include an increment in iodine for pregnant or lactating women. COMA advised on the premise that women of reproductive age should have customary intakes that would enable them to manage pregnancies without any need for supplements. This, and a lack of evidence substantiating an increased requirement for iodine during pregnancy and lactation, led to the decision (DH, 1991) not to adopt specific UK recommendations for these groups, and emphasised the importance of women achieving the reference intakes at all times. This advice was based on the assumption that women entered pregnancy with adequate thyroid status and iodine stores. However, dietary intake data from the National Diet and Nutrition Survey (NDNS) indicate that approximately a fifth of non-pregnant girls aged 11-18 years in the general population are at risk of low iodine intakes (Bates *et al*., 2012; paragraph 94).

71.   The SACN Subgroup on Maternal and Child Nutrition (SMCN) considered there was insufficient evidence to substantiate revisions to the UK DRVs for iodine for pregnant and lactating women. Given that changes to thyroid function happen early in gestation, the iodine status of a woman as she entered pregnancy was arguably as important as introducing iodine-containing supplements only after the pregnancy had been recognised, and, possibly after a critical period of the fetus' neurodevelopment. Furthermore, it is estimated that around half of all pregnancies in the UK are unplanned (DH, 2000), which limits the value of recommendations aimed at women planning or entering pregnancy.

72.   WHO recommends that pregnant and lactating women have an iodine intake of 250 µg/day (WHO, 2007). This value was based on assumptions about iodine absorption, estimated metabolic needs, fetal needs, and the typical daily losses in the faeces and urine, including increased GFR in pregnant women, and, subsequently, losses during lactation.

73. Other bodies have different recommendations for pregnant and lactating women (National Health and Medical Research Council (NHMRC), 2006; IOM, 2001; Health Canada, 1997).

74. During pregnancy, a population with no iodine deficiency would have, according to the WHO, a median UIC of 150-249 µg/L (WHO, 2007)[viii]. The median UIC was based on the theoretical assumption that these values broadly correspond to the recommended daily iodine intake for pregnant and lactating women of 250 µg/day (Delange, 2007).

75. Breast milk iodine levels correlate with urinary iodine/g Cr; at median UICs of 114 µg/L (Pearce *et al*., 2007) and 46.8 µg/L (Chan *et al*., 2003).

76. The RNI for iodine for infants aged six months and younger in the UK is between 50-60 µg/day (DH, 1991). Data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) shows that infants aged four-six months in the UK have a mean iodine intake of 94 µg/day (range 52-148) from all sources, including dietary supplements (Lennox *et al.,* 2013). DNSIYC data reflects the nutrition of all participating infants; no distinction between breast-fed and non-breast-fed infants was made.

Evidence on the functional effects of biochemically severe iodine deficiency (UIC <20 µg/L) and supplements

77. Several studies have investigated the effect of iodine supplementation on cognitive outcomes, particularly in areas of endemic goitre. A review of 13 studies (five RCTs, four cross sectional studies and four nested case control studies) evaluating the association of iodine deficiency with cognitive defects was published in 2010 (Ristic-Medic *et al.*). The choice of treatment dose (in the case of RCTs) or intake assessment (e.g. urinary iodine, TSH etc.) and cognitive function test (e.g. intelligence quotient (IQ), picture concepts, psychometric tests etc.) varied between studies.

78. The observational studies carried out in populations classified as biochemically severely iodine deficient, indicated a strong relation between iodine intake or status and mental impairment. Results from the RCTs were inconsistent, which may have been due to high or moderate risk of bias in most of the included studies. The few studies conducted in biochemically moderately iodine deficient populations had methodological limitations. Since this is a scoping exercise, and because of the uncertainties associated with these studies, SACN has not critiqued them fully.

79. The difficulties of carrying out and relying on cognitive and psychomotor testing and characterising populations and intakes in supplementation studies, are referred to in a systematic review of RCTs by Zhou *et al*., (2013).

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viii For lactating women, a median UIC of 100 µg/l can be used to define adequate iodine intake, but no other categories of iodine.

intake are defined. Although lactating women have the same requirement as pregnant women, the median UIC is lower because

iodine is excreted in breast milk.

80. Studies have investigated the effects of delaying iodine supplementation to pregnant women at different gestational periods. In 1966, a double-blind intervention trial was undertaken in Papua New Guinea in which women were alternately given injections of iodised oil or saline, and then followed up for the next three years. The results indicated iodine treatment was probably most effective in preventing endemic cretinism in the offspring when administered prior to conception (Pharoah *et al.,* 2012).

Evidence on the functional effects of biochemically mild iodine deficiency (UIC 50-99 µg/L)

81. A placebo-controlled, double-blind RCT in New Zealand investigated the effects of daily supplements of 150 µg iodine in children aged ten-13 years (n=184) for 28 weeks (Gordon *et al.,* 2009) on four cognitive tests with a test-retest reliability of 0.74 (picture concepts), 0.73 (matrix reasoning), 0.59 (letter-number sequencing) and 0.55 (symbol search) (Wechsler, 2005). At baseline, children had a median UIC of 63 µg/L. After 28 weeks, UIC in the supplemented group (median UIC 145 µg/L; interquartile range (IQR) 93-298) increased significantly (p=0.001) compared to the placebo group (median UIC 81 µg/L; IQR 60-102). In the intervention group, scores for two of the four cognitive subtests (picture concepts and matrix reasoning) improved significantly, compared to scores from children taking the placebo.

82. Urinary iodine analysis was performed on spot urine samples collected from pregnant women enrolled in the Avon Longitudinal Study of Parents And Children (ALSPAC) cohort (Table 5) (Bath *et al.,* 2013b). After adjusting for 21 potential confounders (such as ethnic origin, smoking status, maternal alcohol intake, socioeconomic status, use of fish oil supplements during pregnancy etc.), UIC <150 µg/g Cr was associated with an increased risk of suboptimal cognitive outcomes (defined as scores in the bottom quartile) in the child for verbal IQ, reading accuracy and comprehension and reading score. Results for other aspects of cognitive testing were not significantly different.

83. Methodological limitations make drawing conclusions difficult (for instance, maternal UICs were based on single spot urine samples, child iodine status (via urinary iodine analysis for example) was not measured, and milk in the early 1990s had approximately half the iodine content of milk analysed more recently (FSA, 2008; Ministry of Agriculture, Fisheries and Food (MAFF), 1991), although milk intakes were probably higher at this time).

84. Both the Gordon *et al*. and Bath *et al*. studies concluded mild maternal iodine deficiency could prevent offspring from attaining their full intellectual potential. As the units of measurement for urinary iodine and cognitive tests varied between the studies, it is difficult to meaningfully compare the outcomes.

Sources of iodine intake of the UK population

85. Milk and dairy foods are the major sources of iodine for the UK population, providing 33% of an adult's daily intake (and a larger proportion for children) (Bates *et al*., 2011[ix]). In the UK, iodine concentrations in cows' milk can fluctuate according to the level of supplementation in animal feed and/or from hygiene products used in the dairy industry (Flynn, 1992). The seasonal variation in cows' milk iodine levels may be explained by the use of cow fodder fortified with iodine during winter months.

86. The average iodine content of UK cows' milk in 2007 was 30 μg/100g (range 7–100) (FSA, 2008), and had not substantially changed since the late nineties (MAFF, 1997; MAFF, 2000). These results are, however, higher than the average iodine concentrations found in earlier studies (15-17 μg/100g) (MAFF, 1985; MAFF 1991; Lee *et al*., 1994)[x]. The increase may be due to the addition of iodine to animal feed and the use of iodophors used as sterilants of cows' teats and milking vessels (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), 2003).

87. Organic milk in the UK is 42% lower in iodine content than conventional milk (Bath *et al.,* 2012), which may be explained by differences in animal feeding practices.

88. In the European Union the maximum permitted total levels for iodine (mg/kg) in complete feed with a moisture content of 12% (typical for most dry feeds) are 5 mg/kg (or 5 with no units) for dairy cows and laying hens, 20 for fish and 10 for other species or categories (Commission Regulation No 1459/2005, 2005). The European Food Safety Authority (EFSA) is considering reductions to these limits, as a modelling exercise has suggested that the upper limit for iodine is exceeded by 95th percentile adult and toddler consumers of milk and eggs by a factor of two and four respectively (EFSA, 2013). However, EFSA calculations were based on European level data; UK iodine intakes for high consumers are much lower (see paragraph 98).

89. Tables 1 and 6 set out the iodine content of selected foods and their percentage contribution to mean daily iodine intakes.

90. Iodine, as iodide, is present in multivitamin and mineral supplements and is a component of kelp products. Kelp supplements or products are not recommended as an iodine source, especially during pregnancy and lactation, because they contain varying amounts of iodine that can cause excessive iodine ingestion (Teas *et al.,* 2004; Leung *et al.,* 2009). The iodine content of supplements on sale in the UK aimed at pregnant and lactating women and those planning a pregnancy, range from 0-200 μg per dose.

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ix Secondary analysis of data from the NDNS 2008/09 – 2009/10. Food sources only (excluding supplements).

x Owing to a lack of comparable food composition data, it is not possible to describe trends in the iodine content of other dairy products over the same period of time. However, on the basis that they are made largely or solely from milk, other dairy products, such as cheese and yoghurt, are also likely to have increased in iodine since 1985.

91. Salt iodisation (the addition of iodine to salt intended for human or animal consumption), is a cost-effective and viable solution to prevent iodine deficiency disorders (WHO, 2007). The iodine content of iodised salt in the UK is recommended to be 10–22 mg/kg salt (through the addition of potassium iodide) (European Commission Health and Consumer Protection Directorate-General, 2010). However, iodised salt for discretionary domestic use, although once readily available to buy in the UK is not so now, and few manufacturers worldwide use it in the preparation and manufacture of foods (Bath *et al.,* 2013a; Lazarus and Smyth, 2008).

Dietary intakes of iodine in the UK

92. Data from the NDNS (2008/10) (Bates *et al.,* 2011)[xi] indicates that mean daily iodine intakes[xii] from food sources only are above the RNI for adults aged 19 years and older and most children (Table 7). The mean iodine intake for girls aged 11-18 years from food sources only (110 µg/day; range 45-272) is below the RNI (82%)[xiii].

93. Iodine intakes for 11-18 year olds and 19-64 year olds have reduced in absolute terms and in relation to the LRNI since previous surveys in the NDNS series, which may be due to reduced milk consumption. There has been no change in intakes by young children.

94. Data for different population groups on the average daily intakes of iodine below the LRNI from food sources only are outlined in Table 8. Notably, 21% of girls aged 11-18 years had intakes below the LRNI from food sources only, an increase from 14% since the previous survey in 1997. When intake from dietary supplements was included, the proportion of girls with low intakes reduced by one percentage point (Bates *et al.,* 2012).

95. The Low Income Diet and Nutrition Survey (LIDNS) (Nelson *et al.,* 2007)[xiv] presents selected data for four broad ethnic groups 'white', 'black', 'Asian' and 'other'. LIDNS indicates 23% of black women and 18% of Asian women aged 19 years and older have iodine intakes below the LRNI from food sources only. Small sample sizes prevent meaningful conclusions being drawn for other age and sex groups.

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xi The most recent NDNS report includes results from years 1, 2 and 3 combined (2008/09-2010/11). Where possible, data is taken from this report, however due to the limited analyses carried out, data relating to iodine intakes have also been taken from the previous report covering years 1-2 (2008/09-2009/10).

xii The quality of iodine data in food composition tables depends on whether the iodine analysis for a given food is up-to-date and the extent to which natural variability in iodine content is taken into account.

xiii Mis-reporting of food consumption, particularly underreporting, is known to be a problem in the NDNS, as in all dietary surveys. Nutrient intake data from surveys in the NDNS series have not been adjusted for under-reporting.

xiv LIDNS provides nationally representative data on the dietary habits and nutritional status of the "low income" population in the UK (data collected between 2003 and 2005). The term "low income" refers to the bottom 15% of the population in terms of material deprivation.

96. Aside from the limited data available from LIDNS, no nationally representative nutritional data are available for people from ethnic minorities and pregnant and lactating women. The format of the NDNS means that it is not suitable for collecting data on groups such as these.

97. There are currently no nationally representative UK data on urinary iodine levels. Since April 2013, non-fasting, spot urine samples are being obtained from a representative sample of children and adults aged four years and over in the NDNS and will be measured by ICP-MS. Subject to data quality and sample sizes, initial UIC data may be available in 2015.

98. There are no concerns about excessive dietary iodine intakes in the UK (COT, 2003). Data from the NDNS shows that daily intakes of iodine from food sources at the upper 2.5 percentile were 440 µg for men and 290 µg for women (Bates *et al.,* 2011).

UK studies with measures of urinary iodine concentrations (UIC)

99. The UICs of UK schoolgirls aged 14-15 years were measured by Vanderpump *et al*., in 2009. The researchers used the findings, which, according to WHO cut-offs indicated this group had mild iodine deficiency, to suggest that the UK population as a whole was now iodine deficient. Urinary iodine is at the nadir in early morning urine, thus concentrations may be artificially lower than that of samples "casually" collected over the day. Given the timing of the urine sampling and that the cut-off for iodine sufficiency in a population of older children may be nearer 60-70 µg/L (paragraph 50), it is possible that the proportion at risk of iodine deficiency has been overestimated.

100. However, two further UK studies investigating the iodine status of women in early pregnancy provide similar findings (Kibirige *et al.,* 2004; Pearce *et al.,* 2010).

101. A full review of the literature has not been undertaken for this scoping document. The three UK studies referred to above are summarised in Table 5, along with the assessment of Bath *et al*., (2013b). Preliminary reports of three further studies examining the iodine status of pregnant women and women of childbearing age in the UK have not been reviewed here as full papers were not available (Bath *et al.,* 2008; Lampropoulou *et al.,* 2012; Rayman *et al.,* 2008).

Groups that may be at risk of low iodine status in the UK

102. Mean iodine intakes of teenage girls aged 11-18 years are not meeting the RNI (Table 7) (Bates *et al*., 2012) and may be at risk of low iodine status. It is important that women entering reproductive years have adequate iodine intakes, as poor maternal iodine status during pregnancy can impair fetal development (noted earlier).

103. Individuals that have lower UICs are also low dairy consumers (Soriguer *et al.,* 2011). NDNS data indicates consumption of milk has fallen since previous surveys. For example, mean daily consumption of liquid cows' milk fell from 136g in 1997 to 110g in 2008-11 for girls aged 11-18 years (Bates *et al.,* 2012).

104. Because they exclude dairy products and fish from their diets, vegans in Britain may also be at risk of low iodine status (Appleby *et al.,* 1999). A study of 39 "healthy" British vegan volunteers showed this group had a median UIE of 20.1 μg/L; which, according to WHO criteria, is indicative of severe iodine deficiency (Lightowler and Davies, 1998). The small number of vegans sampled in the NDNS means the diets of this group cannot be separately considered.

105. Sufferers of milk allergy, lactose intolerance, fish allergy or ethnic minority groups that do not consume milk and milk products may also be at risk (EFSA, 2006). There is no evidence of other age/sex groups having low iodine intakes.

International experience in addressing iodine deficiency

106. Salt iodination programs have been adopted by certain countries to address the prevalence of iodine deficiency. The UK has not implemented such a programme. WHO recommends an iodine concentration of 20-40 mg/kg of salt, which is based on an assumption of an average intake of 10g salt/day in adult populations (WHO, 2007). Iodine levels in the urine increase when iodised salt is consumed (Zimmermann and Andersson, 2012). There is an inverse correlation between household access to iodised salt and prevalence of low iodine intake (Wu *et al.,* 2002; Remer and Neubert, 1998). Globally about 70% of households have access to iodised salt (United Nations Children's Fund (UNICEF), 2008).

107. The iodine fortification of yeast-leavened bread became mandatory in Australia and New Zealand in 2009 (Ministry of Agriculture and Forestry, 2012) following a successful voluntary iodine fortification programme in Tasmania (Seal *et al.,* 2003). Risk/benefit assessments of mandatory fortification of breads with iodised salt have been prepared for Australia (Food Standards Australia New Zealand (FSANZ), 2008a) and New Zealand (FSANZ, 2008b).

108. Following fortification, the median UIC of eight-13 year old Tasmanian children was 129 μg/L, higher than 73 μg/L measured in children of a similar age prefortification (p< 0.001) (Hynes *et al.,* 2004). The proportion of UIC results <50 μg/L reduced from 17.7% to 3.4% (p< 0.001). The 56 μg/L increase in median UIC was consistent with the predicted increase in mean dietary iodine intake estimated by dietary modelling in 2008 (FSANZ, 2008a).

109. The median UIC of New Zealand children aged eight-ten years increased after fortification, from 66 μg/L (28% <50 μg/L) in 2002 (Ministry of Health, 2003) to 113 μg/L (12% <50 μg/L) in 2010-2011 (Skeaff and Lonsdale-Cooper, 2013). However, concentrations of Tg were elevated, which may indicate that the increase in UIC was not sufficient to normalise thyroid function.

110. Monitoring of urinary iodine in the adult population since fortification was introduced, is now underway in New Zealand and Australia.

111. The use of iodised salt in the food industry is compulsory in 18 out of 43 countries in the WHO European Region. France and Poland prohibit the commercial use of iodised salt, while its use is either voluntary or not regulated at all in 23 countries (Bohac *et al*., 2009). In the US, iodised salt and seafood are the major dietary sources of iodine. At 164 µg/L, median UICs measured in NHANES indicates the US population has adequate iodine nutrition (Caldwell *et al.,* 2011).

112. Iodised oil is an alternative method of iodine supplementation in areas where salt iodisation programmes have failed or when iodised salt is not widely available. Iodised oil can supply individuals with iodine for one year when administered orally and up to three-seven years when administered intramuscularly (Azizi, 2007). Some of the studies and goitre intervention programmes which have used iodised oil (particularly in areas of endemic goitre) are included in the Ristic-Medic *et al.* (2010) review (discussed in paragraph 77).

Summary and conclusions

113. Iodine is a constituent of thyroid hormones and inadequate intakes of the element are associated with defective thyroid hormone production and with consequent defects in growth, physical and psychomotor development; the precise character, reversibility and severity of which vary according to timing and severity of the iodine deprivation.

114. Globally, iodine deficiency is a major preventable cause of growth and intellectual impairment and, as such, it has significant societal and socio-economic impact. Effective prevention programmes based on the mandatory or discretionary use of iodised salt, or on the administration of iodised oil have been implemented by national and regional health agencies, and the World Health Organization (WHO). The UK has no current salt iodination programme.

115. The spectrum of iodine deficiency disorders is well recognised but apart from profoundly deficient intakes, there are no good dose-response data relating the onset and features of deficiency to iodine intakes. In part this is because accurately measuring iodine intake is difficult, and also because adaptations in the handling of iodine to ensure an adequate supply of iodine for the synthesis of thyroid hormones obscures any such relationship.

116. Urinary iodine concentrations (UICs) are a convenient but imperfectly validated marker of iodine intake and of "iodine deficiency". Originally 24-hour urinary iodine excretion (UIE) was assumed to correspond to dietary intake of iodine, but this is uncertain because urinary iodine content more closely relates to systemic adaptation to iodine supply, rather than being a reliable marker of the risks of iodine inadequacy. However UIE may be a useful marker of adequacy or excess, and of severe iodine deficiency but its value at marginally adequate or inadequate intakes is uncertain.

117. Corroborative markers of adaptation of iodine use, acquisition, homeostasis and hormone production may be useful e.g. thyroid enlargement, or thyroid stimulating hormone (TSH) levels.

118. The WHO developed, for use at a population level, a classification tool to inform those responsible for preventing and managing endemic iodine deficiency of the likelihood that some individuals in that population will be sufficiently iodine deficient to have features of iodine deficiency disorders, according to the median UIC in that population as a whole. The Committee recognises that WHO methods are useful in the context of population monitoring, however, the selection of the terms "mild, moderate and severe" as applied to entire populations has arguably led to inappropriate use of the categorisation as a diagnostic tool. The categories are not suitable for use for identification of iodine deficiency in individuals.

119. Intake data from the National Diet and Nutrition Survey (NDNS) suggest that children aged ten years and younger and adults aged 19 years and older in the UK generally have adequate iodine intakes, in relation to the Reference Nutrient Intake (RNI), although 21% of girls aged 11-18 years have intakes below the Lower Reference Nutrient Intake (LRNI). However, insecurities surrounding food composition data for iodine and the phenomena of underreporting in dietary assessments are sources of error and uncertainty in the estimation of iodine intakes. The NDNS does not provide data for pregnant or lactating women.

120. There are currently no nationally representative data on the iodine status of the general UK population, nor of the subgroups of particular interest. Results from individual research studies, which have analysed urine samples from girls of reproductive age and pregnant women in specific areas of the UK, support the findings of NDNS dietary data on the population group at risk of iodine deficiency (girls of reproductive age and women prior to pregnancy). Fish and dairy avoiders may also be at risk of consuming insufficient iodine, as these are the main sources of iodine in the UK diet.

121. WHO and the Institute of Medicine (IOM) have made higher recommendations on iodine intakes in pregnancy and lactation, which are at variance with UK RNIs.

122. There is very limited evidence on the functional significance of the WHO criteria for iodine sufficiency based on UIC, how iodine requirements vary during pregnancy and lactation and the extent of any adaptive phenomena. The Subgroup on Maternal and Child Nutrition (SMCN) advised that without further evidence, it would not be feasible to carry out a robust review of the UK DRVs for iodine for pregnant and lactating women.

123. Current UK advice states that most people are able to meet requirements for iodine by consuming a varied and balanced diet. Analysis of NDNS data shows that adolescents are more likely than other groups not to achieve this type of dietary pattern. For girls, the intake of milk is particularly low.

124. A small number of observational studies raise concerns that "moderate" iodine deficiency is associated with cognitive impairment. Limitations with the sampling and analyses however, mean results should not necessarily be interpreted against the WHO criteria. Likewise, it is difficult to extrapolate findings from studies carried out in malnourished populations, to UK population subgroups unaffected by malnutrition.

125. Notwithstanding the uncertainties surrounding the WHO criteria discussed previously, the current NDNS survey of random spot samples should enable an assessment of the UK profile against the WHO template. This exercise should therefore inform whether any more specific research addressing the issues raised in this report is necessary.

126. This scoping paper highlights that the issue of iodine intakes is of considerable public health significance, although the Committee is cautious in drawing conclusions on current evidence due to the limitations of the available data, as have been said. It is appropriate to examine data gathered in the NDNS on the UIC of the general UK population, provisionally available in 2015, before a full risk assessment on iodine and health is considered. The Committee will keep a watching brief on the arising evidence to inform future research in this area and any updates to the public health guidance on iodine for the UK population.

Research recommendations

127. There is a need to have some systematic, physiologically relevant, and quality assured data to enable measurement and a risk assessment of current iodine intakes in the UK, particularly in the population groups that are thought to be at greatest risk of iodine deficiency; namely girls of reproductive age, pregnant and lactating women, and dairy and fish avoiders. Currently UIC is used for this, but although it may be the easiest marker to use, it needs to be better characterised.

128. The use of UIE and UIC of iodide in the assessment of iodine supply needs to be reassessed and validated appropriately against currently accepted standards for biomarkers for use in the population cohorts.

129. A validated marker of early iodine deficiency is needed. This would probably need to be representative of the early homeostatic adaptation to low iodine intakes.

Table 1: Iodine content of selected foods in the UK (FSA, 2002)

Food	Description	Iodine content (µg/100g)
Mussels, cooked	Purchased	247 (DH, 2013a)
Cod, baked	Baked in the oven, flesh only	161 (DH, 2013a)
Egg yolk, boiled	Chicken eggs	137 (DH, 2013b)
Eggs, whole, boiled	Chicken eggs	52 (DH, 2013b)
Milk chocolate		51 (DH, 2013c)
Sea salt		50
Whole milk, pasteurised, average	Average of summer and winter milk	31
Semi-skimmed milk, pasteurised, average	Average of summer and winter milk	30
Skimmed milk, pasteurised, average	Average of summer and winter milk	30
Cheddar cheese	Mild and mature English cheddar	30
Ice cream, dairy	Vanilla flavours, soft scoop	30 (DH, 2013c)
Whole milk yoghurt, fruit	Assorted flavours including bio varieties	27
Kippers, grilled	Analysed without butter	24 (DH, 2013a)
Peanuts, plain	Kernels only	20
King prawns, cooked	Purchased	12 (DH, 2013a)
Tuna, canned	In brine, drained	12 (DH, 2013a)
Infant formula	Commercial products as made up	10-13[a]
Beer, bitter, canned		8 (Wenlock *et al.*, 1982)[b]
Human milk, mature		7
Chicken breast	Grilled without skin, meat only	7
Butter, spreadable	75-80% fat	4 (DH, 2013c)
White bread, sliced		4
Spinach, raw	Baby spinach	4 (DH, 2013d)
Bananas	Flesh only, raw	3 (DH, 2013d)
Onions, raw	Standard onions (not red)	2 (DH, 2013d)

[a] data presented as µg/100ml. The term 'infant formula' refers to a food that can provide an infant with all its nutritional needs during the first six months of life. The data presented is the range for commercial products as declared on labels available in September 2013.

[b] data presented as µg/100ml. The iodine content of beer and lager available in the UK has not been analysed as part of Public Health England's rolling programme of nutrient analysis since the late 1970s. As such, composition data may not be representative of the beverages currently on the market.

Table 2: Iodine deficiency disorders according to physiological group (Hetzel, 1983)

Physiological group	Health consequences of iodine deficiency
All ages	Goitre Hypothyroidism
Fetus	Spontaneous abortion Stillbirth Congenital anomalies Perinatal mortality
Neonate	Endemic cretinism including mental deficiency with a mixture of mutism, spastic diplegia, squint, hypothyroidism and short stature Infant mortality
Child and adolescent	Impaired mental function Delayed physical development Iodine-induced hyperthyroidism
Adults	Impaired mental function Iodine-induced hyperthyroidism

Table 3: Features of iodine deficiency disorders and World Health Organization (WHO) stratification by median urinary iodine excretion (UIE) of populations (WHO, 2007) adapted from Clugston and Hetzel (1994)

	Degrees of iodine deficiency disorders, expressed as percentage of the total of the number of children surveyed			
	None	Mild	Moderate	Severe
Population median UIE μg/day	>100	100 - 50	49 - 25	<25
Prevalence of goitre	0.0 - 4.9%	5.0 - 19.9%	20.0 - 29.9%	≥30%
Cretinism	0%	0%	0%	0-5%

Table 4: UK Dietary Reference Values for iodine (DH, 1991)

Age	Lower Reference Nutrient Intake (LRNI) (μg/day)	Reference Nutrient Intake (RNI) (μg/day)
0-3 months	40	50
4-6 months	40	60
7-9 months	40	60
10-12 months	40	60
1-3 years	40	70
4-6 years	50	100
7-10 years	55	110
11-14 years	65	130
15-18 years	70	140
19-50 years	70	140
50+ years	70	140
Pregnancy	No increment	
Lactation	No increment	

Table 5: Summary of recent UK studies obtaining urinary iodine concentration (UIC) measures

Study reference	Study design	Sample	Study population	Exclusions	Urinary iodine concentration measure	Remarks
Bath *et al.*, 2013a

Cohort enrolled and urine samples obtained in the early 1990s | Cross-sectional study

Objective: to investigate the association between maternal iodine status and child cognitive performance | Non-fasting single spot urine samples (n=958)

FFQ assessing intakes of n-3 fatty acids (from seafood) and iron at 32 weeks gestation

Measure of offspring's IQ at 8yrs and reading ability at 9yrs | Subset of the study cohort from the Avon Longitudinal Study of Parents and Children (ALSPAC) in the former Avon area

Volunteer pregnant women ≤13 weeks gestation (median 10 weeks; IQR 9-12), mean age 29.6 yrs | Women with non-singleton pregnancies, women with UIC >500 µg/L (concerns about test strip contamination), thyroid hormone medication users, women with inconsistent laboratory iodine measurements | Median UIC 91.1 µg/L; IQR 58.3-143 µg/L (110 µg/g Cr; IQR 74-170)

Children of women with <150 µg/g Cr more likely to have scores in lowest quartile for verbal IQ (OR 1.58 95% CI 1.09-2.30), reading accuracy (OR 1.69 95% CI 1.15-2.49) and reading comprehension (OR 1.54 95% CI 1.06-2.23) than children of mothers with ≥150 µg/g Cr | 99% of the cohort were white

Maternal seafood intake of ≤340g/week was associated with an increased risk of the offspring being in the bottom quartile of verbal IQ compared to intake >340g/week

Iodine status of child not assessed

Milk in the early 1990s had approximately half the iodine content of milk analysed more recently, although milk intakes were probably higher at this time |
| Vanderpump *et al.*, 2011

Carried out between June-July 2009 and November-December 2009 | Cross-sectional study

Objective: to assess iodine status in schoolgirls aged 14-15 years attending secondary schools in nine UK centres | 20ml non-fasting sample of early morning urine (n=737)

5ml tap water samples (n=30)

FFQ assessing sources of iodine (n=664) | Girls (14-15 yrs) attending secondary schools (n=810) from 9 UK centres (Aberdeen, Belfast, Birmingham, Cardiff, Dundee, Exeter, Glasgow, London, Newcastle/ Gateshead) | No information given | Median UIC 80.1 µg/L; 95% CI 76.7-83.6 µg/L

Median UIC was significantly different between centres: highest in Dundee (98.4 µg/L) & lowest in Belfast (64.7 µg/L) | Sampling during summer (p<0.0001), geographical location (p<0.0001), low milk intake (p=0.02) were associated with low UIC

Iodine concentrations of tap water were <3 µg/L, apart from London (5.2-18.2 µg/L)

Dietary habits of participants |

						who did not provide a urine sample (n=73) were not significantly different from those who did
Kibirige *et al*., 2004 Carried out between March 2000-March 2001	Case-control study Objective: to establish the prevalence of reduced iodine intake according to WHO specifications during pregnancy by determining UIE at 15 weeks gestation	20ml non-fasting sample of early morning urine for pregnant (n=227) and non-pregnant women (n=227) Diet was not assessed	White or Asian pregnant women at 15 weeks gestation (n=227), mean age 28.3 yrs (range 15.9-39.2) attending an antenatal clinic in Middlesbrough Volunteer non-pregnant age-matched controls (n=227), mean age 28.5 yrs (range 15.3-39.9)	Women with known thyroid disease or other systemic illness	UIC<50 µg/L for 16 pregnant women (7%) and 20 non-pregnant controls (9%) 40% of pregnant women had UIC of 50-100 µg/L	Asian women had a lower mean UIC than white women (p<0.05)
Pearce *et al.,* 2010 Cohort enrolled and samples taken between 2002-2006	Cross-sectional study Objective: to determine whether thyroid function in pregnant women, particularly those with low iodine intake, is adversely effected by environmental perchlorate	Non-fasting spot urine samples for hypothyroid/ hyprothyroxine mic women (n=374) and euthyroid women (n=383) Diet was not assessed	Subset of the study cohort from the Controlled Antenatal Thyroid Screening Study (CATS) in Cardiff, Wales. Volunteer pregnant women ≤16 weeks gestation (n=854), mean age 29.6 yrs	Women with non-singleton pregnancies; Women taking thyroid medication; Women with laboratory values consistent with central hypothyroidism	Median UIC for hypothyroid/ hyprothyroxinemic women 98 µg/L (range 12-847 µg/L) Median UIC for euthyroid women 117 µg/L (range 2-497 µg/L)	

	exposure and/or by thiocyanate exposure from cigarette smoke and dietary sources					

Table 6: Percent contribution of selected food groups to daily mean iodine intakes for adults aged 19-64 years in 2008/09 – 2009/10[c]

Food group	Percentage contribution
Milk and milk products total,	33%
of which cows' milk	23%
Fish and fish dishes	11%
Beer and lager	11%
Cereal and cereal products	10%
Eggs and egg dishes	6%
Other	29%

[c] Secondary analysis of data from the NDNS 2008/09 – 2009/10 (Bates *et al.*, 2011). Food sources only (excluding supplements).

Table 7: Mean daily iodine intakes of the UK population, from food sources only. Data from the National Diet and Nutrition Survey (NDNS)

Population group (years)	Mean iodine intake (µg) (2008/09 - 2009/10 NDNS) (Bates *et al.*, 2011)	Mean iodine intake (µg) (2000/01 NDNS) (Henderson *et al.*, 2003)[d]	Mean iodine intake (µg) (1997 NDNS) (Gregory *et al.*, 2000)[d]	Mean iodine intake (µg) (1994/95 NDNS) (Finch *et al.,* 1998)[e]
Boys 4-10	153		154	
Girls 4-10	133		135	
Boys 11-18	138		171	
Girls 11-18	110		134	
Men 19-64	192	221		
Women 19-64	143	161		
Men 65+	216			187
Women 65+	169			149

[d] mean intake was recalculated for previous NDNS surveys of seven days duration to represent four days of assessment.
[e] the apparent increase in iodine intakes for adults aged 65 years and older is due to the use of different milk composition data. For the 1994/95 NDNS, the analytical data available at that time indicated milk had on average 15-17µg iodine/100g; approximately half the iodine content of milk analysed during the late nineties onwards.

Table 8: Proportion of UK population groups with mean daily intake of iodine from food sources only below the Lower Reference Nutrient intake (LRNI). Data from the National Diet and Nutrition Survey (NDNS)

Population group (years)	%age below LRNI (2008/09 - 2010/11 NDNS) (Bates *et al.,* 2012)	%age below LRNI (2000/01 NDNS) (Henderson *et al.,* 2003)[f]	%age below LRNI (1997 NDNS) (Gregory *et al.,* 2000)[f]	%age below LRNI (1994/95 NDNS) (Finch *et al.,* 1998)
Boys 4-10	2		2	
Girls 4-10	3		4	
Boys 11-18	8		5	
Girls 11-18	21		14	
Men 19-64	5	2		
Women 19-64	10	6		
Men 65+	0			2
Women 65+	1			6

[f] the proportion below the LRNI was recalculated for previous NDNS surveys of seven days duration to represent four days of assessment.

Acronyms and Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
CDC	Centers for Disease Control and Prevention (USA)
COMA	Committee on Medical Aspects of Food and Nutrition Policy
COT	Committee on Toxicity of Chemicals in Food
DH	Department of Health
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
DRV	Dietary Reference Values
EAR	Estimated Average Requirement
EFSA	European Food Safety Authority
EGVM	Expert Group on Vitamins and Minerals
FFQ	Food Frequency Questionnaire
FSA	Food Standards Agency
FSANZ	Food Standards Australia New Zealand
fT3	Free (unbound) 3,5,3'-triiodothyronine
fT4	Free (unbound) 3,5,3',5'-tetraiodothyronine
GFR	Glomerular Filtration Rate
ICP-MS	Inductively Coupled Plasma-Mass Spectroscopy
IDD	Iodine Deficiency Disorders
IOM	Institute of Medicine (USA)
IQ	Intelligence Quotient
IQR	Interquartile Range
LIDNS	Low Income Diet and Nutrition Survey
LRNI	Lower Reference Nutrient Intake
MAFF	Ministry of Agriculture, Fisheries and Food
NDNS	National Diet and Nutrition Survey
NHANES	National Health and Nutrition Examination Survey (USA)
NHMRC	National Health and Medical Research Council (Australia)
NIS	Sodium Iodide Symporter
RCT	Randomised Controlled Trial
RNI	Reference Nutrient Intake
SACN	Scientific Advisory Committee on Nutrition
SD	Standard Deviation
SMCN	Scientific Advisory Committee on Nutrition: Subgroup on Maternal and Child Nutrition
T3	3,5,3'-triiodothyronine
T4	3,5,3',5'-tetraiodothyronine
TBG	Thyroxine-Binding Globulin
Tg	Thyroglobulin
TPO	Thyroid Peroxidase
TRH	Thyroid Releasing Hormones
TSH	Thyroid Stimulating Hormone
UIC	Urinary Iodine Concentration
UIE	Urinary Iodine Excretion
UK	United Kingdom
UNICEF	United Nations Children's Fund
US	United States of America
WHO	World Health Organization

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