Committee on Toxicity

Statement on the potential effects that excess iodine intake may have during preconception, pregnancy and lactation

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) is currently conducting a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet.

2. SACN agreed that, where appropriate, other expert committees would be consulted and asked to complete relevant risk assessments e.g. in the area of food safety advice to support their review. Therefore, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to consider whether exposure to excess iodine would pose a risk to maternal health, as part of this review.

Background

3. In the environment, iodine is usually found in the form of iodate salts or organo-iodide compounds synthesised by algae and bacteria. Iodate is reduced in the gastrointestinal tract to iodide which is the biologically active from of iodine (SACN, 2014).

4. Dietary iodine is converted into iodide ion, which is then absorbed throughout the gastrointestinal tract. The iodide ion is bio-available and is almost completely absorbed from food and water. Inorganic iodide is cleared from the circulation via the thyroid and kidney. In the thyroid gland, iodide is used in the synthesis of thyroid hormones. The kidney excretes excess iodine in urine (FAO/WHO, 2001). Unless otherwise specified, the term “iodine” has been used in this statement generically.

Iodine function

5. Iodine is essential in the human diet because it is required for the synthesis of the thyroid hormones tri-iodo- and tetra-iodothyronine (T3 and T4 or thyroxine). The thyroid hormones exert effects on a wide range of bodily functions such as basal metabolism, brain development and bone growth, especially in the fetus, which is exposed to iodine via the placenta, so maternal underexposure due to iodine deficiency can have profound effects on both mother and offspring. Both chronic iodine deficiency and an excess of iodine may lead to compensatory thyroid hypertrophy, known as goitre, in adults and children. Clinical features of acute iodine toxicity include vomiting and diarrhoea, seizure, delirium and collapsing. Sensitivity reactions, such as iodide mumps, can occur following treatment with iodine-containing medication (EVM, 2003).

6. The National Diet and Nutrition Survey (NDNS) has collected spot urine samples for iodine analysis since 2013. The findings show that urinary iodine concentrations in children and adults in the standard NDNS age groups meet the World Health Organisation (WHO) criteria that a population with no iodine deficiency should have median urinary iodine concentrations of between 100 µg/L and 199 µg/L and fewer than 20% of the population below 50 µg/L. The median urinary iodine for women of childbearing age (16 to 49 years) was 98 µg/L with 21% of the population below 50 µg/L in this group. They also fail to meet the stricter criteria for pregnant and lactating women which is a median urinary iodine concentration of 150 - 249 µg/L (WHO, 2007; SACN, 2014). Time trend analysis on urinary iodine in the Rolling Programme Years 9-11 report showed that there have been no statistically significant changes over time for any age/sex groups (Public Health England, 2020; British Nutrition Foundation, 2020).

Status in pregnancy

7. Once iodine is consumed it is quickly absorbed in the body and enters the bloodstream. The thyroid captures the circulating iodine by oxidising it so that it can be used to create the thyroid hormones triiodothyronine (T3) and thyroxine (T4). The thyroid hormones help regulate metabolism and ensure that the heart, brain and other organs function in a healthy manner. The majority of iodine is found mainly in the thyroid glands; however, non-hormonal iodine can also be found in the mammary glands, the eyes, the gastric mucosa, the cervix and the salivary glands (Ahad et al, 2010).

8. Thyroid function and iodine levels are altered during pregnancy. In early gestation, maternal thyroid hormone production increases in response to Thyroid Stimulating Hormone (TSH) (Glinoer, 2001). It is possible that the pregnancy-associated increase in glomerular filtration rate (GFR) results in a decrease in the circulating pool of plasma iodine (Glinoer, 2007; Gaberscek 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 the placental NIS (sodium/iodide symporter) (Glinoer, 2001; Zimmermann, 2009). Iodine is also essential for brain development, which is dependent on an adequate supply of thyroxine (Ahad et al, 2010). Dietary

iodine is vital for brain development during specific time windows, influencing neurogenesis, neuronal and glial cell differentiation, myelination, neuronal migration, and synaptogenesis (Choudhry et al, 2018).

9. Urinary iodine concentration (UIC) is a good indicator of short-term iodine status as >90% of dietary iodine eventually appears in urine (Rohner, 2014). A median UIC of <100 µg/L indicates insufficient iodine intake other than in pregnant women, in whom levels of < 150 µg/L indicate insufficient intake, a median UIC of ≥100 µg/L indicates adequate iodine intake for women who are breastfeeding their infants and children under two years of age and of 150 - 249 µg/L in pregnant women (Harding, 2017). UIC levels of >500 µg/kg are considered excessive in pregnant women (WHO, UNICEF and ICCIDD, 2007).

10. As an alternative to UIC, Katko et al (2018) used plasma thyroglobulin (Tg) as a measure of iodine status in 164 pregnant Hungarian women in week 16 of pregnancy, the period corresponding to major brain development. They found that UIC corresponded with daily iodine intake whereas Tg corresponded with long-term storage levels of iodine.

11. Sixteen healthy lactating American women with no known history of thyroid disease were administered 600 µg oral potassium iodide (KI) (456 µg iodine) after an overnight fast. Iodide measurements were taken from breastmilk and urine at baseline and hourly for 8 hours following iodine intake. All dietary iodine ingested during the study period was also measured. Baseline breastmilk and urine iodine levels were 45.5 µg/L and 67.5 µg/L, respectively. Following KI administration, the median increase in breastmilk iodine levels above baseline was 280.5 µg/L and median peak breastmilk iodine concentration was 354 µg/L. Median time to peak breastmilk iodine levels following KI administration was 6 hours (interquartile range (IQR) 5 - 7 h). Dietary iodine sources provided an additional 36–685 µg iodine intake during the 8-hour study. It was concluded that breastmilk iodine concentrations should be interpreted in relation to recent iodine intake (Leung et al, 2012).

12. Although, iodine-deficiency is a known issue in maternal health, excess iodine intake may also occur and may potentially affect maternal health. Excess iodine intake may occur via the consumption of naturally occurring iodine in water supplies, seaweed, iodine supplements, medication and milk, which contains iodine originating from feed supplements and the use of iodophor disinfectants. Most healthy individuals are unaffected by excess iodine, however susceptible individuals with autoimmune thyroid disease such as Hashimoto's Disease (Mayo Clinic, 2021) and Graves' Disease[1] and neonates are likely to respond adversely to excess iodine.

13. Excessive dietary iodine intake and/or iodine supplementation during pregnancy may cause adverse effects on maternal and fetal thyroid function, birth outcomes, and offspring growth and development (Le et al, 2018). Excess iodine briefly inhibits thyroid hormone synthesis through decreasing organification by an autoregulatory mechanism known as the acute Wolff-Chaikoff effect (Wolff et al, 1949); The Wolff-Chaikoff effect thus prevents the production of excess thyroid

[1] Graves disease: Is a disorder where there is an overproduction of thyroid hormones also known as hyperthyroidism (Mayo clinic, 2021).

hormones in response to the intake of high levels of iodine. Healthy individuals can escape the Wolff-Chaikoff effect via downregulation of the NIS in the thyrocytes, after which normal thyroid hormone synthesis restarts (Eng et al, 1999; Markou et al, 2001). Although the mechanism is not completely understood, individuals with underlying or autoimmune thyroid disease fail to escape the Wolff-Chaikoff effect and thyroid hormone production remains decreased. Under 36 weeks of gestational age, the immature fetal thyroid gland is also unable to escape from the acute Wolff-Chaikoff effect, making the fetus more susceptible to iodine-induced hypothyroidism (Markou et al, 2001).

Excess iodine – human health studies

14. In some countries, such as Denmark, iodine deficiency in the population has been addressed through the mandatory iodisation of salt, including table salt and salt used in commercially-produced bread. In Denmark, monitoring instigated from prior to mandatory fortification found that although iodine status improved, there was an increase in thyroid autoantibodies in the years following fortification. The clinical implications of this are unclear (Laurberg et al, 2006; Rasmussen et al, 2008; Pedersen et al, 2011; Bliddal et al, 2015). Although iodised salt is readily available in UK supermarkets, the UK does not have a mandatory fortification scheme for iodine (SACN, 2014). A shelf survey was conducted in the UK to see if the availability of iodised table salt in the UK was likely to influence population iodine intake. The study was carried out in 5 supermarket chains in Southern England, Wales, and Northern Ireland. Of 72 supermarkets surveyed, iodised salt was available in 32 of them. The iodine concentration in the UK's major iodised salt brand was 11.5 mg/kg. It was concluded that iodised household table salt was unlikely to contribute meaningful amounts to UK iodine intakes (Bath et al, 2012). It should be further noted that the UK government recommends that salt intakes should be reduced for health reasons. (NHS, 2018; WHO, 2013).

15. The association of thyroid nodules (TNs)[2] and iodine intake in pregnant women was investigated in a study by (Gao et al, 2019). Serum and spot urine samples were collected from 2353 pregnant women. UIC and creatinine (Cr) level were determined in spot urine samples, and serum thyroid hormones and thyroid autoantibodies were measured. The UIC and UIC to creatinine ratio (I/Cr ratio) was found to be significantly higher in pregnant women with TNs. Thyroglobulin levels, age, pre-pregnancy body mass index and living in an iodine-excessive region were associated with TNs. The I/Cr ratio was not a significant risk factor for TNs in pregnant women in their second trimester.

16. The effects of high iodine intake on thyroid function in pregnant and lactating women was investigated in China. An epidemiological study was conducted among 130 pregnant women and 220 lactating women aged 19 – 40 years in areas that had a drinking water iodine content of >300 and 50-100 µg/L in Shanxi in 2014. Urinary iodine levels and blood thyroid stimulating hormone levels were examined. It was concluded that excess iodine intake might increase the risk of subclinical

[2] Thyroid nodule (TNs): TNs are solid or fluid-filled lumps that form within the thyroid (Mayoclinic, 2020).

hypothyroidism in pregnant women and lactating women. It was suggested that iodine nutrition and thyroid function should be monitored in women, pregnant women and lactating women who live in areas with high environmental iodine. (Ren et al, 2018).

17. A cross-sectional study was performed in 2010 amongst 111 lactating women in a refugee camp in Algeria who lived in areas with high and very high iodine concentrations in drinking water; 80 (73–92) (median and IQR) µg/L and 254 (230–269) µg/L, respectively. Breast milk iodine concentration (BMIC), UIC and the iodine concentration in the most commonly consumed foods/drinks were measured. A 24-h dietary recall was used to estimate iodine intake. Thyroid hormones and antibodies were measured in serum. Median UIC, BMIC and iodine intake across both areas were 350 µg/L, 479 µg/L and 407 µg/day, respectively. Thyroid dysfunction and/or positive thyroid antibodies were found in 33.3% of the women, of whom 18.9% had hypothyroidism and 8.1% had hyperthyroidism and 6.3% had positive antibodies with normal thyroid function. Elevated thyroid antibodies were in total found in 17.1% of the women. There was no difference in the distribution of thyroid dysfunction or positive antibodies between the high iodine and very high iodine drinking water areas. However, there was an association found between BMIC and thyroid dysfunction and positive antibodies, which indicated that thyroid dysfunction may be caused by an excessive iodine intake. It was concluded that BMIC could be a better indicator for iodine status among lactating women than UIC. The high prevalence of thyroid dysfunction and the chronically high intake of iodine might have adverse health consequences for the women and their children. (Akare et al, 2015).

18. Three years after the baseline study described above (Akare et al, 2015) a follow-up study was conducted. This included seventy-six children from the original study with a new sample of randomly selected children being included to increase the sample size to 289. At follow-up, urinary iodine, and blood levels of thyroid hormones and serum thyroglobulin were measured. Excessive iodine intake (defined as urinary iodine levels of ≥ 300 µg/L) was identified in 88% of the group at baseline (children aged 0 – 6 months) and 72% at follow-up (3 years later). At follow-up, 24% of the study group had thyroid hormone disturbance and 9% had subclinical hypothyroidism. Children with subclinical hypothyroidism showed poorer growth and were more likely to be underweight than their healthy counterparts (Aakre et al, 2016).

19. Case reports were collected following the recall of a prenatal supplement containing excessive iodine levels in Brazil. In all cases, the infant was born with goitre. In the first case, a pregnant woman at 22 weeks' gestation was diagnosed with fetal goitre via a prenatal ultrasound examination. It was reported that she had taken 2 prenatal vitamin pills/day bought from a local pharmacy. The maternal UIC on the 24th week of gestation was 902 µg/24 h (normal range 100 – 460 µg/24 h). The prenatal vitamin was analysed and found to contain 40 mg of potassium iodide per pill, so the pregnant woman was exceeding the recommended dose of 200 µg by 200-fold. The prenatal vitamins were discontinued. No iodine doses were reported in the remaining case reports (de Vasconcellos Thomas and Collett-Solberg, 2009).

20. There is also evidence that excessive iodine supplementation during

pregnancy can increase serum TSH concentration. In one observational study, pregnant women who ingested supplements containing >200 µg/d were found to be at an increased risk of hyperthyrotropinemia and a TSH above 3 µU/ml (Rebagliato et al, 2010).

21. Human epidemiological studies have shown variations in the incidence of thyroid cancer. In the past, Iceland has been known for its population's excess iodine intake from seafood and milk. Between 1944 to 1964, surgical specimens from Iceland and northern Scotland were compared. The PTC (Papillary thyroid cancer):FTC (Follicular thyroid cancer) ratio was 6.5 in Iceland and 3.6 in Scotland. The age-specific incidence rates for papillary carcinoma were approximately five times higher in Iceland than in Scotland in adults older than 35 years of age. It was hypothesised that high iodine intakes contributed to the high incidence of thyroid cancer. However, against this, it was argued the high rates are due to the volcanic nature of the island (Williams et al, 1977; Feldt-Rasmussen, 2001). Between 2003 and 2008 the German population had sufficient iodine intakes from voluntary iodization of salt. The incidence rate of thyroid cancer rose from 2.7 to 3.4 (men) and from 6.5 to 8.9 (women) per 100,000 per year and this was mainly PTC (Radespiel-Troger et al, 2014). The reasons for this increase are unknown.

Excess iodine – animal studies

22. Rats were fed a diet containing excess iodine (~120 mg of iodine per day) or a control diet for 9 months. There was a 40% increase in thyroid weight, and histological changes included enlarged follicles with increased colloid lined by flattened epithelia, but no thyroid tumours were found (Correa et al, 1960).

Health based guidance values

23. The Expert Group on Vitamins and Minerals (EVM) looked in detail at the metabolism of iodine and the effect of excess iodine in 2003. The EVM were unable to set a safe upper limit (SUL) due to lack of data. It was noted that supplemental doses of 0.5 to 1.5 mg iodine/day were associated with a decrease in thyroid hormone levels (Paul et al, 1988; Chow et al, 1991; Gardner et al, 1988). The Saxena et al, 1962; Freund et al, 1966 studies indicated that supplemental doses of 2 mg/day in addition to dietary iodine suppressed further iodine uptake. For guidance purposes, the EVM indicated that a level of 0.5 mg/day of supplemental iodine in addition to the background intake of 0.43 mg/day (equivalent to 0.015 mg/kg bw/day in a 60 kg adult) would be unlikely to cause adverse effects in adults based on slight decreases in serum thyroid hormone levels at supplemental doses of 0-2 mg/day, in a range of human studies.

24. In 2002, the European Scientific Committee on Food (SCF) published an opinion on the tolerable upper intake levels of vitamins and minerals. For iodine, they set a tolerable upper level (TUL) for total iodine intake of 600 µg/day, based on the finding that biochemical changes in TSH levels and the TSH response to thyroid releasing hormone (TRH) administration were marginal and not associated with any clinical adverse effects at estimated intakes of 1700 and 1800 µg/day. The studies on which these UL estimates were based were all only of short duration, with a small

number of individuals but the results were supported by a 5-year study of exposure with an iodide intake of 30 µg/kg bw/day (equivalent to1800 µg iodide/day for a 60 kg adult), where there was no clinical thyroid pathology. An uncertainty factor (UF) of 3 was considered adequate and provided the UL for adults The UL of 600 µg was also considered to be acceptable for pregnant and lactating women based on of lack of adverse effects at significantly higher exposures (SCF, 2006).

25. JECFA established a provisional Maximum Tolerable Daily Intake (PMTDI) of 17 µg/kg bw/day (equivalent to 1020 µg/day for a 60 kg adult) for iodine from all sources, based on an epidemiological study in which 750 men and women were exposed to iodinated water in prison and consumed 1-2 mg of iodine per day for various time periods. Adverse effects were observed in four women who had previous thyroid issues before entering prison and became more symptomatic on receiving the iodinated water supply. Out of 15 tested inmates, two had impaired organification of thyroidal iodine (JECFA, 1989).

26. The COT noted that the different HBGVs were all based on limited data and the relevant studies on which they were established did not allow accurate estimation of dietary intakes. In addition, different assumptions were involved in establishing each of the HBGVs. The Committee was unable to identify a single HBGV that it considered the most scientifically robust and hence used all three in the risk characterisation below.

Iodine exposures in maternal health

Sources of iodine exposure

Food

27. Iodine levels have been measured in the composite food samples of the 2014 Total Diet Study (TDS) (FSA, 2016). The richest dietary sources of iodine are milk and diary products, fish and seafood, and eggs (FSA, 2016; NHS, 2020)

28. Seaweed has been used for centuries as a staple food in Asian countries. In some Asian countries, it is customary to serve seaweed soup to new mothers (Moon et al, 2009). Seaweed consumption is also popular in people who are on a plant-based diet (EFSA, 2019). A study found that seaweed consumption was greatest in those on a vegan diet, often resulting in dietary iodine exposure that was considered excessive (Eveleigh et al, 2020). EFSA conducted an analysis and risk assessment on seaweed, based on samples of seaweed cultivated and harvested in Denmark. Estimated mean exposures to iodine ranged from 94.9 (sea lettuce) – 11,512.3 (sugar kelp/kombu) µg/day, depending on the species of seaweed. Estimated 95th percentile exposures to iodine ranged from 86.0 – 18,677.2 µg/day (EFSA, 2019).

Cows’ milk and milk products

29. Iodine based compounds have been used to clean the udders of

cows during milk collection and these leach into the milk, adding to the natural levels of iodine present. A survey of cows' milk carried out in 1998-1999 found that the overall mean iodine concentration in cows' milk was 311 µg/kg. Mean iodine concentrations were found to be lower in summer (200 µg/kg) compared to winter (430 µg/kg). The higher concentrations in winter may reflect greater use of supplemented compound feedstuffs during this period. At these levels, the COT concluded that the concentrations of iodine in cows' milk were unlikely to pose a risk to health, even in those children who were high level consumers (COT, 2000). However, in the Total Diet Study conducted in 2014, the overall mean iodine concentration in cows' milk was 260 µg/kg (FSA, 2016). According to the Veterinary Medicines Directorate database, a concentrate for teat dip and spray solution containing 2% w/v iodine is still an approved iodophor product (Veterinary Medicines Directorate, 2021).

Drinking water

30. Iodine was detected at low levels (8 µg/L) in tap water in the 2014 TDS (FSA, 2016).

Supplements

31. A range of supplements that contain iodine are promoted to women who are trying to conceive as well as pregnant women and breastfeeding mothers. These supplements contain multiple components and can contain up to 150 µg of iodine per dose. Women are usually advised to consult their doctor before taking these supplements. The NHS states that adults need to have a daily iodine intake of 140 µg, however, most people should be able to obtain the required amount of iodine by eating a varied and balanced diet. People who follow a strict vegan diet and do not consume any fish are advised to take an iodine supplement (NHS, 2020). The UK Dietary Reference Values (DRVs) do not include an increment in iodine for pregnant or lactating women. The Committee on Medical Aspects of Food and Nutrition Policy (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. In its statement on iodine and health, SACN considered there was insufficient evidence to substantiate revisions to the UK DRVs for iodine for pregnant and lactating women (SACN, 2014). No data specifically focusing on the influence of regular use of iodine supplements on levels of iodine in breast milk of UK mothers were identified.

32. The ingestion of supplements and food fortified with iodine on the breast milk iodine concentration in deficiency areas was reviewed by Machamba et al, 2021. In Italy, the effects of dietary iodine (as well as zinc and copper) supplements on breast milk concentration were investigated in 22 women. All the women who finished the study completed a 3 day dietary record. Nutrient analysis showed that the mean daily dietary iodine intake was 145 mg. Samples of 10 ml of milk were collected at 3, 30, 90 day postpartum. An early sharp decline in milk iodine level was seen in all lactating subjects, independently of iodine supplementation (Chierici et al, 1999).

33. After the first month of lactation break milk iodide levels remained stable in all

subjects in the study. No significant differences between the two study groups were observed. The lack of correlation between the iodide level in breast milk and maternal dietary intake of iodine was not in agreement with previously published reports. The present results indicated that in healthy, well-nourished lactating Italian women, whose diet is adequate, the levels of iodine in milk were not influenced by short-term supplementary intakes and that the milk levels of the element were maintained over different levels of intake (Chierici et al, 1999).

34. Studies of iodine in human milk were reviewed by Dror et al. This systematic review indicated that supplementation with high-dose or daily iodine during lactation was effective in increasing breast-milk iodine concentrations, with some evidence of dose-response relationship. Anderson et al looked at how iodine concentrations in milk and in urine during breastfeeding are differently affected by maternal fluid intake. One hundred and twenty-seven breastfeeding women were examined after the introduction of mandatory iodine fortification of salt in Denmark. Breast milk samples and maternal spot urine were obtained at a median of 31 days after delivery, and the participants were asked about iodine supplements after delivery. The median breast milk concentration (MIC) was 83 µg/L (61–125 µg/L) and was also higher in iodine-supplemented mothers; 112 µg/L (80–154 µg/L) versus 72 µg/L (47–87 µg/L) (Andersen et, 2014).

Environmental – Dust and soil

35. Iodine levels in soil are highly variable. A median value of 5.9 mg/kg and a 90th percentile value of 14.2 mg/kg have been reported for UK soil by the British Geological Survey (BGS 2016). No specific value for dust was identified from the literature.

Air

36. According to the expert panel on Air Quality Standards, concentrations of particle bound iodine in UK air between 1996 and 2001 ranged from 0.8×10^{-6} - 2.0×10^{-6} mg/m^3 (DEFRA, 2006).

Medication

37. Iodine is used as a topical antiseptic, which can result in its absorption through the skin. Excessive iodine intakes can occur following the ingestion of iodide-containing pharmaceuticals for the treatment of thyroid conditions, asthma, bronchitis, cardiac conditions (e.g. amiodarone), cystic fibrosis, chronic obstructive pulmonary disease, and goitre. Iodine is also found in mouthwashes, vaginal solutions and burn and wound treatments (SCF, 2006). Absorption in infants appears to be greater than in adults (Leung and Braverman, 2014). There are other medications that also contain iodine, which may be released metabolically into the systemic circulation. The iodide/iodine content in some UK medications is listed below in table 1 (Electronic medicines compendium, 2020).

Table 1- UK medications that contain iodine/iodide.

Name of medicinal product	Medicinal product use	Iodide/iodine content
Aqueous iodine oral solution BP	Used for the pre-operative management of hyperthyroidism	Iodine: 5,000,000 µg (5.0% w/v) Potassium Iodide: 10,000,000 µg (10.0% w/v)
Forceval Capsules	Used for when the intake of vitamins and minerals is at an inadequate level due to immune deficiency syndromes.	Iodine: 140 µg
Minims Povidone Iodine eye drops, solution	Used for cutaneous peri-ocular and conjunctival antisepsis prior to ocular surgery and/or intravitreal injection to support post-procedural infection control	Iodine: 5,000,000 µg (5.0% w/v)
ThySat	Used to prevent the uptake of radioactive iodine in a nuclear accident or during a nuclear medicine investigation	Potassium iodide: 65,000 µg (65.0 mg) equivalent to 50,000 µg (50.0 mg iodine)

Exposure assessment

Exposure estimates based on the TDS

38. A Total Diet Study (TDS) is described as a complementary approach to traditional monitoring and surveillance programs (EFSA, 2011). The TDS is used to calculate population dietary exposure to a range of chemicals in food and to assess the safety and/or nutritional quality of food. TDSs involve selecting, collecting and analysing commonly consumed foods purchased at retail level, processing the food as for consumption, pooling the prepared food items into food groups that are representative, homogenising the pooled samples and analysing them for harmful and/or beneficial chemical substances (FSA, 2019).

39. Table 2 summarises total dietary exposures to iodine calculated using the iodine concentrations determined from food groups in the 2014 TDS. The exposure assessment was carried out for women of childbearing age (16 – 49 years old) using food groups and consumption data from years 1 – 8 of the NDNS survey (Bates et al., 2014; 2016; 2018). The NDNS (Bates et al., 2014; 2016; 2018) does not provide data for pregnant or lactating women so while the data are for women of

childbearing age, they may not necessarily be representative of the maternal diet. Mean chronic iodine exposures from the total diet of women aged 16- 49 years old was 1.7 µg/kg bw/day and the 97.5th percentile chronic exposure was 3.7 µg/kg bw/day.

40. This TDS comprises 27 food groups. The food group making the highest contribution to iodine exposure in the TDS was milk, followed by fish and seafood. It should be noted that it is advised that pregnant women should avoid particular types of cheese, dairy products, meat, eggs, fish and avoid drinking alcohol (NHS, 2020b). Therefore, pregnant, or breastfeeding women may have a different diet compared to non-pregnant or breastfeeding women in the same age range as they may choose to increase or decrease consumption of certain foods or drinks due to this advice, which may result in differences in iodine exposure.

Consumer- based and population-based exposure estimates based on foods in the Total Diet Study (TDS).

Table 2. Estimated chronic exposure for iodine from the total diet in women aged 16 – 49 years old (TDS 27 groups) (Bates et al., 2014; 2016; 2018).

Consumers (n)	**Chronic exposure**	**Chronic exposure**	**Chronic exposure**
Consumers (n)	**Mean (µg/kg bw/day)**	**P97.5th (µg/kg bw/day)**	**Respondents in population group (n)**
1874	1.7	3.7	1874

Exposure estimates for seaweed

41. Seaweed is a rich source of iodine, particularly in people on a plant-based diet or from a culture where dietary seaweed consumption is high. For this reason, iodine levels in seaweed have also been used to obtain exposure estimates.

42. A search within the recipes database of the NDNS (Bates et al., 2014; 2016; 2018) was conducted to retrieve seaweed and seaweed products which had been recorded in the survey. These can be seen in column one of table 3. Column three is the assumption made for the type of seaweed in each food, where it has not been specified. These assumptions were based on common uses of seaweed.

Table 3. Seaweed or seaweed-containing foods recorded in the NDNS (Bates et al., 2014; 2016; 2018).

Food as recorded in NDNS	**Description of food**	**Assumed type of seaweed**
Higher nature energy breakfast shake dry powder	Meal replacement shake	Kelp/ kombu
Laverbread	Welsh seaweed dish	Laver seaweed aka Nori
Sushi, tuna based	NA	Nori

Sushi, vegetarian	NA	Nori
Sushi, salmon based	NA	Nori
Soup with tofu and seaweed	NA	Wakame
Vecon	Vegetable stock	Kelp/ kombu
Seaweed wakame dried raw	NA	Wakame

43. It should be noted that the levels of iodine vary between types of seaweed; this can be seen in the EFSA 'Analysis and Risk Assessment of Seaweed' where sugar kelp/kombu (Saccharina latissima) had a higher iodine concentration in comparison to other seaweed species (EFSA, 2019). In this case, iodine concentration in kelp ranged from 333.0 – 4,782.2 µg/g freeze dried weight. Three other species had lower ranges of 137.8 - 451.2 µg/g, 105.2 - 961.4 µg/g and 17.2-20.8 µg/g of freeze-dried weight (fdw).

44. The levels of iodine in kelp/ kombu can be compared to those in wakame and nori (Yeh et al, 2014), which is more specific to the data available from the NDNS. In this case, the range for nori was 29.3 – 45.8 µg/g, for wakame 93.9 – 185.1 µg/g and for kombu 241- 4921 µg/g in dried seaweed weight.

45. Seaweed harvested from different countries may also have differing levels of iodine, which is also illustrated by Yeh et al, 2014. Ten samples each of nori, wakame and kombu harvested from China, Japan, Korea and Taiwan were analysed with varied results (Yeh et al, 2014).

46. Another uncertainty was that seaweed consumption based on the foods in table 3 and NDNS survey data for women of childbearing age (16 – 49 years) yielded consumption data based on very few consumers (Bates et al., 2014; 2016; 2018). Exposure or consumption estimates based on very few consumers should be treated with caution, particularly 97.5th percentile estimates based on less than 60 consumers. Furthermore, as mentioned previously, the NDNS does not consider pregnant or lactating women so these estimates may not be representative of the target population. The chronic consumption estimates can be seen in table 4.

Table 4. Chronic consumption estimates of seaweed in women aged 16 – 49 years old (Bates et al., 2014; 2016; 2018).

Consumers (n)	**g/ person/day***	**g/person/day***	**g/kg bw/day***	**g/kg bw/day***	**Respondents in population group (n)**
Consumers (n)	**Mean**	**P97.5th**	**Mean**	**P97.5th**	**Respondents in population group (n)**
36	1.1	3.8	0.017	0.060	1874

*rounded to 2.s.f.

47. Further to the data considered from literature in paragraphs 41 – 43, real time data was consulted. The Rapid Alert for Food and Feed (RASFF Portal) is a tool that provides information on public health warnings issued by food safety authorities and food companies. It also provides the latest information on food recall

notices. Between March 2019 to August 2020, there were 37 reported instances whereby levels of iodine were detected in seaweed samples at above the alert, recall or ‘information for follow-up’ level according to the RASFF Portal. The concentrations of iodine in these seaweed samples ranged from 25 µg/g to 20,620 µg/g. Countries of origin in order of contribution were: South Korea, China, Germany, Spain, Japan, Belgium and Austria. These are similar to the countries from which samples were derived by Yeh et al, 2014. This range is much greater than that seen by the EFSA analysis of kelp from a single source (EFSA, 2019) and is considered to be a worst-case scenario.

48. After reviewing all of the information in paragraphs 42– 43 and tables 3 and 4, exposure estimates were calculated using NDNS seaweed consumption data and the iodine concentration range measured in 16 kelp samples by EFSA, 333.0 – 4,782.2 µg/g fdw (EFSA, 2019). Due to the various uncertainties discussed such as the varying levels of iodine in different types of seaweed and the limited consumption data available in the NDNS this was considered the most realistic scenario.

Table 5: Chronic exposure estimates using chronic consumption data from table 4 and the iodine concentration range measured in kelp by EFSA, 2019 (minimum: 333.0 µg/g fdw, maximum: 4,782.2 µg/g fdw).

Age group	Number of consumers	Chronic exposure µg/ person/ day*	Chronic exposure µg/ person/ day*	Chronic exposure µg/ person/ day*	Chronic exposure µg/ person/ day*	Chronic exposure µg/kg bw/day*	Chronic exposure µg/kg bw/day*	Chronic exposure µg/kg bw/day*	Chronic exposure µg/kg bw/day*
Age group	**Number of consumers**	**Mean**	**Mean**	**97.5th Percentile**	**97.5th Percentile**	**Mean**	**Mean**	**97.5th Percentile**	**97.5th Percentile**
woman 16-49 years	36	Min	Max	Min	Max	Min	Max	Min	Max
n/a	n/a	360	5200	1300	18000	5.5	79	20	290

*rounded 2.s.f.

49. The exposure data in table 5 should be treated with caution because it is based on consumption data from a limited number of consumers, particularly the 97.5th percentile estimates, assuming all consumption is of a single seaweed species, with appreciable higher iodine concentrations than those of other species. Another important caveat is that the use of unprocessed seaweed biomass is a conservative approach for exposure assessments which is likely to lead to an overestimation. The minimum and maximum seaweed iodine values are based on only 16 samples. The effects of cooking and processing as well as bioavailability are not taken into account for this assessment as the data from EFSA 2019 is based on freeze dried samples of seaweed (EFSA, 2019).

Risk characterisation

50. In 2003, the EVM set a guidance level for iodine of 15 µg/kg bw/day that would not be expected to cause adverse effects in the majority of the population. It should be noted that this is a guidance level only as there was insufficient data from human or animal studies to establish a Safe Upper Level for iodine. Therefore, its applicability to maternal health is uncertain. The exposure estimates in Table 2 are below the guidance value. As seen in table 5, the estimated mean exposure for seaweed based on the minimum value of 333.0 µg/g freeze dry weight (fdw) of iodine was 5.5 µg/kg and is below the guidance value. The estimated mean exposure for seaweed based on the maximum value of 4782.2 µg/g fdw of iodine was 79 µg/kg bw/day and is above the guidance value. The estimated 97.5th percentile exposures for seaweed based on the minimum and maximum values of 333.0 µg/g and 4782.2 µg/g fdw iodine were 20 and 288 µg/kg bw/day, respectively. The estimated exposures are above the guidance value. Iodine levels in cows' milk and milk products and tap water resulted in exposures that were below the guidance value.

51. JECFA established a provisional Maximum Tolerable Daily Intake (PMTDI) of 17 µg/kg bw/day for iodine from all sources, based on the same longer-term studies in adults used by SCF in 2002 to support the TUL. The exposure estimates in Table 2 are below the PMTDI. As seen in table 5, the estimated mean exposure for seaweed based on the minimum value of 333.0 µg/g fdw of iodine is below the PMTDI. The estimated mean exposure for seaweed based on the maximum value of 4782.2 µg/g fdw of iodine is above the PMTDI. The 97.5th percentile exposure estimates for seaweed based on the minimum (333.0 µg/g fdw) and maximum iodine (4782.2 µg/g fdw) values are above the PMTDI. Iodine levels in cows' milk and milk products, and tap water resulted in exposures that were below the guidance value.

52. The SCF established a UL of 600 µg/day for pregnant and lactating women based on lack of adverse effects at significantly higher exposures (SCF, 2000). The exposure estimates in table 2 are below the UL. The estimated mean exposure for seaweed based on the minimum value of 333.0 µg/g fdw of iodine was below the UL. The estimated mean exposure based on the maximum value of 4782.2 µg/g fdw iodine was above the UL.

53. The estimated 97.5th percentile exposures for seaweed based on the minimum (333.0 µg/g fdw) and maximum iodine (4782.2 µg/g fdw) values are above the UL. Iodine levels in cows' milk and milk products, tap water and supplements resulted in exposures that were below the guidance value.

54. Medications that contain free iodine/iodide are listed in Table 1. Iodine levels range from 5.0% w/v to 140 µg. Medications that contain iodine are usually used to treat hyperthyroidism, hypothyroidism, immune deficiency syndromes, cutaneous peri-ocular and conjunctival antisepsis prior to ocular surgery. It is assumed that these medicines will be consumed short term. In prescribing medicines for clinical use, the benefits to the individual patient are assessed relative to the possible risks to the patient. This includes possible risks to the developing fetus. ThySat is a high

potassium iodide-containing product used in nuclear medicine to prevent the uptake of radioactive iodine by the thyroid gland after a nuclear accident. This treatment can also be used as a preparation for nuclear medicine diagnostics to prevent unnecessary exposure of the thyroid to tracers containing radioactive iodine I-131 (Radioiodine I-131). However, repeated administration is contraindicated for pregnancy and lactation (Electronic medicines compendium, 2020).

55. Potential exposures to iodine via soil, dust and air were previously considered for 6 to 12-month olds and 1 to 5-year-old children. It was concluded that these exposure sources made a minimal contribution to exposure. Therefore, potential soil and dust exposures for women of childbearing age are similarly likely to make a minimal contribution to overall exposure.

Conclusions of the Committee

56. Iodine is essential in the diet to produce thyroid hormones which are involved in cell metabolism, growth and development.

57. Iodine status in the individual is difficult to assess since healthy people excrete excess iodine in urine so it is not a good marker for individual exposure.

58. Exposure to excess iodine in pregnancy may cause adverse effects on maternal and fetal thyroid function, birth outcomes, offspring growth and development.

59. Iodine exposure from the total diet is within the HBGVs established by bodies such as EFSA, JECFA and the EVM for adults and would not be a risk to maternal health.

60. There are no toxicological concerns at the levels of iodine exposure in the general population, however, high consumers of seaweed may be exposed to levels of iodine that could pose a toxicological risk to maternal health. Currently, available data are not sufficient to assess the applicability of the HBGVs to pregnant women, and there is a lack of exposure data in relation to pregnancy and lactation to enable a risk assessment to be performed.

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Abbreviations

BGS	British Geological Survey
BMIC	Breast milk iodine concentration
BW	Body weight
Cr	Creatinine
COMA	Committee on Medical Aspects of Food and Nutrition Policy
COT	Committee on the Toxicity of Chemicals in Food, the Environment and Consumer Products
DEFRA	Department for Environment, Food & Rural Affairs
DRVs	Dietary Reference Values
EVM	Expert Group on Vitamins and Minerals
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organisation
FDW	Freeze dry weight
GFR	Glomerular Filtration Rate
ICCIDD	International Council for Control of IDD
IDD	Iodine deficiency disorders
I/Cr	Urinary iodine concentration to creatinine
JECFA	Joint FAO/WHO Committee on Food Additives
KI	Potassium iodide
Kg	Kilogram
Mg	Milligram
NDNS	The National Diet and Nutrition Survey
NIS	Sodium Iodide symporter
PTC	Papillary Thyroid Cancer
PMTDI	Provisional Maximum Tolerable Daily Intake
SACN	Scientific advisory Committee on Nutrition
SCF	The European Scientific Committee on Food
T3	Triiodothyronine
T4	Thyroxine
TDS	Total Diet Study
Tg	Thyroglobulin
TNs	Thyroid nodules
TSH	Thyroid Stimulating Hormone
TRH	Thyroid Releasing Hormone
TUL	Tolerable Upper Level
UF	Uncertainty Factor
UL	Upper Limit
UIC	Urinary iodine concentration

UNICEF	United Nations Children's Fund
WHO	World Health Organisation
µg	Microgram

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