



Australian Government

National Health and  
Medical Research Council

N H M R C

# **Iodine Supplementation During Pregnancy and Lactation**

Literature Review

**IODINE SUPPLEMENTATION DURING PREGNANCY AND LACTATION**  
Literature Review- October 2009

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## INTRODUCTION

The National Iodine Nutrition Survey (2006) identified that the Australian population is mildly iodine deficient (Li et al 2006, Li et al 2008). Food Standards Australia New Zealand (FSANZ) (2008a) investigated options for iodine fortification in Australia and New Zealand to correct this deficiency. The aim was to determine a level of fortification that maximised iodine intakes while minimising the proportion of the population with inadequate or excessive dietary iodine intakes. Mandatory fortification of bread with iodised salt was gazetted based on dietary intake assessments, modelling and cost-benefit analysis. However, mandatory bread fortification, at levels recommended to prevent excess iodine consumption in children, will not provide sufficient dietary iodine intake for pregnant and lactating women. This literature review was undertaken to investigate the efficacy and safety of iodine supplementation to improve iodine status in pregnant and lactating women.

## PART A: BACKGROUND

In its natural form iodine can be found in sea water, marine plants and in some minerals and soil. The iodine content in food and water depends on factors such as altitude, fertilisers, rainfall and microbes in soil (APHDPC 2007). Iodine can also be found in some medications and cleansers.

Iodine is a trace element essential for synthesis of the thyroid hormones; triiodothyronine (T3) and thyroxine (T4). These hormones play a vital role in the early growth and development stages of most organs, in particular the brain. Iodine is accumulated in the digestive system and enters the blood stream where it is transported to the thyroid gland and extrathyroid tissues, such as the mammary gland (NHMRC & NZ MoH 2006, Perez-Lopez 2007).

### *1. Role of iodine in pregnancy and lactation*

Iodine plays a critical role in neuropsychological development of the foetus throughout gestation and in the first two years of life. Iodine uptake by the thyroid is higher in pregnancy and the iodine reserve in the thyroid can decrease to approximately 40% of preconception levels. The increased clearance rate can lead to an increase in thyroid volume in pregnant women in iodine deficient areas. There is no or little change in thyroid volume observed in pregnant women in areas with sufficient dietary iodine intake (Glioner 1997, Perez-Lopez 2007, Zimmerman 2009).

The thyroid stores iodine from the diet and as such maternal iodine status is not entirely dependent on the current dietary intake during gestation. If preconception iodine nutrition is adequate there will be sufficient stored thyroid hormone to support the mother and foetus, at least in the first trimester. However if preconception dietary intake is deficient the increasing demands of later pregnancy may produce a deficit which untreated can result in a hypothyroxinaemic state (Smyth 2006). There is some evidence suggesting that in areas of mild to moderate iodine deficiency, the maternal thyroid is able to adapt to meet the increased thyroid hormone requirements of pregnancy (Zimmerman 2009).

During the first two trimesters of pregnancy the foetus is entirely dependent on the maternal thyroid hormone supply as the foetal thyroid does not develop until 13-15 weeks gestation (Smyth 2006, Gliener 1997). As the foetus progresses into the third trimester, it develops the ability to produce its own thyroid hormones but it is still dependent on maternal iodine for hormone synthesis (Becks and Burrow 2000).

Breast fed infants are dependent on breast milk for iodine, and therefore on the maternal dietary iodine intake. Most infant formulas are supplemented with iodine, though concentrations vary significantly. The Nutrient Reference Values for Australia and New Zealand (NRVs) recommend an Adequate Intake of iodine for infants of 90µg/d from 0-6 months old, and 110µg/d from 7-10 months old (NHMRC 2006).

## 2. *Optimal iodine levels*

The NRVs outline the levels of intake of essential nutrients considered to be adequate to meet the known nutritional needs of practically all healthy people. The NRVs aim to prevent deficiency states and provide advice in the form of Estimated Average Requirement (EAR)<sup>1</sup>, Recommended Dietary Intake (RDI)<sup>2</sup>, Adequate Intake (AI)<sup>3</sup> and Upper Level of Intake (UL)<sup>4</sup>.

The EAR, RDI and UL for iodine nutrition as stated in the NRVs are presented in **Table 1** below.

**Table 1. Nutrient Reference Values for Australia and New Zealand - Iodine**

<b>Recommendation</b>	<b>Women</b>	<b>Pregnant women</b>	<b>Lactating women</b>
<b>EAR</b>	95/100µg (14-18/>18)	160µg	190µg
<b>RDI</b>	150µg	220µg	270µg
<b>UL</b>	900/1100µg (14-18/>18)	900/1100µg (14-18/>18)	900/1100µg (14-18/>18)

Values in this table are sourced from NHMRC & NZ MoH (2006).

## 3. *Measuring iodine status*

Urinary iodine concentration (UIC) is a universally accepted measure of iodine status. UIC is a good indication of the previous day's dietary iodine intake as up to 90% of iodine is excreted in the urine (Travers et al 2006). It is generally accepted that a UIC of 100µg/L in adults equates to an iodine intake of 150µg/d (Becker et al 2006) and in children equates to iodine intake of 110µg/d. Selection of participants and sample size

<sup>1</sup> The EAR is a daily nutrient level estimated to meet the requirements of half the healthy individuals in a particular life stage and gender group.

<sup>2</sup> The RDI is the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in a particular life stage and gender group.

<sup>3</sup> The AI is used where the RDI cannot be determined. The AI is the average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group of apparently health people that are assumed to be adequate.

<sup>4</sup> The UL is the highest average daily nutrient intake level likely to pose no adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases (NHMRC & NZ MoH, 2006).

are critical for UIC to be a reliable marker of iodine nutrition. The World Health Organization (WHO) recommends sample sizes of at least 300 participants (WHO 1994). For this reason, school children are routinely measured as they are a large and easily accessible population. The WHO/ United Nations International Children’s Emergency Fund (UNICEF)/International Council for the Control of Iodine Deficiency Disorders (ICCIDD) have developed epidemiological criteria which are presently recommended for assessing iodine nutrition based on median UIC in school-age children. The median urinary iodine concentration from spot samples is used to define the status of the whole population. Because urinary iodine is responsive to recent intake, a single sample does not permit estimation of the standard deviation of usual iodine status in the population and, additionally, cannot be used to assess usual status of individuals. These criteria are presented in **Table 2** below.

**Table 2. WHO/UNICEF/ICCIDD criteria for assessing population iodine status using population median urinary iodine concentration**

<b>Iodine Status</b>	<b>General Population (ug/L)</b>	<b>Pregnant and lactating women (ug/L)</b>	<b>School children ≥ 6 years old (ug/L)</b>
<b>Excessive*</b>	≥300	≥500	≥300
<b>Above requirements</b>	200-299	250-499µg/L	200-299µg/L
<b>Iodine Sufficient</b>	100-199µg/L	150-249 µg/L	100-199µg/L
<b>Mild Iodine Deficiency</b>	50-99µg/L	<150µg/L	50-99µg/L
<b>Moderate Iodine Deficiency</b>	20-49µg/L	<20-49µg/L	20-49µg/L
<b>Severe Iodine Deficiency</b>	<20µg/L	<20µg/L	<20µg/L

\*The term “excessive” means in excess of the amount required to prevent and control iodine deficiency. Values in this table are sourced from WHO/UNICEF/ICCIDD (2007a)

#### **4. Iodine deficiency**

Severe iodine deficiency provokes a range of disorders including endemic goiter, hypothyroidism, cretinism, decreased fertility, miscarriage, increased infant mortality, hypothyroxinaemia, trophoblastic or embryonic foetal disorders and mental retardation (Perez-Lopez 2007). Mild maternal hypothyroidism or asymptomatic hypothyroxinaemia can result in intellectual deficit and/or neuropsychomotor deficits (Vermiglio et al 2004). Iodine deficiency in Australia is mild and as a result the more severe disorders such as cretinism, which are only found in very severe iodine deficient areas, are unlikely to be seen.

The effects of mild to moderate iodine deficiency are less clear and are likely to cause more subtle cognitive and neurological impairments (Zimmerman 2009). There is reasonable evidence of sub-optimal neurological development in areas with mild iodine deficiency. It has been suggested that a dose-response relationship exists such that an increased neurological impact is seen as iodine deficiency increases and iodine supplementation can prevent the degree of damage (APHDPC 2007).

A recent 28 week New Zealand study (Gordon et al 2009) on children aged 10-13 taking a 150µg/d iodine supplement vs. placebo found significant improvement in UIC (baseline 66µg/L, post treatment 145µg/L,  $p < 0.001$ ) and Tg (baseline 16.5µg/L, post treatment 8.5µg/L,  $p < 0.001$ ). The children were also tested on cognitive ability before and after the 28 weeks. The study found significant improvement in picture concepts (treatment effect 0.81,  $p 0.023$ ) and matrix reasoning tests (treatment effect 0.63,  $p 0.040$ ) representing perceptual reasoning, a higher-order cognitive ability. There was not a significant difference in symbol search (treatment effect 0.16,  $p 0.608$ ) or letter-number sequencing (treatment effect 0.18,  $p 0.480$ ). This has shown that mild iodine deficiency prevents children from attaining their full intellectual potential and that iodine supplementation improves UIC, Tg and cognitive performance.

A reduction of up to 13.5 Intelligence Quotient (IQ) points has been observed in moderate to severe iodine deficient regions (APHDPC 2007). A US study comparing IQ scores of seven to nine year old children of mothers with subclinical hypothyroidism during pregnancy found IQ scores of seven points lower than controls (Zimmerman 2009). A meta-analysis of 37 studies (Qian et al 2005) of IQ in iodine deficient regions in China found a reduction of 12.45 IQ points when compared to iodine sufficient regions. This loss was reduced to 8.7 IQ points when iodine supplementation was introduced during pregnancy and after birth. A 12 point increase in IQ was found 3.5 years after the introduction of iodine supplementation. The study concluded that iodine supplementation before and during pregnancy to women in iodine deficient areas could prevent their child from intellectual deficit.

It is hypothesised that iodine deficiency may be associated with Attention Deficit Hyperactivity Disorder. A study conducted in a moderately iodine deficient area in Sicily found that 11 of 16 participants were diagnosed with ADHD by age 10, as compared to none in the marginally iodine sufficient control group (Vermiglio et al 2004).

### **5. Iodine status in Australia**

In 1992 the median UIC levels in Australia were 200µg/L (Eastman 1993), which is on the border between sufficient and above requirement (Table 1) More recent studies in Tasmania, New South Wales and Victoria have shown median levels  $< 100\mu\text{g/L}$  indicating mild deficiency (Seal et al, 2007, Li et al 2006). In pregnant women, levels have been found to be well below 100µg/L indicating inadequate iodine intake in these states. In 2009 WHO, based on the national median urinary iodine concentration of 96µg/L (Li et al 2008a), has classified Australia as a mildly iodine deficient country.

The recent decline in iodine status in Australia appears to be related to changes in the dairy industry, with chlorine-containing sanitisers replacing iodine-containing sanitisers. Another likely factor is the minimal use of iodised salt, which is used by few, if any, manufacturers (Li et al 2006) with iodized salt sales at approximately 10% of total edible salt sales (Li et al 2008b). Interestingly, after a brief media campaign on iodine deficiency disorders and the benefits of using iodized salt, iodized salt sales increased by 5.2% (Li et al 2008b). Only 55% of Australian women aged 16-44 years always or regularly use salt at the table and in cooking (FSANZ, 2008).

The National Iodine Nutrition Study (NINS) conducted in 2003-4 investigated the iodine status of more than 1700 school children from across Australia. The NINS found that the median urinary iodine concentration now lies in the mild deficiency range (96µg/L) NINS specifically found that iodine deficiency is endemic in New South Wales and Victoria and borderline in South Australia (Li et al, 2006). **Table 3** below shows the iodine status of Australian children aged 9 years old in states surveyed as part of the NINS.

**Table 3. Iodine Status in Australian children aged 9 years, 2003-4**

State	Median UIC (µg/L)	Interquartile range (µg/L)	Population Status
<b>New South Wales</b> N= 427	89	65 - 123	Mild deficiency
<b>Victoria</b> N= 348	73.5	53 - 104	Mild deficiency
<b>South Australia</b> N= 317	101	74 - 130	Borderline deficiency
<b>Western Australia</b> N= 323	142.5	103 - 214	Sufficient
<b>Queensland</b> N= 294	136.5	104 - 183	Sufficient
<b>Weighted total</b> N= 1709	96		Mild deficiency

\*Values in this table are sourced from the Australian National Iodine Nutrition Survey (Li et al 2006, Li et al 2008).

The median UIC found in Australia indicates a mild iodine deficiency in children (Li et al 2006). Iodine deficiency at levels found in Australia can have a negative impact on mental and nervous system development in children and increase risk of hyperthyroidism in the elderly. The most vulnerable group is the developing foetus and children up to 3 years old (FSANZ 2008a).

It has been recommended that all Australian and New Zealand women who are pregnant, lactating or planning to conceive be encouraged to take an iodine supplement (Burgess et al 2007, Eastman 2005, Hamrosi et al 2005). The only exception being those women with known thyroid conditions or high iodine intakes from other sources (Eastman 2005). It has been recommended that supplementation be in the range of 100 to 200µg/d, as there is no demonstrable benefit above 250µg/d (Eastman 2005).

In addition, mandatory iodisation of all edible salt (Li et al 2006, Seal et al 2007) and ongoing surveillance of the iodine nutrition of Australians particularly pregnant and lactating women has been recommended (Chan et al 2003, Guttikonda et al 2003, Hamrosi et al 2005).

However, the introduction of universal salt iodisation in Australia was investigated by FSANZ and was found to raise significant issues including technical constraints, export and import challenges, increased industry cost, minimising choice for

consumers and inconsistency with the Council of Australian Governments (COAG) requirement to ensure minimum effective regulation (COAG 2007).

### ***Iodine fortification***

In 2001, the Tasmanian Department of Health and Human Services entered into a Memorandum of Understanding with bakers to introduce an iodine supplementation program. As a result, 80% of bread baked and sold in Tasmania is made with salt containing iodine at 25-65 (average 45mg iodine /kg salt in place of regular salt. The Tasmanian government implemented this program as an interim measure pending a national strategy (Seal et al 2007, Burgess et al 2007).

FSANZ Proposal *P230 Consideration of Mandatory Fortification with Iodine* was initiated in response to a request from the Australia and New Zealand Food Regulation Ministerial Council (FSANZ 2008a).

Initially, Proposal P230 was intended to address iodine deficiency in both Australia and New Zealand. However, prior to completion, the Australia and New Zealand Food Regulation Ministerial Council asked FSANZ to defer its consideration of mandatory iodine fortification for Australia while Australian Health Ministers Conference (AHMC) re-evaluated the evidence on the prevalence and severity of iodine deficiency in Australia. In the interim, in recognition of the magnitude and severity of iodine deficiency in New Zealand, Proposal P230 was finalised as a separate Standard for New Zealand.

The Australian Population Health Development Principal Committee (APHDPC) of the Australian Health Ministers Advisory Committee (AHMAC) released a report *The prevalence and severity of iodine deficiency in Australia* (2007) to inform AHMC's consideration of this issue. The report reviewed the prevalence of iodine deficiency in Australia, the health consequences of mild iodine deficiency and the degree of deficiency that has prompted intervention in other developed countries. In March 2008, FSANZ received advice from the AHMC confirming that iodine deficiency is prevalent and severe enough to warrant intervention in Australia, and that mandatory fortification is considered the most cost-effective strategy to redress this.

While Proposal P230 was finalised as a New Zealand only Standard, considerable work and consultation had been conducted for Australia during its development. The aim of Proposal *P1003 Mandatory Iodine Fortification for Australia* was to amend the New Zealand only to be a joint Australia/New Zealand standard for mandatory replacement of non-iodised salt with iodised salt (25-65mg iodine/kg salt) in bread with the exception of organic bread (FSANZ 2008a).

Prior to mandatory fortification, 43% of the Australian population over 2 years old were estimated to have inadequate iodine intakes. Modelling conducted by FSANZ predicts this to fall below 5% with mandatory bread fortification (FSANZ 2008a).

While mandatory bread fortification will provide the general population with adequate iodine, approximately 70% to 90% of pregnant and lactating women will have an inadequate intake (FSANZ 2008b). This may be an overestimate as these estimates are based on intakes of non-pregnant women because a sufficient sample of pregnant women was not included in the National Nutrition Survey to allow separate estimation. Fortification to levels optimal for pregnant and lactating women would

put children under three years old at risk of excess iodine consumption, i.e. above the UL (FSANZ 2008b). Therefore pregnant and breastfeeding women will still need additional iodine from other sources.

## **6. *International iodine status***

Iodine deficiency is a worldwide health problem which continues to affect 2.2 billion people (Perez-Lopez 2007). In its severe form iodine deficiency is the leading cause of preventable mental retardation (Smyth 2006). The United Nations (UN) supported *Declaration for the Survival, Protection and Development of Children*, to which Australia is a signatory, maintains that 'every child has the right to an adequate supply of iodine to ensure its normal development' (United Nations 1990).

Iodine status varies considerably around the world with iodine sufficiency in some countries including Sweden, Switzerland, Norway, China, Finland and The Netherlands, and mild to moderate deficiency in other countries including Ireland, Germany, Belgium, Italy, Denmark and Spain. While most women in Europe are classified iodine deficient during pregnancy (achieving only approximately half of the recommended daily iodine intake), only 13- 50% receive iodine supplementation (Zimmerman and Delange 2004).

The most utilised method for correcting iodine deficiency worldwide is Universal Salt Iodisation (USI), with concentrations ranging from 7 to 100mg iodine / kg salt. Salt is used because its intake is universal across socioeconomic status and throughout all seasons of the year (Perez-Lopez 2007).

Iodine supplementation has been recommended across countries with varying levels of iodine deficiency as an effective means of protecting vulnerable populations specifically, pregnant and lactating women and children (Azizi 2007, Becker et al 2006, Burgess et al 2007, Costiera et al 2009, Hamrosi et al 2005, Hollowell et al 2007, Kurtoglu et al 2004, Nawoor et al 2006, Skeaff et al 2005, Yan et al 2005, Zimmerman and Delange 2004).

In some developing countries massive annual doses of slow release iodinated oil are used where iodised salt is not accessible. Iodinated oil is usually provided at doses of 400mg for adults and 200mg for children and provides a cheap and effective supplementation option in developing countries. Iodinated oil is not used in Australia as it is not approved for use by the Therapeutic Goods Administration (TGA). Iodinated oil is not the ideal delivery system physiologically as it leads to a massive initial increase in UIC which is not stable over time and may not sustain iodine sufficiency.

WHO/UNICEF/ICCIDD (2007a) recommends iodine supplementation in pregnancy and infancy in countries or regions where <90% of households are using iodised salt and the median UIC in school age children is <100µg/L (Zimmerman 2009). Following mandatory fortification of bread, the median UIC of primary school aged children in Australia will no longer meet these criteria as shown by the results from the Tasmanian intervention with less than complete coverage of iodised salt in bread (Seal et al, 2007).

WHO/UNICEF/ICCIDD (2007a) recommends iodine supplementation of 250µg/d for pregnant and lactating women, 150µg/d for women of reproductive age or an annual dose of 400mg of iodised oil. These are generic recommendations and intended to allow for the needs of countries with severe iodine deficiency as well as less severe forms.

## **PART B: METHODOLOGY**

### ***1. Literature Search***

A search of the literature was undertaken in the MEDLINE, EMBASE, Australasian Medical Index and Libraries Australia databases. The search was limited to articles published from 2004, in English and with human subjects. The search was conducted in June 2008 and 104 citations were identified. One reviewer assessed the eligibility of abstracts, 43 articles were considered potentially eligible for inclusion in the review. After the review of the full papers, 37 citations were included in the review. The remaining studies were excluded on the basis of unspecified sample size or relevance. Studies excluded as not relevant were measuring outcomes not related to the research questions, for example the effect of maternal smoking on iodine nutrition. An additional search was conducted in July 2009 to capture any newly published studies, however, no articles on original studies were found.

The search terms included:

Concept 1 terms: iodine ; iodine/ ; iodine/do [Dosage] ; Iodine Deficiency/di [Diagnosis] ; Iodine/ae,df [Adverse Effects, Deficiency] ; Iodine/po,to [Poisoning, Toxicity] ; and

Concept 2 terms: nutrition\* ; diet\* ; exp nutrition/ ; Nutritional Requirement/ ; Nutritional Status/ ; Nutritional Assessment/ ; nutritional reference value ; nutrient reference value; and

Concept 3 terms: excess\* ; exp pregnancy/ ; fetus development/ ; Infant/ ; Child/ ; Adult/ ; LACTATION/ ; upper limit\* ; Cost-Benefit Analysis/ or benefit\* ; Pregnancy/ ; exp Lactation/ ; Fetal Development/ ; adolescent/ ; adult/ ; child/ ; infant/ ; upper limit

### ***2. Data extraction***

Data extracted from all reviews and individual studies included information about the study design, sample population, outcome measures, results and recommendations. The evidence summaries are included at Appendices A and B.

The majority of the literature reported on cross-sectional studies with good sample sizes from various countries. Randomised control trials were reported on in included reviews. The primary measure used throughout the studies to determine iodine status was UIC. Some studies also measured breast milk iodine concentration (BI), TSH, thyroid volume and thyroid hormones.

### ***3. Research Questions***

The literature review was undertaken to answer the following questions:

- 1. What is the iodine status of Australians?*
- 2. Will taking an iodine supplement during pregnancy/lactation improve iodine status?*
- 3. Does taking an iodine supplement during pregnancy/lactation lead to an excessive intake of iodine? (>1,100µg/d)*
- 4. What are the risks of taking an iodine supplement during pregnancy/lactation?*

## **PART C: REVIEW RESULTS**

### ***1. What is the iodine status of Australians?***

In 2009 WHO, based on the national median urinary iodine concentration of 96µg/L (Li et al 2008a), has classified Australia as a mildly iodine deficient country. This is based on recent studies of children in Tasmania, New South Wales and Victoria which have shown median UIC levels <100µg/L indicating mild deficiency (Seal et al, 2007, Li et al 2006, APHDPC 2007). In pregnant women, levels have been found to be well below 100µg/L indicating inadequate iodine intake in these states (APHDPC 2007). For further background information, see Part A, Section 5.

### ***2. Will taking an iodine supplement during pregnancy and lactation improve iodine status?***

A review of six randomised control trials (RCTs) (Zimmerman and Delange 2004) found a significant increase in UIC with iodine supplementation. Iodine dose in the studies varied from 50 to 230µg/d and produced variable increases in UIC. These studies also found that supplements are generally effective at minimising increases in thyroid volume during pregnancy (Zimmerman 2009). However, there was no clear effect on total or free thyroid hormone concentrations (Zimmerman and Delange 2004, Zimmerman 2009). Iodine supplementation was considered efficacious for both maternal and newborn iodine status.

The review of iodine status in pregnant women in Europe (Zimmerman and Delange 2004) concluded that supplements appear to be generally safe and recommends that pregnant and lactating women and women planning to become pregnant, take an iodine supplement of 150µg/d. The authors also recommend that prenatal supplement manufacturers be encouraged to include adequate iodine in their products.

### ***3. Does taking an iodine supplement during pregnancy and lactation lead to an excessive intake of iodine? (>1,100µg/d)***

Iodine supplementation, at the recommended doses of 50 to 250µg/d, will not lead to an iodine intake in excess of the UL of 1100µg/d. Currently, recommendations for iodine supplementation in areas of mild to moderate deficiency vary from 50 to 250µg/d. (Perez-Lopez 2007, Skeaff et al 2005, WHO/UNICEF/ICCIDD 2007a, Zimmerman and Delange 2004). Supplements containing these levels of iodine even when dietary intake and UIC are sufficient are rarely going to exceed 1100µg/d in Australia.

However, caution should be exercised in selecting a prenatal supplement. A survey of 15 prenatal supplements available in Australia (FSANZ 2009a) found iodine content of between 150 and 270µg/d, with one leading brand containing no iodine. A survey of iodine levels in 223 prenatal supplements available in the US found that only 114 (49%) contained iodine and only 101 contained 150µg or more of iodine (Leung et al 2009). Kelp and seaweed based supplements should be avoided as the iodine content has been found to be highly variable and could exceed the upper level, with levels reported from 16µg/g to 8165 ± 373µg/g (Teas et al 2004, Zimmerman 2004,

Thomson 2004). The Medical Information Management System (MIMS) Online database lists four kelp products, three of which list pregnancy as a contraindication. There is also concern that kelp and seaweed based products carry the risk of potential contamination with heavy metals.

Dietary modelling has shown that the baseline iodine intake in Australia, with additional iodine from fortification of bread and an iodine supplement of 150µg/d would lead to an average intake of 290µg/d and a 95<sup>th</sup> centile of 365 (FSANZ 2009b).

#### **4. What are the risks of taking an iodine supplement during pregnancy/lactation?**

There is little evidence of harm from iodine supplements when used in the ranges recommended worldwide (50 to 250µg/d). However there is some evidence to suggest that iodine levels in excess of defined Upper Levels are not safe. The ICCIDD have recently released the *Iodine Safety Declaration* (ICCIDD 2009) which states that:

“Mild thyroid hyperfunction may occur following an increase of iodine intake within the recommended range as a consequence of pre-existing autonomous nodular goiter due to long standing iodine deficiency. This is a transient effect. The single relevant adverse effect is iodine induced overt hyperthyroidism, only observed in severely iodine deficient populations after a rapid introduction of excessive iodine supplementation which should and can be avoided.

Excessive iodine intake may lead to a transient small increase in the prevalence and incidence of subclinical hypothyroidism and thyroid autoimmunity, especially in older individuals... optimal iodine intake supported by adequate monitoring has been widely shown to improve the quality of various health aspects. The benefits of iodine supplementation far outweigh the relatively small risks of iodine excess”

Adverse effects of iodine intake above the Upper Levels are almost exclusively found in people over the age of 50. Adverse effects of supplementation are extremely unlikely to be seen in healthy women of reproductive age. Women with pre-existing thyroid conditions should speak to their doctor (Becker et al 2006).

Studies of iodine supplementation in iodine deficient pregnant women have not reported data on infant or child development. However, they frequently report on measures of infant development such as maternal and newborn thyroid function. Measures of thyroid function, including thyroid volume, indicate that iodine supplementation preconception and during pregnancy and lactation has a protective effect for the mother and newborn (Zimmerman and Delange 2004). The risks of iodine deficiency markedly outweigh any potential risks from iodine supplementation in women of reproductive age.

## **5. Further research**

The literature reviewed suggests a need for further research to determine the iodine status of Australians, particularly pregnant and lactating women and infants, using a combination of iodine deficiency indicators. The Australian Institute of Health and Welfare has been tasked with monitoring the impact of mandatory iodine fortification on urinary iodine concentration in children and women of childbearing age. It would also be worthwhile to monitor the uptake of iodine supplementation to evaluate the effectiveness of the public health message and UIC changes in people taking supplements. Any adverse effects of supplementation on pregnancy or the neonate should be monitored.

In addition, further research is warranted to determine the optimal dose of iodine supplementation across mild, moderate and severe deficiency states taking into account the effect of pre-conception nutrition. The bioavailability of iodine from multinutrient preparations and efficacy in terms of long term clinical outcomes also warrant further research (Zimmerman and Delange 2004). These studies should ideally be RCTs with sufficient sample sizes.

The impact of breast milk iodine concentration on neonatal TSH levels and infant development is currently poorly understood (Chan et al 2003). These relationships should be investigated as breast milk iodine levels found in Australia (Chan et al 2003) and New Zealand (Skeaff et al 2005) fell far below the Adequate Intake of 90µg/d for children age 0-6 months recommended by the NHMRC and New Zealand Ministry of Health (NHMRC & NZMoH, 2006) prior to mandatory fortification.

Further research into the cognitive effects of iodine deficiency and supplementation using a similar model to Gordon et al (2009) with a larger sample and follow up would be useful to determine if cognitive changes persist after cessation of supplementation.

## **6. Conclusions**

Iodine requirements increase substantially in pregnancy and lactation to support the neuropsychological development of the foetus. Mandatory fortification of bread is estimated to increase population intakes by an average of 46µg/day (FSANZ, 2008). This will meet the needs of most of the population including women who are not pregnant. Although it will also increase intakes in pregnant and lactating women, a higher increase would be desirable.

There is good evidence of the safety and efficacy of iodine supplementation in pregnant and lactating women. The risks of iodine deficiency significantly outweigh any potential risks during the perinatal period. The median UIC found in Australia indicates mild iodine deficiency in the children (Li et al 2006) who are used as an indicator for status in the general population, and mild to moderate iodine deficiency in pregnant and lactating women. On this basis, iodine supplementation seems to be an appropriate solution in the Australian context.

Optimal iodine intake supported by adequate monitoring has been widely shown to improve the quality of various health aspects. The benefits of iodine supplementation far outweigh the relatively small risks of iodine excess (ICCIDD 2009).

## PART D: REFERENCES

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## APPENDIX A: EVIDENCE SUMMARY – EXPERIMENTAL STUDIES

Reference	Study Design (country)*	Population	Intervention (Iodine ug/day)	Outcomes		Recommendation
				Baseline value	Post-supplement value	
<b>Zimmerman and Delange 2004</b>	Review of Randomised Controlled Trials (Europe)					In all studies maternal UIC increased significantly. No clear dose-response relationship was found for UIC, TSH, Tg, TV or thyroid hormones.
Romano et al 1991	Level II Evidence	35 pregnant women from first trimester	120-128µ/d	37µg/L	100µg/L	Iodine supplementation is efficacious for the mother and newborn.
Pederson et al 1993		54 pregnant women from 17 weeks	200µg/d	55µg/L	90-110µg/L	Supplements appear to be generally safe- no increase in maternal thyroid autoimmunity or in prevalence or severity of post partum thyroid dysfunction.
Glioner et al 1995		120 pregnant women from 14 weeks	100µg/d	36µg/L	80-90 µg/L	Recommends that pregnant women and women planning a pregnancy should take supplements of 150µg/day.
Liesenkotter et al 1996		108 pregnant women from 11 weeks	230µg/d	53µg/g cr	104µg/g cr	Prenatal supplement manufacturers should be encouraged to include adequate iodine in their products.
Nohr et al 2000		66 pregnant women from 11 weeks	150µg/d	50µg/L	105µg/L	
Antonangeli et al 2002	Open label, randomisation method not described	67 pregnant women from 18 weeks	50µg/d 200µg/d	65µg/g cr (19µg/L) 18-26 weeks 91µg/g cr (38.2µg/L) 29-33 weeks	128µg/g cr (65.4µg/L) 230µg/g cr (140.5µg/L)	

<b>Gordon et al 2009</b>	Randomised Controlled Trial ( New Zealand)  Level II Evidence	166 children (10-13 years old)	150µg/d  Placebo  For 28 weeks	UIC 66µg/L Tg 16.5µg/L  UIC 62µg/L Tg 15.2µg/L	UIC 145µg/L Tg 8.5µg/L  UIC 81µg/L Tg 11.6µg/L	Significant increase in UIC (p<0.001) and reduction in Tg (p<0.001).  Significant improvement in performance on two of four tests of cognitive function: treatment effect- picture concepts, 0.81 (p<0.023), matrix reasoning 0.63 (p<0.040). Non significant treatment effects for symbol search, 0.16 (p<0.608) and letter-number sequencing, 0.18 (p<0.480).
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\* Study Design and levels of evidence are assessed using NHMRC criteria (NHMRC 2000)

## APPENDIX B: EVIDENCE SUMMARY – COMPARATIVE STUDIES

The majority of the comparative studies summarised below aimed to investigate the iodine status of the sample population. On the basis of iodine status, and taking into account WHO/UNICEF/ICCIDD recommendations, many authors make recommendations for further monitoring or intervention such as iodine fortification or supplementation to improve iodine status of the population.

Reference	Study Design (country)	Population	Measures	Outcomes
<b>Burgess et al 2007</b>	Pre and post intervention, cross-sectional (Australia)	285 pregnant women  517 pregnant women	UIC  (2000/01- before fortification)  (2003/06- after fortification).	Iodine deficiency persists in pregnant women despite being corrected in Tasmanian children. Bread alone has been an ineffective vector for correcting iodine nutrition in pregnancy.  The American Thyroid Association has recommended a 150µg/d supplement for pregnant and lactating women to prevent gestational ID. The UIC found in Australia is half of the USA level.
<b>Chan et al 2003</b> Small sample size	Cross-sectional (Australia) Convenience sample	50 postpartum women (3-9 days) and neonates	UIC BI TSH	Moderate to severe ID found in 58% of the population group. Median BI 84µg/L, neonates would be consuming 51.8µg/d. 6% neonates TSH >5mIU/L. TSH values were positively correlated with higher BI, no association was found with UIC. Median (range) iodine concentration in 12 infant formulas was 101 (35-147) µg/L.
<b>Guttikonda et al 2003</b>	Cross-sectional (Australia) Convenience sample	324 children: 180 boys, 144 girls (70% of total school)	UIC TV BSA	3% and of girls and 2% of boys had TV above WHO/UNICEF/ICCIDD criteria by median age. 1% of boys and girls had TV above WHO/UNICEF/ICCIDD criteria by BSA.  TV - Median 82mg/L indicating mild ID. Similar to findings in Sydney and Melbourne studies (70mg/L)
<b>Hamrosi et al 2005</b>	Cross-sectional (Australia)	802 pregnant women: 263 Vietnamese 262 Indian/ Sri Lankan 277 Caucasian	UIC	Median UIC Vietnamese 58µg/L, Indian/ Sri Lankan 61µg/L, Caucasian 52µg/L Proportion of UIC <50µg/L: Vietnamese 38.4%, Indian/ Sri Lankan 40.8%, Caucasian 48.4%  Figures indicate a mild ID for each group. The Association of ethnicity is likely the result of differing dietary patterns.

Reference	Study Design (country)	Population	Measures	Outcomes
<b>Li et al 2006</b>	Cross-sectional (Australia) Representative of mainland states	1709 children (8-10 year olds: 881 boys, 828 girls) from 88 schools across NSW, VIC, SA, WA, QLD	UIC TV BSA	Nationally, children are borderline ID- UIC 104µg/L SA are borderline ID 101µg/L (47.5% <100µg/L) NSW and VIC are mildly ID 89µg/L (58% <100µg/L) and 73.5µg/L (72.6% <100µg/L) QLD and WA are iodine sufficient 136.5µg/L and 142.5µg/L respectively  With the exception of VIC, children had larger thyroid glands than in iodine sufficient children when compared with WHO/ICCIDD international reference values, adjusted by BSA or age. No significant association between UIC and TV.
<b>Seal et al 2007</b>	Pre-Post-intervention, cross-sectional (Australia)	347 children - 2003 430 children - 2004 401 children - 2005. Children were 8-11 years old	UIC	Modest but significant improvement in UIC (90-109g/L increase) since fortification (consistent with predictions from modelling). Iodine nutrition in Tasmanian children is considered to be optimal.
<b>Skeaff et al 2005</b> BI sample very small	Cross-sectional (New Zealand)	Sample for each city is proportional to the cities population. 217 Christchurch, 66 Dunedin, 40 Invercargill 6-24 month old children and there breastfeeding mothers	UIC (n=230) BI (n=39) Dietary patterns	Mild ID – Maternal UIC 67µg/L (37% <50µg/L) Formula fed infants - UIC 99µg/L (13.7% <50µg/L) BI 22µg/L (11.7% <20µg/L, 51.2% <50µg/L, 67.4% <100µg/L) Children who consumed formula, fortified with iodine had a better iodine status than children who were breast fed because breast milk contained low levels of iodine.
<b>Travers et al 2006</b>	Cross-sectional (Australia)  Convenience sample	815 pregnant women ≥28 weeks gestation 824 neonates	UIC TSH	Median UIC 85µg/L - mild ID (16.6% <50µg/L) 2.2% of newborns had TSH levels >5mIU/L No statistically significant correlation between neonatal TSH level and maternal UIC. Maternal UIC significantly higher for women who gave birth in private hospital (51.2% >100µg/L) compared to public hospital (36.6% >100µg/L). Median for both groups was still well below the optimal iodine nutrition during pregnancy.

## **APPENDIX C: ACRONYMS AND ABBREVIATIONS**

UIC: Urinary Iodine Concentration

BI: Breast Milk Iodine Concentration

TV: Thyroid Volume

BSA: Body Surface Area

USI: Universal Salt Iodisation

ID: Iodine Deficient

TSH: Thyroid Stimulating Hormone

T3: Triiodothyronine

T4: Thyroxine

Tg: Thyroglobulin

FT3: Free Triiodothyronine

FT4: Free Thyroxine

RDI: Recommended Dietary Intake

AI: Adequate Intake

EAR: Estimated Average Requirement

UL: Upper Level of Intake

NRVs: Nutrient Reference Values for Australia and New Zealand

NINS: National Iodine Nutrition Study (Australia)

NHANES: National Health and Nutrition Examination Survey (USA)

COAG: Council of Australian Governments

AHMAC: Australian Health Ministers' Advisory Council

ANZFRMC: Australian and New Zealand Food Regulation Ministerial Council

FSANZ: Food Standards Australia New Zealand

NHMRC: National Health and Medical Research Council

UN: United Nations

WHO: World Health Organization

UNICEF: United Nations International Children's Emergency Fund

ICCIDD: International Council for the Control of Iodine Deficiency Disorders