

Australian and New Zealand Nutrient Reference Values for Iodine

A report prepared for the Australian Government

Department of Health

By

Expert Working Group for Iodine

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May 2015

| | | |
|------------|--|-----------|
| 1 | EXECUTIVE SUMMARY | 4 |
| 2 | SUMMARY OF RECOMMENDATIONS..... | 7 |
| 3 | INTRODUCTION | 8 |
| 3.1 | BACKGROUND TO DEVELOPMENT OF THE NUTRIENT REFERENCE VALUES..... | 8 |
| 3.2 | NUTRIENT REFERENCE VALUES | 9 |
| 3.2.1 | TERMINOLOGY | 9 |
| 3.3 | NUTRIENT BACKGROUND INFORMATION | 10 |
| 3.3.1 | IODINE | 10 |
| 3.3.2 | IODINE STATUS IN AUSTRALIA AND NEW ZEALAND..... | 11 |
| 3.4 | CURRENT RECOMMENDED INTAKES OF IODINE | 13 |
| 4 | SCOPE AND PURPOSE | 15 |
| 5 | EVIDENCE REVIEW | 16 |
| 5.1 | SELECTION OF BIOMARKERS | 16 |
| 5.1.1 | URINARY IODINE | 16 |
| 5.1.2 | THYROID STATUS | 17 |
| 5.1.3 | RADIOACTIVE IODINE..... | 18 |
| 5.1.4 | BRAIN FUNCTION | 18 |
| 5.2 | SELECTION OF EVIDENCE AND DATA | 19 |
| 5.2.1 | DEFINING THE QUESTION..... | 19 |
| 5.2.2 | ADULTS..... | 23 |
| 5.2.3 | PREGNANCY..... | 24 |
| 5.2.4 | CHILDREN | 26 |
| 5.3 | REVIEW OF EVIDENCE | 27 |
| 5.3.1 | ASSESSMENT OF THE QUALITY OF EVIDENCE..... | 27 |
| 5.3.2 | EVIDENCE CONSIDERED IN ESTIMATING THE EAR AND RDI FOR ADULTS | 28 |
| 5.3.3 | EVIDENCE CONSIDERED IN ESTIMATING THE EAR AND RDI FOR PREGNANT WOMEN..... | 29 |
| 5.3.4 | EVIDENCE CONSIDERED IN ESTIMATING THE UL FOR CHILDREN AND ADOLESCENTS AGES 1 THROUGH 18 YEARS..... | 31 |
| 6 | GUIDELINE RECOMMENDATIONS..... | 35 |
| 6.1 | PROPOSED RECOMMENDATIONS..... | 35 |
| 6.2 | VALIDITY | 37 |
| 6.2.1 | UL FOR CHILDREN | 37 |
| 6.3 | IMPLICATIONS AND ONGOING CHALLENGES | 37 |

| | | |
|------------|--|------------|
| 6.3.1 | IMPLICATIONS OF CHANGES TO THE UL FOR CHILDREN..... | 37 |
| 6.3.2 | ONGOING CHALLENGE OF MEETING PREGNANCY AND LACTATION RDI | 38 |
| 6.3.3 | INTERNATIONAL CONSISTENCY..... | 38 |
| 6.3.4 | PRIORITIES FOR REMAINING QUESTIONS..... | 38 |
| 6.3.5 | RESEARCH REQUIRED TO INFORM NRVs | 39 |
| 7 | APPENDICES..... | 41 |
| 7.1 | STUDIES RELATING TO EAR FOR ADULTS | 42 |
| 7.2 | STUDIES RELATING TO EAR FOR PREGNANCY | 56 |
| 7.3 | STUDIES RELATING TO UL FOR CHILDREN | 92 |
| 7.4 | MEMBERSHIP OF GROUPS AND COMMITTEES INVOLVED IN THE DEVELOPMENT PROCESS | 111 |
| 7.4.1 | MEMBERSHIP OF THE NUTRIENT REFERENCE VALUES STEERING GROUP..... | 111 |
| 7.4.2 | MEMBERSHIP OF THE NUTRIENT REFERENCE VALUES ADVISORY COMMITTEE | 111 |
| 7.4.3 | MEMBERSHIP OF THE NUTRIENT REFERENCE VALUES IODINE EXPERT WORKING GROUP..... | 111 |
| 8 | ABBREVIATIONS AND GLOSSARY | 113 |
| 8.1 | ABBREVIATIONS | 113 |
| 8.2 | GLOSSARY..... | 114 |
| 9 | REFERENCES..... | 117 |

1 Executive Summary

The Nutrient Reference Values (NRVs) are a set of recommended nutrient intakes used to assess dietary requirements of individuals and population groups. The current NRVs for Australia and New Zealand were published in 2006 (NHMRC 2006) after a comprehensive review process of the Recommended Dietary Intakes commissioned by the Australian Government Department of Health (Aus DoH) and the New Zealand Ministry of Health (NZ MoH). The National Health and Medical Research Council (NHMRC) who carried out the review recommended that these be reviewed every five years. In 2011 Aus DoH, in consultation with the NZ MoH, commissioned a scoping study for undertaking a review of the NRVs, which resulted in the development of a Methodological Framework for the review by Nous and a consortium of experts (Nous Group 2013). The purpose of the present review is to test this framework on three nutrients, sodium, fluoride, and iodine; the focus of this report is iodine.

Iodine is an essential nutrient for all mammals as an integral component of the pro-hormone thyroxine (T_4) and the more potent active form 3,5,3' tri-iodothyronine (T_3), a key regulator of important cellular processes. Iodine deficiency results in a wide range of disorders, collectively termed 'iodine deficiency disorders' (IDD), including goitre, hypothyroidism, impairment of mental and physical development, and cretinism.

In New Zealand and Australia, endemic goitre in the early part of the 20th century was due to very low levels of iodine in the soils. Iodisation of salt, assisted by iodine contamination of dairy products through the use of iodophors as cleaning agents in the dairy industry, resulted in a reduction of goitre incidence and adequate iodine status from the 1960s to 1980s. A re-emergence of mild iodine deficiency in New Zealand and Australia was observed in the 1990s that coincided with a reduction in the use of iodophors and in the use of iodised salt. A new public policy on food fortification was developed to correct iodine deficiency, and mandatory fortification of bread with iodised salt in both Australia (October 2009) and New Zealand (September 2009) was implemented. Iodine status has increased in both countries as a result of fortification.

The Methodological Framework set out a number of steps to be followed in the process of the review including:

1. Define the question: The Expert Working Group (EWG) for iodine established a number of questions for the review of iodine NRVs. Since the purpose of the review was primarily to test the methodological framework and the timeframe was limited, the EWG chose to review the following NRVs only:

- Estimated Average Requirement (EAR) Recommended Dietary Intake (RDI) for healthy adults.
- EAR and RDI for healthy pregnant women.
- Upper Levels of Intake (UL) for children.

2. Selection of biomarkers: Biomarkers included urinary iodine concentration (UIC), thyroid function (thyroid volume, thyroid hormones, thyroid stimulating hormone (TSH), thyroglobulin (Tg), radioactive iodine uptake), and brain function (development and cognition).

3. Selection of evidence: The NRVs for iodine were last reviewed by Thomson in 2002 (Thomson, 2003) (later incorporated into the 2006 NRVs (NHMRC 2006). Therefore this report only includes original studies published since 2002. International reviews and other expert group reports were also considered.

4. Assessing the quality of evidence: Evidence was assessed according to the guidelines of the NHMRC (2009) and the body of evidence given a grade of recommendation.

5. Derivation of the NRV recommendations:

EAR and RDI for healthy adults: The EWG concluded that the most recent studies on iodine status and thyroid function in adults (i.e., published between 2002-2014) did not present any new evidence and that the current EAR (100 µg/day) and RDI (150 µg/day) should remain unchanged.

Table 1:1 Recommended EAR and RDI for iodine for adults 19 years and older.

| Men and Women | EAR | RDI |
|---------------|------------|------------|
| 19-30 years | 100 µg/day | 150 µg/day |
| 31-50 years | 100 µg/day | 150 µg/day |
| 51-70 years | 100 µg/day | 150 µg/day |
| > 70 years | 100 µg/day | 150 µg/day |

EAR and RDI of healthy pregnant women: Studies relevant to cognitive outcomes in children, and maternal and infant biochemical indices that could be used to set or modify the EAR or RDI in pregnancy were considered. However, the EWG concluded that there was insufficient new evidence to change the EAR and RDI set in 2006, and proposes to keep the current EAR (160 µg/day) and RDI (220 µg/day) for pregnant women.

Table 1:2 Recommended EAR and RDI for pregnant women

| Category | Microgram (µg) per day |
|----------|------------------------|
| EAR | 160 µg/day |
| RDI | 220 µg/day |

UL for children aged 1-3, 4-8, 9-13, 14-18 years: In view of very limited suitable data to define a dietary intake that corresponds to an adverse effect in thyroid function, the EWG chose to establish a series of Provisional Upper Levels of Intake in children. One study provided a sound basis to determine a threshold dose for an increase in thyroid volume in response to excess dietary iodine (Zimmermann et al 2005). Data in children aged between 6 and 12 years were used to establish a provisional UL for the age group 9-13 years and those for the other age groups were extrapolated from this value using the metabolic weight formula specified in the Methodological Framework (Nous Group 2013) and used for the NRVs 2006 (NHMRC 2006).

Table 1:3 Recommended Provisional UL for children 1-18 years

| Children | Provisional UL |
|-------------|----------------|
| 1-3 years | 250 µg/day |
| 4-8 years | 350 µg/day |
| 9-13 years | 550 µg/day |
| 14-18 years | - |
| Male | 800 µg/day |
| Females | 700 µg/day |

The EWG strongly recommends that future work needs to consider the remaining research questions generated, with the next priorities being: EAR and RDI for children, EAR and RDI for lactation, and UL for pregnancy and lactation.

2 Summary of Recommendations

Iodine is an essential nutrient as part of thyroid hormones, which are required for normal growth and metabolism. These hormones are important during early growth and development, in particular in the brain where they are essential for normal development of cognitive function. Iodine deficiency results in a wide range of disorders (coined iodine deficiency disorders or IDD), including goitre, hypothyroidism and impairment of mental and physical development.

This guideline includes the review of the EAR and RDI for adults and pregnant women and the UL for children and adolescents aged 1 to 18 years.

The Iodine Expert Working Group (EWG) concluded that the most recent studies on iodine status and thyroid function in adults (ie published between 2002-2014) did not present any new evidence and that the current EAR (100 µg/day) and RDI (150µg/day) should remain unchanged from that set in 2006.

For the EAR and RDI of pregnant women, the EWG considered studies of cognitive outcomes in children as well as maternal and infant biochemical indices. The EWG again concluded that there was insufficient new evidence to change the EAR and RDI set in 2006 and proposed to keep the current EAR (160µg/day) and RDI (220 µg/day).

For the UL for children and adolescents, only one study was found that provided evidence of an adverse effect as a result of excess intake of iodine. This study was used to calculate a Provisional UL for children and 1-3 years (250 g/day), 4-8 years (350 µg/day), 9-13 years 550 µg/day), 14-18 years (male, 800 µg/day; female, 700 µg/day).

The EWG strongly recommended that the other NRVs should be reviewed, with priority given to EAR and RDI for children, EAR and RDI for lactation and ULs for pregnancy and lactation.

3 Introduction

3.1 Background to Development of the Nutrient Reference Values

Nutrient Reference Values (NRVs) are a set of recommended nutrient intakes designed to assist nutrition and health professionals assess the dietary requirements of individuals and groups. Public health nutritionists, food legislators and the food industry also use the NRVs for dietary modelling and/or food labelling and food formulation.

The current NRVs for Australia and New Zealand were published in 2006 after a comprehensive review process of the Recommended Dietary Intakes (the only type of nutrient reference value that had been produced at the time), commissioned by the Australian Government Department of Health (DoH) in conjunction with the New Zealand Ministry of Health (NZ MoH).

The review resulted in a new set of recommendations known as the Nutrient Reference Values (NRVs) for Australia and New Zealand (2006). The National Health and Medical Research Council (NHMRC) carried out the 2006 review and recommended that these guidelines be reviewed every five years to ensure values remain relevant, appropriate and useful.

In 2011 Aus DOH, in consultation with the NZ MoH, commissioned a scoping study to determine the need and scope for a review of NRVs. The scoping study considered developments in comparable countries, expert opinions, stakeholder consultation and public submissions. The scoping study concluded there was sufficient justification for conducting a review and as a result, Aus DoH and the NZ MoH engaged the Nous Group and a technical team led by Baker IDI to develop a Methodological Framework to guide future NRV reviews.

A Steering Group is overseeing the review process and is responsible for all strategic, funding and technical decisions of the review. It consists of representatives from both funding agencies, Aus DoH and the NZ MoH. The Steering Group is also responsible for the ongoing monitoring of triggers for a new review, and ensuring nutrient reviews are conducted in a timely manner. Reviews are being conducted on a rolling basis to ensure NRVs remain relevant and appropriate. The process complies with the *2011 NHMRC Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines*. The scoping study also identified the rationale and triggers for reviewing specific nutrients including changes or developments to NRVs in comparable OECD countries, emergence of new evidence, impact on public health priorities and/or concerns regarding the strength of the underlying methodology or evidence. Iodine was identified as a priority nutrient for review.

The Steering Group has appointed an Advisory Committee as an expert reference and advisory group that also acts as an independent moderator of nutrient recommendations. The Advisory Committee comprises members with a broad range

of expertise, including experts in the areas of micronutrients, toxicology, public health, end user needs, research, chronic disease, nutrition and macronutrients.

The Steering Group (with the advice of the Advisory Committee), established a group of experts to conduct this iodine review. The Expert Working Group (EWG) was primarily responsible for examining scientific evidence and establishing nutrient values. Membership of the groups involved in the development of the NRV guidelines can be found in [Appendix 7.4](#).

3.2 Nutrient Reference Values

3.2.1 Terminology

The suite of NRVs outlined in the 2006 document (NHMRC 2006), adapted from the US/Canadian Dietary Reference Intakes (DRI), were considered to remain applicable for this NRV review with no change of name to the reference indicators, which are defined as follows (NHMRC 2006, Nous Group 2013).

EAR Estimated Average Requirement

A daily nutrient level estimated to meet the requirements of half the healthy individuals in a particular life stage and gender group.

RDI Recommended Dietary Intake

The daily intake level that is sufficient to meet the requirements of nearly all (97-98%) healthy individuals in a particular life stage and gender group.

AI Adequate Intake

The average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate.

EER Estimated Energy Requirement

The average dietary energy intake that is predicted to maintain energy balance in a healthy adult of defined age, gender, weight, height and level of physical activity, consistent with good health. In children and pregnant and lactating women, the EER is taken to include the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health.

UL Upper Level of Intake

The highest level of 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 effect increases.

AMDR Acceptable Macronutrient Distribution Range

An estimate of the range of intake for each macronutrient for individuals (expressed as per cent contribution to energy), which would allow for an adequate intake of all the other nutrients whilst maximising general health outcome.

SDT Suggested Dietary Target

A daily average intake from food and beverages for certain nutrients that will help in prevention of chronic disease.

3.3 Nutrient Background Information

3.3.1 Iodine

Iodine is an essential nutrient for all mammals as an integral component of the pro-hormone thyroxine (T_4) and the more potent active form 3,5,3' tri-iodothyronine (T_3), a key regulator of important cellular processes. The thyroid hormones are required for normal growth and metabolism and are particularly important during early growth, development and maturation of most organs. The developing brain is a key target organ of the thyroid hormones, which therefore play an essential role in the development of neurological and cognitive function. The thyroid hormones are also important for energy production and oxygen consumption in cells, thereby maintaining the body's metabolic rate (Zimmerman 2009).

Iodine deficiency, resulting from inadequate intakes and consequently altered thyroid function, results in a wide range of disorders, collectively termed 'iodine deficiency disorders' (IDD). These have been well documented in a number of excellent reviews (Zimmerman 2009, WHO/UNICEF/ICCIDD 2007, Hetzel 1983, Zimmerman et al 2008) and will be described briefly here. The most damaging effect of iodine deficiency is during pregnancy when the fetal brain is developing and can result in adverse effects such as neurological cretinism with severe intellectual impairment, deafness, spastic paresis of the limbs and other psychomotor disorders. Iodine deficiency during neonatal life, in children and adults can lead to goitre and hypothyroidism as well as impairment of mental and physical development. While endemic goitre is the most visible consequence of IDD, the most significant and profound effects are on the brain. Impaired intellectual development of people living in iodine deficient areas is of particular concern, especially when all of the adverse effects of iodine deficiency can be prevented by long-term, sustainable iodine prophylaxis.

In New Zealand and Australia endemic goitre in the early part of the 20th century was due to very low levels of iodine in the soils. Iodisation of salt, assisted by iodine contamination of dairy products through the use of iodophors as cleaning agents in the dairy industry, resulted in a reduction of goitre incidence and reports of adequate iodine status from the 1960s to 1980s. A re-emergence of mild iodine deficiency in New Zealand was observed in the 1990s which coincided with replacement of iodophors used in the dairy industry with chlorine-based and organic sanitizers (Thomson 2004). A similar situation pertains to Australia where iodine deficiency was also recognized in the 1990s and later documented nationally in school children in the 2003-2004 National Iodine Nutrition Study (NINS) (Li et al 2006). These observations became the main driver for the development of new public policy on food fortification to correct iodine deficiency in Australia and New Zealand. As a result, the mandatory fortification of bread with iodised salt in both

Australia (October 2009) and New Zealand (September 2009) was fully implemented with the intention of correcting iodine deficiency in the population.

On the other hand, the effects of high iodine intake on thyroid function are variable depending chiefly on the magnitude of the excessive iodine intake and on the response of people with underlying thyroid disease, particularly autoimmune thyroid disease (Teng et al 2006, Prummel et al 2004). Adverse effects of high intakes include both hyperthyroidism and hypothyroidism, with or without goitre, and an increased incidence of autoimmune thyroid disease (Thomson 2003).

3.3.2 Iodine status in Australia and New Zealand

Information on dietary intakes of iodine in Australia and New Zealand is limited because of inadequate food composition data, and because of the difficulty in quantifying the use and intake of iodised salt at the table and in cooking. Iodine intake can be estimated from urinary iodine excretion as the majority of intake (approximately 90%) of dietary iodine is excreted in urine (Anderson et al 2009).

The most comprehensive and recent data on iodine status of Australians is provided by the 2011-12 Australian National Health Survey (NHS) (Australian Bureau of Statistics 2013), obtained after the mandatory fortification of bread with iodised salt in October 2009. These results show that Australian adults had a population median urinary iodine concentration (UIC) of 124 µg/L, ranging from 113 to 144 µg/L across the states and territories, with 12.8% of the population having a UIC of less than 50µg/L. These values are well within the range of iodine sufficiency (ie UIC >100 µg/L and no more than 20% of the population with UIC below 50 µg/L) (WHO/UNICEF/ICCIDD 2007). There are a lack of national data examining the iodine status of pregnant women. A pre-post comparison of surveys conducted in a regional area of New South Wales indicates that mandatory fortification has improved the overall median UIC of pregnant women but that non-users of iodine-containing supplements remain at risk of inadequacy (Charlton & Eastman 2013).

Comparison between the 2003-04 NINS of school children 8-10 years in five Australian states prior to mandatory fortification (which showed that these children as a group were mildly iodine deficient) and the 2011-12 NHS after fortification, shows that the median UIC of 8-10 year old children has significantly increased in each of these states as indicated in Table 3.1. Children generally had a higher median UIC than adults: those 5-11 years had the highest median UIC (177 µg/L), followed by those aged 12-17 years (149 µg/L).

Table 3:1 Comparison of UIC in adults pre-fortification and post-fortification

| Location | Pre-fortification | Post-fortification |
|------------------|-------------------|--------------------|
| Australia | | |
| Adults | ~89-110 µg/L | 113-144 µg/L |
| Pregnant Women | ~74-110 µg/L | 163 µg/L |

| Location | Pre-fortification | Post-fortification |
|--------------------|-------------------|--------------------|
| New Zealand | | |
| Adults | 53 µg/L | 73 µg/L |
| Pregnant Women | 35/47 µg/L | 105/85 µg/L |

A time series analysis of cross-sectional urinary iodine surveys of Tasmanian school-aged children shows a progressive and stepwise improvement in iodine status from pre-fortification (median UIC 73 µg/L; 16.9%<50 µg/L), through a period of state-wide voluntary iodine fortification of bread from 2001 to 2009 (median UIC 108 µg/L; 9.6%<50 µg/L), and following mandatory iodine fortification of bread in 2009 (median UIC 129 µg/L; 3.4%<50 µg/L) (DePaoli et al 2013).

National data for New Zealand are not as recent and come from the New Zealand Adult Nutrition Survey 2008/09 (ANS) and the New Zealand National Children's Nutrition Survey 2002 (CNS), both of which were carried out before implementation of mandatory fortification of bread with iodised salt had any impact on iodine status (University of Otago & NZ Ministry of Health 2011, Ministry of Health 2003).

In the ANS, the median UIC of New Zealanders aged ≥15 years was 53 µg/L (males 55 µg/L; females 50 µg/L) falling within 50-99 µg/L indicating mild iodine deficiency (University of Otago & NZ Ministry of Health 2011). Of note was the high proportion of adults (47%) with UIC <50 µg/L. In 2012, a study to determine if the mandatory fortification of bread had improved iodine status chose a representative sample of 300 adults aged 18-74 years living in Wellington and Dunedin using 24-hour urine samples (Ministry for Primary Industries 2013). The median UIC was 73 µg/L, still falling in the mild iodine deficiency range, but significantly higher than that reported in the 2008/09 ANS (University of Otago & NZ Ministry of Health 2011), showing that there has been an increase in iodine status probably as a result of mandatory fortification. Mean 24-hour urinary excretion, which is a better estimate of daily iodine intake, was 124 µg/L (males 147 µg/L, females 104 µg/L), which falls above the current Estimated Average Requirement (EAR) of 100 µg/day (NHMRC 2006). In a small study in Palmerston North of pregnant and lactating women before mandatory fortification in 2009 (n=25 and 32) and after fortification in 2011 (n=34 and 36), median UIC in 24-hour urine samples was higher in 2011 compared with 2009 in pregnant (85 and 47 µg/L) and breastfeeding (74 and 34 µg/L) women (Brough et al 2013).

In the 2002 CNS, the median UIC of 1153 New Zealand schoolchildren 5-14 years was 68 µg/L indicating mild iodine deficiency, and 29% of children had UIC <50 µg/L. In 2010-2011, a study to assess the impact of iodine fortification on 147 children aged 8-10 years found a median UIC of 113 µg/L and 12 % of children had a UIC <50 µg/L (Skeaff & Lonsdale-Cooper 2013). These results indicated adequate iodine status suggesting that fortification of bread has had a significant effect on iodine status of New Zealand children. The discrepancy between the current iodine status of the Australian and New Zealand populations two to three years following

implementation of the same level of iodine fortification in both countries is likely to be a result of a number of different factors including the lower soil iodine content in New Zealand soil and differences between the two countries in farming practices and bread manufacturing.

3.4 Current Recommended Intakes of Iodine

The current Australian and New Zealand recommendations for iodine are an EAR of 100 µg/day and an RDI of 150 µg/day, and for pregnancy an EAR of 160 µg/day and RDI of 220 µg/day (NHMRC 2006). The recommended intakes of iodine for adults and pregnant and lactating women in various countries are summarised in Table 3:2; most recommendations are for an EAR of 100 µg/day and RDI or equivalent of 150 µg/day. There is more variation in the recommended intakes (RDI or equivalent) for pregnancy and lactation.

Table 3:2 Overview of RDI for iodine

| | NHMRC 2006 | | FNB/IOM 2001 | | WHO Secretariat et al 2007 | | EFSA 2014 | |
|-----------|-------------------|------------|---------------------|------------|-----------------------------------|------------|------------------|------------|
| Children | 0-6 mo | 90 µg/day | 0-6 mo | 90 µg/day | | | 7-11 mo | 70 µg/day |
| | 7-12 mo | 110 µg/day | 7-12 mo | 110 µg/day | | | 1-3 years | 90 µg/day |
| | 1-3 years | 90 µg/day | 1-3 years | 90 µg/day | 0-11 mo | 90 µg/day | 4-6 years | 90 µg/day |
| | 4-8 years | 90 µg/day | 4-8 years | 90 µg/day | 1-5 years | 90 µg/day | 7-10 years | 90 µg/day |
| | 9-13 years | 120 µg/day | 9-13 years | 120 µg/day | 6-12 years | 120 µg/day | 11-14 years | 120 µg/day |
| | 14-18 years | 150 µg/day | 14-18 years | 150 µg/day | >13 years | 150 µg/day | 15-17 years | 130 µg/day |
| Adults | 150 µg/day | | 150 µg/day | | 150 µg/day | | 150 µg/day | |
| Pregnancy | 220 µg/day | | 220 µg/day | | 250 µg/day | | 200 µg/day | |
| Lactation | 270 µg/day | | 290 µg/day | | 250 µg/day | | 200 µg/day | |

4 Scope and Purpose

The Australia and New Zealand NRVs for Iodine were last reviewed by Thomson in 2002 (Thomson 2003) (and later incorporated into the Nutrient Reference Values for Australia and New Zealand (NHMRC 2006)). Therefore this review focuses on whether there is any new evidence since 2002 that might change the 2006 NRVs.

It is important that NRVs are reviewed and updated regularly to reflect new research and knowledge of the nutrients. The purpose of this review was primarily to test the methodological framework and iodine was one of three nutrients chosen for this pilot. Iodine is of particular interest for Australia and New Zealand as, in response to the re-emergence of mild iodine deficiency in the two countries, mandatory fortification of bread with iodised salt was introduced in Australia (October 2009) and New Zealand (September 2009).

As the timeframe for the review was limited, this guideline includes the review of the EAR and RDI for adults and pregnant women and the UL for children and adolescents aged 1 to 18 years only. The NRVs for these groups were evaluated as follows:

- Estimated Average Requirement (EAR) and Recommended Dietary Intake (RDI) for healthy adults for the maintenance of normal thyroid function, as measured by thyroid hormones and thyroid volume.
- EAR and RDI for healthy pregnant women to maintain normal thyroid function, as measured by maternal thyroid function and neurodevelopment in their children.
- Upper Levels of Intake (UL) for children aged 1-18 years above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels.

The iodine EWG strongly recommends that future work needs to consider the remaining NRVs for iodine, with the next priorities being: EAR and RDI for children, EAR and RDI for lactation and ULs for pregnancy and lactation.

5 Evidence Review

5.1 Selection of Biomarkers

There are a number of biomarkers that can be used to assess iodine status including urinary iodine concentration (UIC), thyroid function [thyroid volume, thyroid hormones, serum Thyroid Stimulating Hormone (TSH), serum thyroglobulin (Tg), thyroidal radioactive iodine uptake], and brain function (development and cognition). Such data are typically collected in both observational and intervention studies.

5.1.1 Urinary Iodine

Approximately 90% of dietary iodine is excreted in the urine (Andersen et al 2009; Zimmermann 2009), thus the most commonly used biomarker of iodine status is urinary iodine concentration (UIC). Because UIC has high intra- and inter-individual variation (König et al 2011), UIC should not be used to assess iodine status in individuals. WHO/UNICEF/ICCIDD state that a median UIC $<100 \mu\text{g/L}$ in groups of school aged children and non-pregnant adults and $<150 \mu\text{g/L}$ in groups of pregnant women including lactating mothers indicate iodine deficiency in that population (WHO/UNICEF/ICCIDD 2007). Table 5.1 outlines the recommended cut-offs for UIC including ranges used to categorise the severity of iodine deficiency as well as iodine excess. Casual or spot urine samples are typically obtained from subjects although UIC can also be determined in 24-hour samples, but the higher respondent burden associated with such samples limits their practical use in many studies. One advantage of 24-hour urine samples is that they are able to provide an objective estimate of daily iodine intake (Zimmermann 2009). WHO/UNICEF/ICCIDD recommendations are based on UIC in spot samples; caution should be used when interpreting data obtained from 24-hour samples as urine volumes greater than 1.0 L, found in New Zealand adults (Ministry for Primary Industries 2013) may lower UIC resulting in an overestimation of iodine deficiency.

Table 5:1 Recommended cut-offs for urinary iodine concentration (UIC)

| Population Group | UIC µg/L | Iodine Status |
|--|----------|---------------------|
| Children Non-pregnant adults Lactating women | <25 | Severe Deficiency |
| As listed in the first row | 25-49 | Moderate Deficiency |
| As listed in the first row | 50-99 | Mild Deficiency |
| As listed in the first row | 100-299 | Sufficiency |
| As listed in the first row | >300 | Excess |
| As listed in the first row | <150 | Deficiency |
| Pregnant Women | 150-250 | Sufficiency |
| | >250 | Excess |

(WHO/UNICEF/ICCIDD 2007)

5.1.2 *Thyroid Status*

An adequate intake of iodine is needed to maintain normal thyroid function. The thyroid gland undergoes a number of adaptive changes when iodine intake falls, which ensures that a continual supply of thyroid hormones, in particular T₃, is available for normal growth and development. A fall in T₄ stimulates the production of TSH, which subsequently causes an enlargement in the thyroid gland, increased uptake of iodine from the blood, increased synthesis of Tg, and a shift in the ratio of T₄ to T₃ (preferential T₃ secretion) released into the blood.

An increase in thyroid volume or goitre is a classic sign of iodine deficiency. Goitre can be measured by palpation by trained physicians and graded according to criteria of WHO/UNICEF/ICCIDD. This manual and highly labour intensive skill is now replaced by thyroid technique, which produces consistent and reproducible results with normal reference ranges published for school-aged children (Zimmerman et al 2000). The presence of goitre in >5% of the population indicates iodine deficiency (WHO/UNICEF/ICCIDD 2007).

TSH, T₄, and T₃, although readily and routinely measured in many populations, are insensitive indices of iodine status except in severe iodine deficiency and in newborns. Elevated neonatal TSH (i.e. >5 IU/mL) in >3% of newborns indicates iodine deficiency, however, despite routine assessment of neonatal TSH measurement in most countries for diagnosis of congenital hypothyroidism, its use in assessing iodine status in populations is not generally recommended because of

many unresolved technical issues in the application of this technology Li & Eastman 2010). In older children and adults, in milder forms of iodine deficiency the body maintains these hormones within normal reference ranges, leading WHO/UNICEF/ICCIDD to state that these blood parameters should not be used to assess iodine status (WHO/UNICEF/ICCIDD 2007).

The secretion of Tg from the thyroid gland increases in iodine deficiency and has been positively correlated with thyroid volume. The use of Tg as an index of iodine status is relatively new with the primary focus on school-aged children. Over the last six to seven years Zimmermann and colleagues have published a number of large studies of children living in a number of different countries, with varying degrees of iodine deficiency as assessed by UIC (Zimmerman et al 2013). These studies have determined the normal reference range for Tg as well as recently proposing that a median Tg >13 µg/L indicates iodine deficiency in this age group (Zimmerman et al 2013). However, the usefulness of Tg in assessing iodine status in non-pregnant adults and pregnant women has yet to be confirmed. It should be emphasised that measurement of changes in serum Tg response to changing iodine intake is simply an index of adaptation by the thyroid but does not necessarily indicate thyroid dysfunction.

5.1.3 Radioactive Iodine

The uptake of radioactive ^{131}I is used as a test of thyroid function in clinical settings (Gibson 2005). This involves determining the fraction of an orally administered dose of ^{131}I that is concentrated in the thyroid gland; in iodine deficiency, a larger proportion of the radioactive iodine will be rapidly taken up by the thyroid gland compared with when the thyroid is replete with iodine. Due to radiation exposure, and its imprecision as a function of insufficient iodine intake, this method of determining iodine deficiency is no longer used. However, ^{131}I was used in the 1960s in a handful of iodine balance studies.

5.1.4 Brain Function

The adverse effects of iodine deficiency on brain development and function are well accepted; neurological cretinism, characterised by classical neurological abnormalities and profound mental impairment, is only observed in regions with severe iodine deficiency. Over the last decade, a growing interest and appreciation that the relationship between iodine deficiency and brain function may be a continuum has resulted in an increasing number of studies attempting to assess the association between maternal iodine status and brain development. The measures used in such studies to assess brain function, however, vary widely depending on the age of the subjects but also in what aspect of brain function they measure. For example, some studies include tests of development (eg Bayley's Infant Scales of Development, Brunet-Lezine) cognition (IQ measured by Weschler Intelligence Scale for Children, Stanford-Binet) and school achievement (eg reading ability). Data obtained from many of these studies using diverse testing methods in several different countries are well summarised in the online text "thyroidmanager.org" (Eastman & Zimmerman, 2014).

5.2 Selection of evidence and data

5.2.1 Defining the question

A series of research questions for consideration as part of this review of the iodine NRVs was generated and are presented in Table 5.2. Given that the purpose of the review was primarily to test the methodological framework and that the timeframe for the review was limited, the EWG prioritised the following questions:

Question 1. EAR and RDI for adults: What is the average intake required by healthy adults in a population to maintain normal thyroid function, as measured by thyroid hormones and thyroid volume? This question was prioritised because the adult EAR and RDI form the basis from which NRVs for other population groups, such as pregnant women, are derived.

Question 3 EAR and RDI for pregnant women: What is the average intake required by healthy pregnant women in a population to maintain normal thyroid function as measured by maternal thyroid function and neurodevelopment in their children? This question was of highest priority as there is current concern about the iodine status of pregnant women in Australia and New Zealand (NHMRC 2010) as more studies suggest that inadequate iodine intakes in pregnancy may negatively affect neurodevelopment in offspring.

Questions 10-13 UL for young children aged 1-3 years, 4-8 years, 9-13 years, 14-18 years: What is the average intake of normal healthy children [aged 1-3, 4-8; 9-13, 14-18 years] above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels? These questions are particularly relevant to the current mandatory fortification of bread, as the 2006 UL was a limiting factor in achieving a higher level of iodine fortification in the food supply (FSANZ 2007; FSANZ 2008). In addition, the previous UL were determined from extrapolation from the adult UL because of lack of research on adverse effects of high iodine intake in children. UL in all age groups for children were considered. The UL for infants (0-1 years) was judged not determinable at this stage because there are insufficient data on adverse effects.

The EWG recommend that the remaining questions (see Table 5:2) require consideration in the future as part of the overall review of iodine.

Table 5:2 Questions for the review of the iodine NRVs

| | Population | Question | Outcome |
|---|-----------------|---|--|
| 1 | Adults | What is the average intake required by healthy adults in a population to maintain normal thyroid function, as measured by thyroid hormones and thyroid volume? | <ul style="list-style-type: none"> • thyroid volume • thyroid hormone levels |
| 2 | Adults | What is the average intake of healthy adults above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels? | <ul style="list-style-type: none"> • increased thyroid volume • abnormal thyroid hormone levels |
| 3 | Pregnant women | What is the average intake required by healthy pregnant women in a population to maintain normal thyroid function as measured by maternal thyroid hormones and thyroid volume and neurodevelopment in their children? | <ul style="list-style-type: none"> • maternal thyroid volume • maternal thyroid hormone levels • neurodevelopment in their children |
| 4 | Pregnant women | What is the average intake of healthy pregnant women above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels? | <ul style="list-style-type: none"> • increased thyroid volume • abnormal thyroid hormone levels |
| 5 | Lactating women | What is the average intake required by healthy lactating women in a population to maintain normal thyroid function as measured by maternal thyroid function, thyroid function in the infants, neurodevelopment in their children? | <ul style="list-style-type: none"> • adequate iodine content of breast milk • maternal thyroid volume • maternal thyroid hormone levels • infant thyroid hormone levels • infant neurodevelopment |
| 6 | Lactating women | What is the average intake of healthy lactating women above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels in mothers and infants? | <ul style="list-style-type: none"> • increased thyroid volume • abnormal thyroid hormone levels in mothers • abnormal thyroid hormone levels |

| | Population | Question | Outcome |
|----|--|--|--|
| | | | in infants |
| 7 | Infants (0-1 years) | What is the average intake required by healthy infants(0-1years) in a population to maintain normal thyroid function, as measured by thyroid hormones and thyroid volume? | <ul style="list-style-type: none"> thyroid volume thyroid hormone levels neurodevelopment |
| 8 | Infants (0-1 years) | What is the average intake of normal healthy infants aged 0-1 years above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels? | <ul style="list-style-type: none"> increased thyroid volume abnormal thyroid hormone levels |
| 9 | Children (1-3; 4-8; 9-13; 14-18 years) | What is the average intake required by healthy children (1-3; 4-8; 9-13; 14-18 years) in a population to maintain normal thyroid function, as measured by thyroid hormones and thyroid volume? | <ul style="list-style-type: none"> thyroid volume thyroid hormone levels neurodevelopment |
| 10 | Children (1-3 years) | What is the average intake of normal healthy children aged 1-3 years above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels? | <ul style="list-style-type: none"> increased thyroid volume abnormal thyroid hormone levels |
| 11 | Children (4-8 years) | What is the average intake of normal healthy children aged 4-8 years above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels? | <ul style="list-style-type: none"> increased thyroid volume abnormal thyroid hormone levels |
| 12 | Children (9-13 years) | What is the average intake of normal healthy children aged 9-13 years above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels? | <ul style="list-style-type: none"> increased thyroid volume abnormal thyroid hormone levels |

| | Population | Question | Outcome |
|----|------------------------|---|---|
| 13 | Children (14-18 years) | What is the average intake of normal healthy children aged 14-18 years above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels? | <ul style="list-style-type: none"> • increased thyroid volume • abnormal thyroid hormone levels |

5.2.2 Adults

As the iodine NRVs for children and pregnant women are extrapolated from the values derived for adults, the first aim of the EWG was to confirm that no new evidence had been published since 2002 to suggest that the current EAR and RDI for adults should be revised. There are few data on the dietary intake of iodine, therefore recommended iodine intakes for adults are based predominantly on iodine excretion.

Review Question 1:

What is the average intake required by healthy adults in a population to maintain normal thyroid function, as measured by thyroid hormones and thyroid volume?

Review Question 1 reframed in PICO format:

Population: Adults 19 years and older

Intervention: Iodine intake from all sources

Comparator: None

Outcome: Thyroid function as measured by thyroid hormones and thyroid volume

5.2.2.1 Search Strategy and Identification of Trials

The search strategy was developed with the assistance of the Science Faculty Librarian at the University of Otago. The same search strategy was used for all questions.

In December 2013 The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to December 2013), PubMed (1966 to December 2013), and Web of Science (1899–the week of 01 Dec 2013) were searched for relevant articles; the same databases and search strategy was used in November 2014 to identify any papers published between December 2013 and November 2014. This was complemented by other relevant material, and contacts with experts. Trials were restricted to English-language citations only. The search was restricted to human studies and studies published after the earlier NRV reports (2001 onwards). Articles were rejected on initial screening if the reviewer could determine from the title and abstract that the study was not a relevant study, or if the study did not meet our selection criteria. When a paper could not be rejected with certainty from the title and abstract, the full text of the article was obtained for further evaluation. The terms used to search for relevant studies are listed in Table 5:3.

Table 5:3 Search terms used to identify studies for relating the Iodine EAR and RDI for Adults

| Search terms | |
|--------------|---------------|
| 1. | Adult* |
| 2. | normal human* |
| 3. | (1) AND (2) |

| Search terms | |
|--------------|--|
| 4. | iodine deficien* |
| 5. | iodine status* |
| 6. | urinary iodine concentration |
| 7. | UIC* |
| 8. | iodine* |
| 9. | iodide* |
| 10. | iodate* |
| 11. | iodized salt* |
| 12. | iodized oil* |
| 13. | (4) OR (5) OR (6) OR (7) OR (8) OR (9) OR (10) OR (11) OR (12) |
| 14. | thyroid funct* |
| 15. | T3* |
| 16. | T4* |
| 17. | TSH* |
| 18. | Goitre |
| 19. | (14) OR (15) OR (16) OR (17) OR (18) |
| 20. | (3) AND (13) AND (19) |

5.2.2.2 Search results:

At the conclusion of the search, 19 studies were identified as being relevant to iodine status in healthy adults (see Table 7:1 in [Appendix 1](#) for details of individual studies). In addition two reports from international experts committees were considered by the EWG in the current report (EFSA, 2014; Gunnarsdottir & Dahl 2012).

5.2.2.3 Data extraction, (selection and coding)

Three members of the research team (SC, ZFM, CS) independently reviewed titles and abstracts of the identified studies. The data extraction tables were used to extract the relevant data fields from each included study by a research assistant.

5.2.3 Pregnancy

The EWG examined the most recent (i.e., since 2002) evidence for iodine status during pregnancy. Effects of iodine status during pregnancy (as measured from UIC) were examined in relation to: maternal biochemical outcomes (e.g. thyroid function); and infant/childhood cognition. The specific question executed in the search strategy was:

Review Question 3:

What is the average intake required by healthy pregnant women in a population to maintain normal thyroid function as measured by maternal thyroid hormones and thyroid volume and neurodevelopment in their children?

Review Question 3 reframed in PICO format:

| | |
|---------------|--|
| Population: | Pregnant women |
| Intervention: | Iodine intake from all sources |
| Comparator: | None |
| Outcome: | Normal thyroid function as measured by maternal thyroid hormones, maternal thyroid volume, and neurodevelopment in the child |

5.2.3.1 Search Strategy and Identification of Trials

[Refer to section 5.2.2.1](#)

Table 5:4 Search terms used to identify studies relating to EAR and RDI for pregnant women

| Search Terms | |
|--------------|--|
| 1. | Pregnan* |
| 2. | iodine deficien* |
| 3. | iodine status* |
| 4. | urinary iodine concentration |
| 5. | UIC* |
| 6. | iodine* |
| 7. | iodide* |
| 8. | iodate* |
| 9. | iodized salt* |
| 10. | iodized oil* |
| 11. | (2) OR (3) OR (4) OR (5) OR (6) OR (7) OR (8) OR (9) OR (10) |
| 12. | thyroid funct* |
| 13. | T3* |
| 14. | T4* |
| 15. | TSH* |
| 16. | (12) OR (13) OR (15) |
| 17. | (1) AND (11) AND (16) |

5.2.3.2 Search results:

At the completion of the search, 23 relevant original studies were identified. (see Tables A2.2 and A2.3 in Appendix 2 for details of individual studies). One meta-analysis and one systematic review studies were also included. No Cochrane Reviews were identified. In addition, two reports from international expert committees were considered by the EWG (EFSA 2014; Gunnarsdottir & Dahl 2012).

The EWG considered that the very recent systematic review assessing the effect of iodine supplementation during pregnancy on maternal iodine status and thyroid function by Zhou et al (2013) was of high quality because it only included randomised controlled trials (RCTs). After an extensive search no additional RCTs were found. Therefore, the supplementary table and data produced by Zhou et al (Zhou et al 2013) were used to inform the EWG.

5.2.3.3 Data abstraction

The research assistant used data extraction tables to extract the relevant data fields from each observational study.

5.2.4 Children

The EWG identified that the current UL for young children (1-3 years; 200 µg/day) was one of the limiting factors in achieving a higher level of fortification. Therefore the group investigated the most recent evidence that has examined iodine intake in young children in excess of the current UL compared to iodine intakes below and the effects on health outcomes (poorer cognition, abnormal thyroid function).

Review Questions 10-13:

What is the average intake of normal healthy children (1-3 years; 4-8 years; 9-13 years; 14-18 years) above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels?

Review Questions 10-13 reframed in PICO format:

Population: Children aged 1-18 years

Intervention: Iodine intake from all sources

Comparator: None

Outcomes: Adverse effects on thyroid function indicated by increased thyroid volume and abnormal thyroid hormone levels

5.2.4.1 Search Strategy and Identification of Trials

[Refer to section 5.2.2.1](#)

Table 5:5 Search terms used to identify studies relating to UL for children

| Search terms | |
|--------------|-------------------------------|
| 1. | children |
| 2. | adolescent* |
| 3. | infant* |
| 4. | (1) AND (2) AND (3) |
| 5. | 4 not premature* not pregnan* |
| 6. | iodine deficien* |
| 7. | iodine status* |
| 8. | urinary iodine concentration |
| 9. | UIC* |
| 10. | iodine* |
| 11. | iodide* |
| 12. | iodate* |
| 13. | iodized salt* |

| Search terms | |
|--------------|--|
| 14. | iodized oil* |
| 15. | (6) OR (7) OR (8) OR (9) OR (10) OR (11) OR (12) OR (13) OR (14) |
| 16. | 15 not zinc |
| 17. | thyroid funct* |
| 18. | T3* |
| 19. | T4* |
| 20. | TSH* |
| 21. | Goitre |
| 22. | Physical grow* |
| 23. | Cognitive disorder* |
| 24. | Behavioral disorder* |
| 25. | (15) OR (16) OR (17) OR (18) OR (19) OR (20) OR (21) OR (22) OR (23) OR (24) |
| 26. | 25 not cancer* not mutation* not thyroiditis* not carcinoma not hashimoto* |
| 27. | (5) AND (16) AND (26) |

5.2.4.2 Search results:

At the completion of the search, 13 original studies were identified as being relevant to the upper level of iodine status in children (see Table 7:12 in [Appendix 3](#) for details of individual studies). One systematic review/meta-analysis was also found. In addition, two reports from international expert committees were considered by the EWG (EFSA 2014; Gunnarsdottir & Dahl 2012).

5.3 Review of Evidence

5.3.1 Assessment of the quality of evidence

Evidence was assessed according to the NHMRC (NHMRC 2009). Studies were graded individually by one member of the EWG using the NHMRC (2009) criteria (NHMRC 2009). The quality rating of level of evidence for each study is presented in the final column of the data abstraction tables (Appendix Tables A1-A3). The overall assessment and critique of the body of evidence for each NRV evaluated in this report was first assessed according to the NHMRC approach (NHMRC 2009) (Table 5.6); Body of Evidence (BOE) statement tables summarising the studies relevant to each review question can be found in the Appendices. (Tables A1.1, A2.1, A3.2-A3.5). Studies that were deemed of sufficient quality to be used to revise the NRV were evaluated using GRADE (Table 7:6).

The components assessed in the quality rating process were:

1. The **evidence base**, in terms of the number of studies, level of evidence and quality of studies (risk of bias).
2. The **consistency** of the study results.

3. The potential **clinical impact** of the proposed recommendation.
4. The **generalisability** of the body of evidence to the target population for the guideline.
5. The **applicability** of the body of evidence to the Australian and New Zealand healthcare context.

Table 5:6 Definition of NHMRC grades of recommendations

| Grade of recommendation | Description |
|-------------------------|--|
| A | Body of evidence can be trusted to guide evidence |
| B | Body of evidence can be trusted to guide evidence in most situations |
| C | Body of evidence provides some support for recommendation(s) but care should be taken in its application |
| D | Body of evidence is weak and recommendation must be applied with caution |

5.3.2 Evidence considered in estimating the EAR and RDI for Adults

5.3.2.1 Previous recommended intake levels for Australia and New Zealand.

In the 2003 report (Thomson 2003) later adopted into the Nutrient Reference Values for Australia and New Zealand (NHMRC 2006), Thomson derived an EAR for adults based on iodine balance studies (Vought & London 1964, Vought & London 1967, Hays et al 2001, Jahreis et al 2001) in accordance with the FMB:IOM (Food and Nutrition Board 2001). The balance studies indicated that iodine balance is achieved at intakes over 100 µg/day but not below 40 µg/day. In addition, Thomson considered a relevant New Zealand study in adults relating urinary iodide to thyroid volume that indicated physiological requirements of 85–100 µg/day (Thomson et al 2001). Therefore, these studies pointed to a value of 100 µg/day, which was adopted as the proposed EAR. The RDI was set assuming a CV of 20% for the EAR (Food and Nutrition Board 2001), and rounded up to reflect the possible influence of natural goitrogens, which gave an RDI of 150 µg/day. Although there is no scientific evidence to show that goitrogens in foods exert an effect on iodine requirements in a Western diet, goitrogens are found in foods commonly eaten in Australasia (i.e. cruciferous vegetables), thus an assumption of a small effect is not unreasonable.

5.3.2.2 Additional evidence published since 2002 and considered in this report

Original studies:

A total of 18 studies published between 2002-2014 were identified, of which two were level II, two were level III-2, one level III-3 and 13 level IV. The EWG agreed that these studies did not provide evidence to change the current EAR (100 µg/day) and RDI (150 µg/day) (Table 7:1 in [Appendix 1](#)).

International Reviews and other expert groups:

The EWG notes that the recent systematic review by Gunnarsdottir and Dahl (Gunnarsdottir & Dahl 2012) and the Scientific Opinion on Dietary Reference Values for iodine produced by the European Food Safety Authority (EFSA 2014) supports the EWG's conclusion that there is no new evidence to inform the EAR and RDI.

The RDI is determined from the EAR plus two SDs, or for iodine, two times the CV of 20% (i.e. $RDI = EAR + (2 \times 20\%EAR)$) (Food and Nutrition Board 2001). The CV for iodine was calculated to be 20% in accordance with the 2003 report (Thomson 2003), which was guided by the US/Canadian DRIs (Food and Nutrition Board 2001). This CV was based on data from Fisher and Oddie (Fisher & Oddie 1969) who calculated from their data on thyroid radio-iodine turnover studies a CV of 40% (Fisher & Oddie 1969), part of which was due to the complexity of the experimental design and calculations used to estimate turnover. Assuming that half of the variation was due to experimental design, a CV of 20% was chosen by Food and Nutrition Board (2001).

The RDI has been rounded to the nearest 50 µg to reflect possible influence of natural goitrogens, giving 150 µg/day for males and females. From the data available, there is no indication that iodine requirement differs by sex.

5.3.3 Evidence considered in estimating the EAR and RDI for pregnant women

5.3.3.1 Previous recommended intake levels for NZ and Australia

The recommendation in 2006 considered several indicators for deriving the iodine requirement for pregnancy (Thomson 2003, NHMRC 2006). These included: 1) the additional requirements of iodine needed during pregnancy due to the hormonal changes and metabolic demands of pregnancy (Glinioer 2001); 2) the impaired cognitive outcomes in infants from mothers with impaired thyroid function (Glinioer & Delange 2000, Morreale de Escobar et al 2000, Henrichs et al 2013, Pop et al 1999); 3) the thyroid iodine content of the newborn (Delange 1993); 4) iodine balance studies (Delange et al 1984); and 5) iodine supplementation during pregnancy (Dworkin et al 1966, Glinioer 1998, Pedersen et al 1993). Taken together, this body of evidence led to the establishment of an EAR of 160 µg /day and - with the addition of twice the CV - an RDI of 220 µg /day (NHMRC 2006).

5.3.3.2 Factorial approach

The factorial approach considers the main factors driving iodine requirements. The highest demand for iodine comes from the thyroid, for which it uses iodine to produce hormones maintaining the euthyroid state and to ensure an adequate level of iodine is stored in the thyroid. Added to this are basal losses from urine, faeces

and sweat. In pregnancy there are additional demands for iodine, which include: 1) the total amount of iodine deposited in the placenta (18–100 µg); 2) amniotic fluid (15 µg); 3) fetal thyroid (100–300 µg); and 4) fetal blood (10 µg) (EFSA 2014). However, these contributions to the fetus are small compared with the daily maternal requirements and the fetal thyroid does not produce significant quantities of thyroid hormone until the third trimester. The EWG agreed that a revision of evidence used to inform values for the factorial approach was warranted. In particular, an examination of the evidence for increased iodine requirements due to losses in urine because of changes in the glomerular filtration rate (GFR) in pregnancy (Krutzen et al 1992) is needed. It is possible that increased iodine clearance does occur in some but not all pregnant women and this should be accommodated in recommendations for iodine intake in pregnant women. An additional 10 µg/day has been included to account for increased GFR in pregnancy.

The main additional requirement during pregnancy results from the increased (~50%) synthesis of thyroid hormones by the mother, corresponding to a need for additional iodine capture by the thyroid of 25 µg/day. The equation of Fisher and Oddie (Fisher & Oddie 1969) derived in non-pregnant euthyroid adults has been used in pregnant women to suggest that an extra 25 µg/day can be accumulated in the thyroid by an additional iodine intake of 44 µg/day (EFSA 2014). The iodine needed for synthesis of thyroid hormones in the fetus is estimated to be around 2–4 µg/day (Evans et al 1967). With the additional 10 µg/day for GFR this leads to a total additional iodine intake in pregnancy rounded to 60 µg/day.

5.3.3.3 Effect on maternal thyroid function

One Level I study with low risk of bias (this included eight supplementation randomised controlled trials (RCT) with two trials conducted in women living in an area of severe iodine deficiency and six trials in women living in areas of moderate to mild iodine deficiency), 10 Level III-2 (cohort) studies, and 19 Level IV studies suggests that despite low UIC observed in some populations thyroid hormone production remains normal in pregnancy. The use of pregnancy-appropriate reference values (i.e. TSH of >2.5 mIU/L in first trimester and > 3.0 mIU/L in trimesters 2 and 3) was not always considered. No obvious dose-response relation was seen. The effect of iodine supplementation on changes in thyroid hormone concentrations in mothers and infants was not consistent (Zhou et al 2013). WHO/UNICEF/ICCIDD do not recommend the use of TSH or thyroid hormones (T3 and T4) to routinely assess iodine status, particularly in populations of moderate to mild iodine deficiency, because these are not sensitive indicators of iodine status (WHO/UNICEF/ICCIDD 2007). Neonatal TSH from a heelprick blood sample could be used as an index of maternal iodine status but was not considered in this report.

5.3.3.4 Effect on infant neurodevelopmental in their children

One meta-analysis of studies published between 1980-2011 in children aged 5 years or younger found that iodine deficient children had 6.9-10.2 IQ points less than iodine replete children (Bougma et al 2013). However, of the 24 studies included in this meta-analysis, only two were Level II (RCT), eight Level III-1, and 13 Level III-2

studies. Two more recent Level II studies found no differences in child neurological development associated with iodine supplementation.

Seven Level III-2 birth cohort studies were largely non-comparable due to the differing iodine status of the samples of pregnant women, both within and between countries. In many cases, supplementation strategies were introduced in the geographical areas under study, but not at the same time during the study follow-up period, thus making measurement of exposure to supplementation unclear. The lack of consistency across studies regarding the use of instruments to measure infant development and cognitive functioning in young children poses additional difficulties in assessing the body of evidence. The most commonly used instruments in young children are Bayley Scales of Infant Development and whereas in school-aged children (8–9 years), Intelligence Quotient (IQ) is measured, as well as literacy and numeracy skills. Various measures of maternal thyroid function were used across studies. Most studies obtained one first trimester urine sample for the determination of UIC, a measure that is known to have high day-to-day variability, and is unlikely to be a true reflection of habitual iodine status for the duration of pregnancy. It is likely that future studies addressing the impact of iodine intake and thyroid function in pregnancy on neurocognitive development of children will include maternal measures of serum T₄ levels, since virtually all the free T₄ available to embryonic and fetal tissues, particularly the brain, comes from maternal serum during the first half of pregnancy and well into the last trimester.

The EWG concludes that there was insufficient evidence with regard to maternal (Table 7:4) and infant biochemical indices (Table 7:4), or cognitive outcomes in children (Table 7:11 in [Appendix 2](#)) that could be used to set or modify the EAR or RDI in pregnancy. Therefore the EWG found no new evidence that challenges the EAR and RDI set in 2006 and proposes to keep the current EAR and RDI for pregnancy. The two recent reviews from Europe (Gunnarsdottir & Dahl 2012, EFSA 2014) also support the EWG's conclusion that there is no new evidence for iodine requirements and pregnancy. However, the EWG notes that in 2007 a WHO Secretariat increased the recommended intake of iodine in pregnancy to 250 µg/day (Delange et al 2007) although they also acknowledge a lack of data in this area.

5.3.4 Evidence considered in estimating the UL for Children and Adolescents ages 1 through 18 years

5.3.4.1 Previous recommended UL for Australia and New Zealand

In the 2003 report by Thomson, the ULs for children and adolescents were extrapolated from the adult UL on the basis of metabolic weight [(bodyweight)^{0.75}]. The adult UL was derived from the Lowest-Observed-Adverse-Effect level (LOAEL) of 1700 µg/day and an uncertainty factor of 1.5, giving a UL of 1,100 µg/day for adults greater than 19 years of age. This adult value was adjusted for children on the basis of body weight, but no UL was established for infants because of lack of evidence (Thomson 2003, NHMRC 2006).

5.3.4.2 *Observational evidence*

A total of 18 observational studies were identified (Table 7:11 in [Appendix 3](#)). The study by Zimmermann et al (2005) presented a dose response relationship with UIC and thyroid volume. This was an observational study of an international sample of children aged 6–12-years ($n = 3319$) from 5 continents with iodine excretion ranging from adequate ($116 \mu\text{g/L}$) to excessive ($728 \mu\text{g/L}$). In the combined sample, after adjustment for age, sex, and body surface area, log (thyroid volume) began to rise at a log (UI concentration) >2.7 , which, when back transformed to the linear scale, corresponds to a UIC of $\sim 500 \mu\text{g/L}$. The EWG noted that other thyroid function markers collected in this study were in the normal range, even at high levels of iodine intake. In addition the EWG considered the 2013 study also by Zimmerman et al (2013), which was similarly conducted in an international sample of 6-12 year old children. The results indicated that compared to iodine-sufficient children, those with iodine deficiency (UIC $<100 \mu\text{g/L}$) had a higher prevalence of elevated Tg values as did those with iodine excess (UIC $>300 \mu\text{g/L}$).

Most of the studies combined the age group 6–12 years which is problematic for assessing the evidence for setting of ULs for the following NRV age categories: 4–8 years, 9–12 years, 13-18 years. For the 14– 18 years age groups, evidence was particularly sparse, with only three Level IV (cross sectional) studies with high risk of bias, two of which were conducted in refugee camps in Africa where iodine excess was related to very high iodine levels in tap water. The other study from Brazil had similar limited generalisability to the Australian and New Zealand situation.

The previous ULs set for these age groups were calculated by extrapolation from the adult UL. No direct experimental evidence was available then and little new evidence has emerged since.

5.3.4.3 *Intervention studies*

Two intervention studies (one Level II (RCT) and a Level III-2 study) were identified in the search for the UL in children (Huda et al 2001, Li et al 2012). However, due to the high risk of bias associated with these intervention studies, the EWG agreed these studies would not be used to set the UL in children.

5.3.4.4 *Derivation of the Provisional UL*

There are few studies that investigate the effects of excess dietary iodine in children for the purpose of establishing a UL. In view of the limited amount of suitable data to define a dietary intake, which corresponds to an adverse effect in thyroid function the EWG decided to establish a series of provisional upper levels of intake in children aged between 1 and 18 years.

The Committee identified one study by Zimmermann et al (2005), which could provide a sound basis to determine a threshold dose for an increase in thyroid volume in response to excess dietary iodine; this paper was evaluated using GRADE (Table 3.1). The EWG noted that an increase in thyroid volume could be considered to be an adaptation in response to high dietary iodine intake. In the absence of other indicators of thyroid dysfunction an increase in thyroid volume is not necessarily an

adverse effect. It is possible, given this, that the UL could be set higher.

Uncertainty factor: As this study which established a threshold dose between an enlarged thyroid gland and dietary iodine involved many children (n=3319) aged between 6 and 12 years across five continents, confidence that a daily iodine exposure resulting in a urinary excretion of 500 µg I/L will result in an enlarged thyroid gland in children is high. Accordingly, an uncertainty factor of 1 was considered appropriate because the data includes a sensitive endpoint in the most vulnerable subpopulation in humans.

The study by Zimmerman et al (2005) in children aged between 6 and 12 years was used to establish a provisional UL for the age group 9-13 years. Provisional ULs for the other age groups were extrapolated from this value using the metabolic weight formula as for the NRVs (NHMRC 2006). The daily median iodine intake was estimated by converting the UIC of 500 µg/L from the Zimmermann et al (2005) study. This was converted to 550 µg/day based on iodine excretion of 90% of dietary intake (Anderson et al 2009) and an assumed 24-hour urine volume for children of approximately 1 L (Mattson & Lindstrom 1995). These considerations result in a Provisional UL for children 9-13 years of 550 µg/day.

The formulae for extrapolating to other age groups were those specified in the Methodological Framework (Nous group 2013) and used for the NRVs 2006 (NHMRC 2006). The formula for 1-3 year age group included an adjustment for the difference in growth rate between 9-13 years (0.15) and 1-3 year olds (0.3) (NHMRC 2006). This was not a necessary consideration in calculating provisional UL for the other age groups because the growth factors for 4-8 and 14-18 year olds are the same as that for 9-13 year olds.

The approximate proportional increase in protein requirements for growth (FAO/WHO/UNU 1985) was used as an estimate of the growth factor (Table 5:7).

Table 5:7 Estimated growth factor by age group

| Age group | Growth factor |
|-------------------|---------------|
| 7 mo – 3 years | 0.30 |
| 4-8 years | 0.15 |
| 9-13 years | 0.15 |
| 14-18 years males | 0.15 |

FAO/WHO/UNU 1985

The reference body weights for children 4 years and older used in the calculation were those generated from data from the 2011-12 Australian Health Survey and ideal BMI for children; the most recent US reference body weight data were used for infants and children aged 1-3 years as no suitable Australian and New Zealand data were available for these age groups.

Table 5:8 'Ideal' body weights for selected age and sex groups

| Gender | Age | 'Ideal' Body Weight (kg) |
|----------|-------------|--------------------------|
| Children | 2-3 years | 12 |
| | 4-8 years | 22 |
| Males | 9-13 years | 39 |
| | 14-18 years | 63 |
| | 19+ years | 67 |
| Females | 9-13 years | 40 |
| | 14-18 years | 57 |
| | 19+ years | 57 |

Thus the Provisional UL (PUL) for the 2-3 year, 4-8 year, 14-18 year age groups are as follows (calculated to the nearest 10µg):

$$\begin{aligned}
 \text{PUL}_{1-3} &= \text{PUL}_{9-13} * (\text{weight}_{1-3} / \text{weight}_{9-13})^{0.75} * (1+0.15) \\
 &= (550 * (12/39)^{0.75} * 1.15) \text{ µg/day} \\
 &= \mathbf{260 \text{ µg/day}}
 \end{aligned}$$

NB This calculation is based on 'Ideal' body weight for 1-3 year old children.

$$\begin{aligned}
 \text{PUL}_{4-8} &= \text{PUL}_{9-13} * (\text{weight}_{4-8} / \text{weight}_{9-13})^{0.75} \\
 &= (550 * (22/39)^{0.75}) \text{ µg/day} \\
 &= \mathbf{360 \text{ µg/day}}
 \end{aligned}$$

$$\text{PUL}_{9-13} = \mathbf{550 \text{ µg/day}}$$

$$\begin{aligned}
 \text{PUL}_{14-18 \text{ males}} &= \text{PUL}_{9-13} * (\text{weight}_{14-18} / \text{weight}_{9-13})^{0.75} \\
 &= (550 * (63/39)^{0.75}) \text{ µg/day} \\
 &= \mathbf{790 \text{ µg/day}}
 \end{aligned}$$

$$\begin{aligned}
 \text{PUL}_{14-18 \text{ females}} &= \text{PUL}_{9-13} * (\text{weight}_{14-18} / \text{weight}_{9-13})^{0.75} \\
 &= (550 * (57/40)^{0.75}) \text{ µg/day} \\
 &= \mathbf{720 \text{ µg/day}}
 \end{aligned}$$

NB. It should be noted that this value for females 14-18 years applies only to those who are neither pregnant nor lactating.

6 Guideline Recommendations

The Iodine Expert Working Group (EWG) concluded that the most recent studies on iodine status and thyroid function in adults (ie published between 2002-2014) did not present any new evidence and that the current EAR (100 µg/day) and RDI (150µg/day) should remain unchanged from that set in 2006 (Table 6:1; Table 6:2). Similarly there was no new evidence to change the EAR (160 µg/day) and RDI (220 µg/day) for pregnant women (Table 6:3). On the other hand the EWG recommends changes to the ULs for children, based on one study which provided a sound basis to determine a threshold dose for an increase in thyroid volume in response to excess dietary iodine (Zimmermann et al 2005). However, in view of the limited data, the EWG recommends that these be renamed Provisional ULs (Table 6:4). These are compared with the current ULs in

Table 6:5.

6.1 Proposed recommendations

Table 6:1 Recommended iodine EAR for adults aged 19 years and older

| Gender groups/age | Measurement of iodine (µg/day) |
|----------------------|--------------------------------|
| EAR for Men | |
| 19-30 years | 100 µg/day of iodine |
| 31-50 years | 100 µg/day of iodine |
| 51-70 years | 100 µg/day of iodine |
| > 70 years | 100 µg/day of iodine |
| EAR for Women | |
| 19-30 years | 100 µg/day of iodine |
| 31-50 years | 100 µg/day of iodine |
| 51-70 years | 100 µg/day of iodine |
| > 70 years | 100 µg/day of iodine |

Table 6:2 Recommended Iodine RDI for adults aged 19 years and older

| RDI for Men | |
|----------------------|----------------------|
| 19-30 years | 150 µg/day of iodine |
| 31-50 years | 150 µg/day of iodine |
| 51-70 years | 150 µg/day of iodine |
| > 70 years | 150 µg/day of iodine |
| RDI for Women | |
| 19-30 years | 150 µg/day of iodine |
| 31-50 years | 150 µg/day of iodine |
| 51-70 years | 150 µg/day of iodine |
| > 70 years | 150 µg/day of iodine |

Table 6:3 Recommended EAR and RDI for pregnant women

| Pregnancy | Measurement of iodine (µg/day) |
|--------------------------|---------------------------------------|
| EAR for Pregnancy | 160 µg/day of iodine |
| RDI for Pregnancy | 220 µg/day of iodine |

Table 6:4 Recommended Provisional UL of intake for children

| Children | Provisional UL |
|-------------------------------|--------------------------|
| 1-3 years | 250 µg/day |
| 4-8 years | 350 µg/day |
| 9-13 years | 550 µg/day |
| 14-18 years Male Female | 800 µg/day 700 µg/day |

Table 6:5 Comparison of 2006 ULs with recommended Provisional ULs for children

| Children | 2006 UL | Provisional UL |
|-------------|------------|------------------|
| 1-3 years | 200 µg/day | 260 (250) µg/day |
| 4-8 years | 300 µg/day | 360 (350) µg/day |
| 9-13 years | 600 µg/day | 550 (550) µg/day |
| 14-18 years | | |
| Male | 900 µg/day | 790 (800) µg/day |
| Female | 900 µg/day | 720 (700) µg/day |

6.2 Validity

6.2.1 UL for children

In the previous review of the NRVs, ULs for children were extrapolated from relatively small (n=30 adults) dose response studies (NHMRC 2006), while in this review an attempt was made to derive the ULs from studies on children. As iodine requirements are influenced by stages of growth, deriving NRVs for children from studies of children is more likely to better reflect nutrient requirements than extrapolating from adults. In determining the UL for children, heavy reliance was placed on evidence from one study by Zimmermann et al (2005). For this reason we chose to set Provisional ULs instead of ULs. However, the study in question included data for over 3000 children aged 6-12 years from across five continents. These data were used to estimate a provisional UL for children aged 9-13 years and ULs for the other 1-3, 4-8 and 14-18 years age groups were extrapolated using metabolic weight.

6.3 Implications and ongoing challenges

6.3.1 Implications of changes to the UL for children

It is not anticipated that the recommended changes to the UL for children will have any significant implications for policy in Australia and New Zealand. During the consideration of mandatory fortification with iodine for Australia and New Zealand in 2008, comprehensive dietary modelling was undertaken. This modelling showed that fortification of bread with iodised salt would result in iodine intakes that would exceed the UL in 6% of children aged 2-3 years (FSANZ 2008). Whilst an increase in the UL for this age group from 200 to 300 µg is likely to reduce the proportion of 2-3 year olds who would exceed the UL, the magnitude of increase is unlikely to justify extending fortification of the Australian and New Zealand food supply.

6.3.2 Ongoing challenge of meeting pregnancy and lactation RDI

In 2010 the NHMRC and New Zealand MOH recommended that pregnant and lactating women require an iodine supplement of 150 µg/day, in addition to their dietary intake, to meet the requirements for pregnancy and lactation. This was in recognition that the mandatory iodine fortification of bread program, introduced in 2009, was designed to meet the needs of the general population but was insufficient to meet the needs of pregnant and lactating women (NHMRC 2010; MOH 2010). Given that the EWG recommended no change in the existing RDI for pregnancy, it may be necessary to continue to recommend iodine supplements for pregnant and lactating women in Australia and New Zealand in order for them to achieve recommended intakes.

6.3.3 International consistency

The recommendations of the EWG are still consistent with the Institute of Medicine (Food and Nutrition Board 2001). EFSA have recommended (not yet adopted) that an Adequate Intake be set rather than EAR and RDI because of the lack of evidence (EFSA 2014). The WHO recommended intake in pregnancy is 250 µg/day, (WHO Secretariat 2007) although some WHO/FAO publications still list the RDI in pregnancy at 200 µg/day. The recommendation of the EWG of 220 µg/day is less than the 250 µg/day from WHO, but more than the EFSA adequate intake of 200 µg/day (EFSA 2014). Thus, across countries and expert bodies, the RDI for iodine in pregnancy currently ranges from 200 to 250 µg/day.

6.3.4 Priorities for remaining questions

Due to time constraints the EWG was not able to consider all the research questions generated in Table 5.2. Future work needs to consider the remaining questions with the next priorities being:

- **EAR/RDI for children** as there is emerging evidence of the adverse effects of mild iodine deficiency on cognitive development.
- **EAR/RDI for lactation** as there is emerging evidence of the effect of inadequate maternal iodine intake on early cognitive development.
- **ULs for pregnancy and lactation** given that the NHMRC and NZ MOH recommend supplementation with an additional 150 µg iodine/day during pregnancy and lactation (NHMRC 2010; MOH 2010). In New Zealand there exists a single subsidised 150 µg iodine tablet which is a registered medicine and subject to appropriate quality controls. In Australia and New Zealand there also exists a range of commercial supplements with varying iodine contents below, at and above 150 µg, that may also contain other nutrients.

6.3.5 Research required to inform NRVs

Establishing NRVs relies on available published evidence. The following areas of research have been identified as priorities that would strengthen future work on NRVs.

Much of the evidence informing requirements for iodine has been drawn from natural experiments either resulting from geographical areas with varying iodine nutrition or from pre-post studies following iodine prophylaxis. It is disappointing that there has been little new evidence upon which to base recommendations for iodine requirements. Focused research on dose-response studies in healthy populations would assist in providing clearer evidence for cut-points for NRVs. However, it is acknowledged that this sort of research is both costly and ethically challenging. For example it may not be ethically acceptable to undertake RCTs to determine the effect of iodine deficiency or excess intake in children or pregnant women.

More research on identifying more robust biomarkers for assessing iodine status in healthy populations, such as Tg, is required. There has been an over-reliance in many studies in using only UIC as an index of iodine status, despite the large intra- and inter-individual variation associated with UIC. This is of particular concern when assessing the iodine status of pregnant women, as many studies in pregnancy use UIC at a single time point as an indicator of iodine status for the duration of pregnancy. Another consideration is the relationship between the iodine content/stores in the thyroid and thyroid hormone synthesis. While serum TSH is regarded as the best marker of thyroid function during pregnancy, the value and appropriateness of free T₄ levels remains unresolved (De Groot et al 2012).

There are very few studies that provide data on dietary iodine intakes, including national surveys. This means that iodine intakes are estimated from UIC; the assumption that 90% of dietary iodine is excreted in the urine has yet to be validated over a range of physiological conditions (i.e. pregnancy, various states of hydration, and over nutrition) and genetic factors (i.e. ethnicity).

There are a lack of data on obstetric/pregnancy complications and outcomes from maternal iodine deficiency. Studies examining the effects of changes in thyroid function, but ignoring the effects of iodine nutrition, show that suboptimal maternal thyroid hormone production may produce profound adverse obstetrical events such as miscarriage, gestational hypertension, pre-eclampsia and premature labour (De Groot et al 2012).

The Provisional ULs for children were determined using extrapolations with metabolic weights and an assumption that there is a positive and linear association between body weight and iodine requirements. Research underpinning this association is needed.

More research is needed on the adverse effects of iodine deficiency on cognitive function in children. Focusing research on specific aspects of cognition that are most likely to be affected and developing a consistent approach to measuring the size of the effect will be invaluable for future nutrient reference value work. Agreement needs to be reached in deciding upon specific, standardised tools used to undertake

these behavioral studies in children as comparisons of results from different methods are often difficult and have not been validated. A complication associated with research into adverse effects of iodine relate to the fact that populations exposed to long term iodine deficiency are at greater risk of responding adversely to increasing iodine nutrition than iodine replete populations (Teng et al 2006).

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7 Appendices

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7.1 Appendix 1: Studies relating to EAR for Adults

Table 7:1 Body of Evidence for EAR and RDI for adults 19 years and older

Review Question 1 *What is the average intake required by healthy adults in a population to maintain normal thyroid function, as measured by thyroid hormones and thyroid volume?*

| Component | Rating | Notes |
|----------------------|--------------|---|
| Evidence Base | Good | 2 Level II + 2 Level III-2 + 1 Level III-3 + 13 Level IV studies |
| Consistency | Excellent | Consistent results for UIC with increasing iodine intake for varying reported intakes/excretion of iodine (UIC). Consistent results for normal thyroid function (TSH, thyroid volume and thyroid antibodies) across a range of UIC |
| Clinical impact | Good | The earlier balance studies indicated that iodine balance is achieved at intakes over 100 µg/day but not below 40 µg/day. Studies support normalising of thyroid function with UIC above 100 µg/L. |
| Generalisability | Satisfactory | Population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population. Countries with severe I deficiency may have more adverse outcomes related to high I intakes compared to replete or mild-moderate I deficient countries such as Australia and New Zealand. |
| Applicability | Good | Applicable to Australian and New Zealand healthcare context with few caveats. |
| Draft Recommendation | | Reviewed studies do not provide evidence to change the current EAR (100 µg/day) and RDI (150 µg/day) for adults. |
| Recommendation | B | Body of evidence can be trusted to guide practice in most situations. |

Table 7:2 Studies relating to the EAR for Adults (Review question 1)

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|---|---|--|--|---------------------------------|---|--|---|
| Aghini Lombardi et al 2013 Pescopagano, Italy | Cross- sectional survey in 1995 & 2010 | N=1148 in 2010 & n= 1411 in 1995 | TV, TSH, FT3, FT4, TgAb, TPOAb,UIE | Use of iodized salt | <p>Goitre rate was lower in 2010 than in 1995 (25.8% vs 46.1%, $P<0.0001$). In 2010 vs. 1995, thyroid autonomy in subjects younger than 45 yrs (3 of 579, 0.5% vs. 25 of 1010, 2.5% $P = .004$) & non-autoimmune hyperthyroidism in subjects older than 45 yrs old (8 of 569, 1.4% vs. 18 of 401, 4.5%, $P = .03$) were less frequent. The rate of hypothyroidism was higher in 2010 vs. 1995 (5.0% vs. 2.8%, $P = 0.005$), mainly because of an increased frequency of subclinical hypothyroidism in subjects younger than 15 yrs (7 of 83, 8.4% vs. 0 of 419, 0.0%, $P < .0001$).</p> <p>Serum thyroid autoantibodies (19.5% vs. 12.6%; $P<0.0001$) & Hashimoto's thyroiditis (14.5% vs. 3.5%; $P<0.0001$) were more frequent in 2010 than in 1995</p> | N/A | Level IV Effect of voluntary iodine prophylaxis |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|------------------------------|--|---|--|---|--|---|---|
| Ayturk et al, 2009 Turkey | Case-control study | N=539 (total) n=278 in the metabolic syndrome group (33.1% male) & n=261 in the control group (30.7% male) Newly diagnosed patients with metabolic syndrome (18-74 yrs) & controls Mild-to moderate ID | TV, TSH, & nodule prevalence, anthropometry, FT3, FT4, TSH . | No information on iodine nutrition (neither urine iodine nor iodine intake) | TSH was correlated with the presence of metabolic syndrome. Insulin resistance, waist circumference & triglycerides independent predictors of TV. TSH was significantly correlated with the presence of MetS. In a multiple linear regression analysis, independent predictors of TV (mL) were (B, 95% CI); waist circumference (cm) 0.335 (0.089- 0.161), triglycerides (mg/dL) 0.136 (0.003-0.016), & insulin resistance 0.143 (0.512- 2.731). | BMI, smoking, fatmass | Level III-3 No measure of iodine status based on the area being mild to moderately deficient |
| Bulow Pedersen et al, 2011 | Denmark Two cross-sectional population studies. | Group 1: n= 4649 (median UI 61 µg/liter) group 2: n= 3570 (median UI 101 | TPO-Ab & Tg-Ab | Not assessed | Antibodies were more common in group 2. Than group 1: TPO-Ab > 30 U/ml, group1 vs. group2: 14.3 vs. 23.8% (p < 0.001); Tg-Ab > 20 U/ml, group1 vs. group2: 13.7 vs. 19.9% (p < 0.001). The group2 vs. | Bread, fish, water & milk intake, estimated salt intake, iodine | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|--|---|--|---|--|--|---|-----------------------------------|
| | | µg/litre) | | | group1 effect was confirmed in multivariate regression models (group1 reference): TPO-Ab: OR (95% CI): 1.80 (1.59-2.04); Tg-Ab: 1.49 (1.31-1.69). The increase in frequency of thyroid antibodies was most pronounced in young females & especially observed at low concentrations of antibodies. | supplements , education, self-rated health, smoking, alcohol intake & physical activity | |
| Camargo et al, 2008 Sao Paulo, Brazil | Population based, cross-sectional study | N= 1085 Population exposed to excessive iodine intake for 5 yrs (table salt iodine concentration 40-100mg/kg salt). | TV, TSH, FT4, UIC, TPO, thyroid echogenicity, | Sample of salt consumed in the home were taken | Table salt at the time of the study was 20-60 mg/kg salt. In 45% UI excretion was above 300 µg/l & in 14.1 above 400 µg/l. Prevalence of Chronic autoimmune thyroiditis (CAT) was 16.9%. 8% of population with CAT had hypothyroidism. Hyperthyroidism was diagnosed in 3.3% & Goitre in 3.1% of population. | | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|---|--|--|--|--|---|---|-----------------------------|
| Combet et al, 2014 Glasgow, UK | A 14-day intervention study Subjects took 356 µg iodine daily | N=42 Mildly iodine deficient | UIC, TSH, TT3, FT3, TT4, FT4 & Tg | Iodine-specific FFQ & 4-day weighed food diary | Median UIC at baseline and 14-day were 78 & 140 µg/L respectively; TSH at 14-day was significantly higher (p<0.001) after supplementation. No significant difference was observed in TT3, TT3, TT4, FT4 and Tg after supplementation. | | Level II |
| Du et al, 2014 Caizhuang, Dongwenzhuang, Fengrun, Yangfang, Xicuan, Shuangzhai, Houhuangtai, Lizhuang, Anrong, Hutong & Tieshangang, China | Cross sectional study | N=2147 Tieshangang (iodine deficient area), Xicuan, Shuangzhai, Houhuangtai, Lizhuang, Anrong & Hutong (iodine sufficient areas) , Caizhuang, Dongwenzhuang, Fengrun & Yangfang (iodine excess areas) | UIC, TSH, FT3, FT4, TgAb, TPOAb, TRAb & TV | Questionnaire on smoking and drinking habits; sample of iodized salt & drinking water taken in preselected iodine deficient area | Median UICs for iodine deficient, iodine sufficient and iodine excess areas were 62, 229 & 750 µg/L, respectively. TSH was significantly correlated with deficient iodine intake ($\beta = -1.219$, $p=0.028$) & excess iodine intake ($\beta = 1.764$, $p=0.001$). | | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|---|---|---|--|--|---|---|---|
| Elahi & Hussain, 2013 Lahore, Pakistan | Cross-sectional study Severely iodine deficient area | N=110 | TSH, FT3 & FT4 | Use of iodized salt | Mean TSH, FT3 and FT4 were 1.4 mU/L, 3.2 pmol/L & 15.6 pmol/L, respectively. 28% of the subjects used iodised salt | | Level IV |
| Leung et al, 2011 Boston, USA | Cross-sectional | n=78 vegetarians , n=63 vegans Without thyroid disease & not pregnant Iodine sufficient | UIC, T4, TSH, perchlorate & thiocyanate concentrations | Soy FFQ & questionnaire on iodine supplement use | Median UIC of vegans (78.5 µg/litre; range 6.8-964.7 µg/litre) was lower than vegetarians (147.0 µg/L; range 9.3-778.6 µg/L) (P < 0.01). Median urinary thiocyanate concentration of vegans (630 µg/L; range 108-3085 µg/L) was higher than vegetarians (341 µg/L; range 31-1963 µg/litre) (P < 0.01). No between-group differences in urinary perchlorate concentrations (P = 0.75), TSH (P = 0.46), & FT4 (P = 0.77). Urinary iodine, perchlorate, & thiocyanate levels were not associated with TSH (P = | Smoking, thiocyanate-rich food consumption | Level IV Low Generalizability to Australian population |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|---|--|---|---------------------|---------------------------------|---|---|-----------------------------------|
| | | | | | 0.59) or FT4 (P = 0.14), even when adjusted for multiple variables. | | |
| Krejbjerg et al, 2014 Copenhagen & Aalborg, Denmark | Longitudinal population- based study | N=2208 Copenhagen (mild iodine deficiency) & Aalborg (moderate iodine deficiency) | UIC & TV | FFQ | At follow-up, the median UIC in Copenhagen increased from 61 to 73 µg/L & in Aalborg from 45 to 76 µg/L respectively. At follow-up, median thyroid volume increased significantly in Copenhagen (p=0.001), whereas median thyroid volume in Aalborg decreased (p=0.07). | Age, gender, smoking status, familial disposition, region, baseline BMI, baseline TSH, baseline TPOAb, baseline hypoechogenicity, baseline thyroid enlargement & baseline multinodularity | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|---|---|--|-------------------------------------|--|--|---|-----------------------------|
| Kocak et al, 2014 Trabzon, Turkey | Cross-sectional study | N=2500 | UIC, TSH, FT3, TPOAb, TgAb, Tg & TV | Questionnaire including the type of salt used. | Median UICs for adults with no goitre and a goitre were 123 and 123 respectively. Mean TSH was significantly higher in adults with no goitre ($p<0.0005$) than adults with a goitre. Mean FT3 was significantly lower in adults with no goitre ($p=0.002$) than adults with a goitre. Mean FT4 was significantly lower in adults with no goitre ($p=0.008$) than adults with a goitre. | | |
| Meisinger et al, 2012 Germany (South vs. Northeast (NE)) | 2 population-based surveys using standardised protocol: the study of health Pomerania (NE) & Kooperative Gesundheit forschung | n=2505 (south) & n=2316 (NE) (Age 25-74 yrs), no known thyroid disease Moderate (NE), moderate-severe (south) ID | UIC, TSH, TV | No assessment | Median UIC was 110 mg/l (64; 169 mg/l) in NE & 151 mg/l (97; 214 mg/l) in South. Median TSH was 0.81 mIU/l (0.56; 1.15 mIU/l) in NE & 1.22 mIU/l (0.84; 1.80 mIU/l) in South. Frequency of elevated TSH (TSH ≥ 2.12 mIU/l) was 4.3% in NE & 14.1% in South ($P<0.001$). Suppressed TSH (<0.25 mIU/l) was seen in 3.5 (NE) & 1.7% (south)($P<0.001$). | Study region, age and sex. Smoking habit | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|---|--|---|-------------------------------------|---------------------------------|---|--|-----------------------------------|
| | (South) | | | | The proportion of ultrasonographic findings was 55.5% in NE & 68.0% in South. The frequency of serum TPO-Abs did not differ between NE & South | | |
| Meng et al, 2013 Gansu, Shandong, Fujian, Jilin, Anhui & Chongqing provinces, China | Cross sectional study | N=699 | UIC, TSH,FT4,Tg, TgAb & TPOAb | Household salt samples | Median UIC, TSH, FT4 and Tg were 260 µg/L, 1.8 mU/L, 16.6 pmol/L & 7.0 µg/L, respectively. TSH decreased from ~ UIC 50 to 300 µg/L and increase from UIC 300 to 550 µg/L. | | Level IV |
| Rasmussen et al, 2008 Denmark | Two cross- sectional studies before & | Group 1: n= 4649 (median UI 61 µg/liter) (before fortification was | | FFQ | UIC increased in all age & sex groups after fortification. However, the iodine intake was still below the recommended in the youngest | Bread, fish, water & milk intake, estimated | Level IV Large groups, |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|---|--|---|--|--------------------------------------|---|---|---|
| | after mandatory fortification | introduced) Group 2: n= 3570 (median UI 101 µg/liter)(after mandatory iodization of salt) | | | age groups in both cities & in women 40–45 yrs of age living in Aalborg. Intake of milk & salt had strong significant direct associations with iodine excretion ($P < 0.001$). | salt intake, iodine supplements , education, self-rated health, smoking, alcohol & physical activity | but different samples (pre and post) Same participants in Bulow Pedersen [59] |
| Rasmussen et al, 2013 Denmark | Prospective cohort (Danish DanThyr cohort) Followed up at 11 yrs | N= 2465 | UIC, Iodine intake, Bodyweight & height, supplement use | FFQ & supplement questionnaire | Median (IQR) UIC increased by 19 (-25-68) µg/L to 83 (47-133) µg/L. Estimated 24-h iodine excretion increased by 36 (-21-95) µg/24-h to 134 (93-206), & calculated total iodine intake (diet plus supplements) increased by 16 (-18- 48) µg/day. Iodine excretion increased in all age & gender groups, but was still below the recommended amount at follow- up. Increase in iodine excretion was positively associated with milk | Bread, fish, water & milk intake, estimated salt intake, iodine supplements , education, self-rated health, smoking, alcohol intake & physical | Level III-2 |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|----------------------------------|--|---|--|---------------------------|---|---|--|
| | | | | | intake, supplement use & bread intake at follow-up. Salt intake, education, self-rated health, smoking, alcohol & physical activity were not associated with the increase in iodine excretion. | activity | |
| Sang et al 2012 Tianjin China | A 4-wk, double-blind, placebo-controlled, RCT Randomly assigned to 1 of 12 intervention groups with various iodine supplement doses ranging from 0 to 2000 µg/d | N= 256 euthyroid adults Iodine sufficient | Total iodine intake, FT4, FT3, UIC, TSH, TPOAb, TGAb, TV | 24-hr recall | The mean iodine intake from the diets & salt intake were 105 ± 25 & 258 ± 101 µg/d, respectively. In comparison with the placebo group, all iodide-supplemented groups responded with significant increases in median UIC (P < 0.05) & in TSH concentration (P < 0.05). TV decreased after 4 wk in the high-iodine intervention groups (1500-2000 µg). Subclinical hypothyroidism appeared in the groups that received 400µg iodine suppl (giving total intake of 800 µg/day) (5%) & 500-2000 µg iodine suppl (15-47%). | | Level II, low risk of bias Dose response study, but n per group small Useful to determine UL (1500-2000 ug in high dose arm) |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|--|--------------------|--|---|---------------------------|--|---|--|
| Teng et al, 2006 3 communities in China (Panshan, Zhangwu and Huanghua) | Prospective Cohort | N= 3018 Panshan & Zhangwu (northeastern China, mild-moderate ID) & Huanghua (excessive iodine intake) | TV, nodules, TSH, UIC, Anti-TPO, TG, TGAb | | <p>Among the mildly deficient iodine intake, those with more than adequate intake, & those with excessive intake, the cumulative incidence of overt hypothyroidism was 0.2%, 0.5%, & 0.3%, respectively; that of subclinical hypothyroidism, 0.2%, 2.6%, & 2.9%, respectively; & that of autoimmune thyroiditis, 0.2%, 1.0%, & 1.3%, respectively.</p> <p>Among subjects with euthyroidism & antithyroid antibodies at baseline, the 5-yr incidence of elevated serum thyrotropin levels was greater among those with more than adequate or excessive iodine intake than among those with mildly deficient iodine intake. A baseline serum thyrotropin level of 1.0 to 1.9 mIU per litre was associated with the lowest subsequent incidence of abnormal thyroid</p> | | <p>Level III-2</p> <p>But with caveats</p> <p>Analysis by region (n = 3 groups). Group defined as mild iodine deficiency had MUIC of 97 (46-137) ug/L – “normal”?</p> <p>No adverse effect on overt hypothyroidism. Good retention (80%), similar across three regions of high MUIC, but some evidence of increased effect at MUIC</p> |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|---------------------------------|---|--|---|---------------------------------|---|--|--|
| | | | | | function. | | > 200 ug/L for subclinical hypothyroidism and autoimmune thyroiditis. 5 yr follow-up may be too short for long latency period disease Generalizability to Australia and NZ questionable |
| Tonacchera et al, 2012 Italy | Intervention Iodized vegetables Vege serve = 100 g potatoes, carrots, | N=50 (age 19-50) Participants consumed a single serving of vegetables /day for 2wks | UI excretion (baseline, during & end of study). TV, TSH, FT4, FT3, TPOAb, TGAb (baseline & end of study) | | The UI concentration measured in volunteers before the intake of vegetables was 98.3 mg/L (basal value), increasing to 117.5 mg/L during the intake of vegetables. 7 days after the discontinuation of vegetable intake, UI was 85 mg/L. UIC increment was 19.6% compared with the basal value (P | | Level IV Non- randomised No control group Before-after design |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|--|--|---|----------------------------|---|--|--|--|
| | tomatoes, or salad containing 45 mg of iodine. | | | | =0.035). | | |
| van de Ven et al, 2014 Nijmegen, Netherlands | Two cross sectional surveys | N=980 | UIC, TSH, TT3, FT4 & TPOAb | No assessment | At follow-up, the median UIC was 130 µg/L. TSH decreased by 5.4% (95%CI 2.5-8.3%) & FT4 increased by 3.7% (95%CI 2.9-4.65). | | Level IV |
| Vejbjerg et al, 2007 Northern Copenhagen, & Aalborg | Two cross-sectional studies before & after mandatory fortification | Group 1: n= 4649 (median UI 61 µg/litre) (before fortification of salt was introduced) Group 2: n= 3570 (median UI 101 µg/litre)(after mandatory iodization of salt) | TV, nodules, UIC | Questionnaire on eating & drinking habits | There was a lower median TV in all age groups after iodization. The largest relative decline was among the younger females from the area with previous, moderate iodine deficiency. After iodization, there were no regional differences in median TV in the age groups younger than 45 yr. After adjustment, a lower mean TV was seen among those with multiple nodules in both areas & in | region, sex, age, lifestyle (tobacco, alcohol, iodine supplementation, & oral contraceptives), familial disposition (at least one first-degree | Level IV Pre-post but in different groups; intervention not controlled by researchers (more like a natural experiment – high risk of bias, no |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments* |
|-------------------------|--------------|---|------------------|---------------------------|--|--|--|
| | | | | | the group with diffuse structure in the area with moderate iodine deficiency. Before the iodization, 17.6% of the total cross-section had thyroid enlargement; after the iodization, 10.9% of the cross-section had thyroid enlargement. | relative with thyroid disease), educational level, parity, & BMI | control of confounders). Rasmussen et al, 2008 [63] |

Abbreviations ID iodine deficiency, TV thyroid volume, TRAb, thyrotropin receptor antibody, BMI Body Mass Index, UIC urinary iodine concentration, FFQ food frequency questionnaire, yr year, *NHMRC reference for quality rating. Aetiology ranking system used for studies used to determine EAR.

7.2 Appendix 2: Studies relating to EAR for Pregnancy

Table 7:3 Body of Evidence for EAR and RDI for pregnant women

Review Question 3: *What is the average intake required by healthy pregnant women in a population to maintain normal thyroid function as measured by maternal thyroid function and neurodevelopment in their children?*

| Component | Rating | Notes |
|---------------|--------|--|
| Evidence Base | Poor | Thyroid function: 1 Level I study with low risk of bias + 10 Level III-2 (cohort) studies + 19 Level IV (cross sectional) studies Neurodevelopment: 2 Level I studies (one includes n=24 studies, but only 2 RCTs; the other includes n=12 RCTs, of which only 2 (with high risk of bias) report cognitive outcomes) + 2 Level II (RCTs) with low risk of bias + 7 level III-2 studies (birth cohort) with moderate risk of bias (potential for confounding, loss to follow-up) |

| Component | Rating | Notes |
|----------------------|--------------|--|
| Consistency | Poor | Lack of consistency between studies. |
| Clinical impact | Moderate | <p>Thyroid function: Despite a low UIC observed in some populations, thyroid hormone production remains normal in pregnancy. Not all studies used pregnancy-appropriate reference values for TSH of >2.5 mIU/L in first trimester and > 3.0 mIU/L in trimesters 2 and 3. No obvious dose-response relation was seen. The effects of iodine supplementation on changes in thyroid hormone concentrations in mothers and infants were not consistent. In the meta-analysis, one of the three iodine intervention studies conducted in mild to moderate iodine deficiency countries reported increased maternal T4 levels; none reported increased maternal T3 levels. Only one of the 6 RCTs found reduced maternal TSH levels after iodine supplementation.</p> <p>Neurodevelopment: Meta-analysis showed benefit of adequate iodine status on IQ in children aged <5 years. The 2 level II studies showed inconsistent results (one positive effect of iodine supplementation on neurocognitive functioning in children aged 5-7 years, the other demonstrated worse outcomes at 6–18 mo, compared to iodised salt use in pregnancy) but the different age groups of children and use of psychomotor instruments between studies is problematic. Two RCTs included in a meta-analysis reported reduced cretinism and improved IQ in children living in areas of severe iodine deficiency associated with maternal iodine supplementation. All studies in older children (5–9 years) consistent and in favour of iodine supplementation.</p> |
| Generalisability | Satisfactory | <p>Thyroid function: Population studies in body of evidence similar to the target population for the guideline</p> <p>Neurodevelopment: Studies undertaken in populations with different iodine status, ranging from severe (China) and moderate (Spain) iodine deficiency to iodine replete (Netherlands). Improved verbal IQ, reading, spelling skills at age 8-9y demonstrated in two large Level III-2 studies in Australia and UK; both countries have mild ID.</p> |
| Applicability | Satisfactory | <p>Thyroid function: Directly applicable to Australian healthcare context (evidence from mild to moderate I deficiency countries).</p> <p>Neurodevelopment: Probably applicable to Australian and New Zealand healthcare context with some caveats.</p> |
| Draft Recommendation | | Thyroid function: There is insufficient evidence with regard to maternal indices or child development that could be used to set or modify the EAR or RDI in pregnancy. In the absence of no new evidence to challenge the EAR and RDI set in 2002, it is |

| Component | Rating | Notes |
|----------------|--------|--|
| | | <p>proposed that the current EAR and RDI for pregnancy is kept at 160 ug/day and 220 ug/day, respectively.</p> <p>Neurodevelopment: Evidence could not be considered for changing EAR for pregnancy based on limited information on neurological outcomes in children.</p> <p>It should be noted that pregnancy outcomes were not evaluated as no studies assessed pregnancy outcomes.</p> |
| Recommendation | C | Thyroid function: Body of evidence provides some support for recommendation(s) but care should be taken in its application. Neurodevelopment: Body of evidence provides some support for recommendation(s) but care should be taken in its application. |

Table 7:4 Studies related to pregnancy EAR and thyroid function during pregnancy (Review Question 3)

Observational studies

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|-------------------------------------|--------------------|---|---|---------------------------|--|---|----------------------------|
| Aguayo et al, 2013 Biscay, Spain | Prospective cohort | <p>N=2014 (1st trimester)</p> <p>N= 1322 (2nd trimester)</p> <p>N=1868 neonatal</p> | <p>TSH, FT4, FT3, TPO-Ab, UIC (spot) in 1st and 2nd trimester</p> <p>Neonatal TSH</p> | No assessment | In the 1 st & 2 nd trimester median UICs were 88.5 µg /L and 140 µg /L, respectively. No relationship was found between UIC & FT4, or maternal & neonatal TSH. In trimester 1&2, 9.7% and 7.5% of women were TPO-Ab positive, respectively. The percentage | | Level III-2 |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|---------------------------------------|---|---|--|---------------------------|---|---|----------------------------|
| | | TSH Baseline Iodine status of population not specified | | | of miscarriages in healthy women was 8.9%, 21.2% women with overt hypothyroidism ($p < 0.001$) and 15.6% in women with subclinical hypothyroidism ($p < 0.025$). The miscarriage rate was not higher in TPO-Ab-positive women. | | |
| Amouzegar et al, 2014 Tehran, Iran | Prospective cohort Followed throughout pregnancy | N=203 pregnant women not taking iodine supplements | UIC, TSH, TT3, TT4, FT4I, TgAb & TPOAb | No assessment | Median UICs in the 1st, 2nd & 3rd trimesters were 218, 160 & 148 $\mu\text{g/L}$, respectively. In the 1st trimester, three spot urine samples were collected. Median TSH was significantly lower in the 1st trimester ($p=0.004$) than in the 2nd & 3rd trimesters. Mean TT4 was significantly lower in the 1st trimester ($p=0.00$) than in the 2nd & 3rd trimesters. No significant difference was observed in TT3 between the trimesters. | | Level III-2 |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|---------------------------------------|--|---|---|---------------------------|---|---|---|
| Antonangeli et al, 2002 Pisa Italy | Prospective cohort Followed up at 1 st antenatal visit, the 18th–26th, & 29th–33rd wk of gestation, & at the 3rd & 6th mth after delivery. | N=86 pregnant women (randomized into 2 groups & treated daily for 6mths after delivery) with 200 µg iodide/day (group A) or 50µg iodide/day (group B). Marginally iodine deficient | TV, TSH, FT4, FT3, and UIC TgAb, TPOAb | No assessment | No significant changes in serum free thyroid hormones and TSH concentrations were found during gestation in either group. | | Level III-2 Supplementation given after delivery |
| Blumenthal et al, 2012 Sydney | Cross-sectional At antenatal visit (between 7 & 11 wks gestation) | N=367 | TSH, FT4 UI excretion (spot) | | Median UIC for all women was 81 µg/l (interquartile range 41-169 µg/l). 71.9% of the women exhibited a UIC of <150 µg/l. 26% of the women had a UIC <50 µg/l, and 12% had a UIC <20 µg/l. The only detectable influences on UIC were daily milk intake and pregnancy supplements. No association between UIC and thyroid function and no evidence for | | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|---|---|--|--|---------------------------|--|---|----------------------------|
| | | | | | an effect of iodine intake on thyroid function | | |
| Brucker-Davis et al, 2013 Nice, France | Prospective, randomised, intervention study Follow throughout pregnancy & 3 mo postpartum. | RCT G1 (n=32): pregnancy vitamins with 150 µg iodine G2 (n=54): pregnancy vitamins without iodine Median UICs for the iodine supplemented and control groups were 111 & 103 µg/L. | UIC, TSH, FT3, TT4, FT4, Tg, TgAb, TPOAb, TBG & TV | | Median UICs in the 2nd & 3rd trimesters were significantly higher in iodine group ($p \leq 0.05$ & $p \leq 0.001$) than placebo group. No significant difference was observed in TSH, FT3, TT4, FT4 & Tg in 2nd & 3rd trimesters between both groups. Both groups received a document on how to achieve optimum dietary intake. | | Level II |
| Charoo et | Prospective cohort | N=51 pregnant women in the 1st | UIC, TSH, TT3, | No assessment | Median UICs in the 1st, 2nd & 3rd trimesters were 144, 134 & 123 µg/L, | | Level III-2 |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|---|---|--|---------------------|---------------------------|---|---|----------------------------|
| al, 2013 Kashmir, India | Followed throughout pregnancy | trimester | FT3, TT4 & FT4 | | <p>respectively. Mean TSH increased from 4.1 in the 1st trimester to 5.1 mU/L in the 3rd trimester. Mean TT3 decreased from 1.7 in the 1st trimester to 1.5 ng/dL in the 3rd trimester. Mean FT3 decreased from 5.7 in the 1st trimester to 4.2 pmol/LL in the 3rd trimester. Mean TT4 decreased from 13.6 in the 1st trimester to 11.6 µg/dL in the 3rd trimester. Mean FT4 decreased from 19.4 in the 1st trimester to 14.2 pmol/L in the 3rd trimester.</p> <p>All pregnant women did not take iodine supplements. Only healthy women were included.</p> | | |
| Elahi & Hussain, 2013 Lahore, Pakistan | Prospective cohort Followed throughout pregnancy | N=254 pregnant women Severely iodine deficient area | UIC, TSH, FT3 & FT4 | Use of iodized salt | <p>Median UIC in the 1st trimester was 67 µg/L. Median TSH was significantly lower in the 1st trimester ($p<0.05$) than in the 2nd & 3rd trimesters. Mean FT3 was significantly lower in the 2nd trimester ($p<0.05$) than in the 1st & 3rd trimesters. Mean FT4 was significantly lower in the 3rd trimester ($p<0.05$) than in the 1st & 2nd</p> | | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|--|--|---|--------------------------------------|---------------------------|---|---|----------------------------|
| | | | | | <p>trimesters.</p> <p>Data on UIC and use of iodized salt were published in Elahi et al. (2009). Only 34% of pregnant women used iodised salt. No data on the use of iodine supplements</p> | | |
| Ferreira et al, 2014 São Paulo, Spain | Cross-sectional | N=191 pregnant women in the 1st trimester | UIC, TSH, TT4, FT4, TgAb & TPOAb | No assessment | <p>Median UIC, mean TSH, TT4 and FT4 in the 1st trimester were 138 µg/L, 1.6 mIU/L, 10.0 µg/dL & 14.2 pmol/L, respectively.</p> <p>All pregnant women did not use iodine supplements.</p> | | Level IV |
| Fister et al, 2009 Ljubljana Slovenia Note: More data on this cohort was | Prospective cohort Followed up at 1 st & 3 rd trimester & 4 mths postpartum | N=118 healthy pregnant women, with thyroid disease Iodine sufficient | UIC, TV (ultrasound), serum TSH, BMI | No assessment | <p>3rd trimester median UIC (176 mg/g creatinine) was higher than 4 & 14 mths after delivery (P = 0.030, P< 0.001, respectively).</p> <p>TV in the 3rd trimester (11.3 ± 3.1 mL) was greater (P < 0.001) than in the 1st trimester (8.7 ± 2.5 mL), 4 mths after delivery (8.6 ± 2.5) & 14 mths after delivery (7.8 ± 2.4 mL).</p> | TSH, BMI, maternal age, parity | Level III-2 |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|--|--|---|-----------------------------|---------------------------|---|---|--|
| reported in a paper by Fister et al in 2011. | | | | | <p>TSH was higher in 3rd trimester than in the 1st trimester & 4 mths after delivery (P = 0.007, P = 0.006, respectively).</p> <p>Colour flow Doppler sonography pattern I was more frequent 4 mths after delivery than 14 mths after delivery (P < 0.001).</p> <p>Peak systolic velocity was higher 4 mths after delivery than 14 mths after delivery (P < 0.001). Linear regression analysis revealed TSH & BMI as significant independent predictors for TV</p> | | |
| Fuse et al, 2013 Chiba Prefecture, Japan | Cross-sectional Prospective cohort Followed throughout pregnancy | <p>N=563 pregnant women: 166 in the 1st trimester, 221 in the 2nd trimester & 176 in the 3rd trimester.</p> <p>N=65 pregnant women in the 1st trimester</p> | UIC, TSH, FT4, TgAb & TPOAb | Semi-quantitative FFQ | <p>Median UICs in the 1st, 2nd & 3rd trimesters were 227, 259 & 205 µg/L, respectively. Median TSH was significantly lower in the 1st trimester (p<0.05) than in the 2nd & 3rd trimesters. Median FT4 was significantly lower in the 2nd and 3rd trimesters (p<0.05) than in the 1st trimester.</p> <p>Median UICs in the 1st, 2nd & 3rd trimesters were 216, 136 & 148 µg/L,</p> | | Two studies Level III-2 Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|--|-----------------|--|--|---------------------------|--|---|----------------------------|
| | | | | | respectively. Mean TSH was significantly lower in the 1st trimester ($p<0.05$) than in the 2nd & 3rd trimesters. Mean FT4 was significantly lower in the 2nd and 3rd trimesters ($p<0.05$) than in the 1st trimester. No significant difference was observed in TT3 between the trimesters. No data on the use of iodine supplements. | | |
| Gowachirapant et al, 2014 Bangkok, Thailand | Cross-sectional | N=514 pregnant women in the 1st trimester | UIC, TSH, TT3, FT3, TT4, FT4, Tg, TPOAb & TV | Household salt samples | Median UIC, TSH, TT3, FT3, TT4, FT4 & Tg in the 1st trimester were 112 µg/L, 1.1 mIU/L, 1.85 nmol/L, 4.9 pmol/L, 118.0 nmol/L, 13.9 pmol/L & 9.5 µg/L, respectively. Of these, 3% had overt hypothyroidism, 7% had subclinical hypothyroidism & 8% had isolated hypothyroxinaemia. All pregnant women did not use iodine supplements. | Socio-demographic, UIC & thyroid function | Level IV |
| Habimana et al, 2014 Lubumbas | Cross-sectional | N=225 pregnant women: 76 in the 1st trimester, 71 in the 2nd | UIC, TSH, FT3, FT4, Tg & TPOAb | No assessment | Median UICs in the 1st, 2nd & 3rd trimesters were 138, 144 & 204 µg/L, respectively. Median TSH was significantly higher lower in the 1st trimester ($p=0.005$) | Socio-demographic, group of | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|---|-----------------|---|---|-------------------------------------|---|---|----------------------------|
| hi, Democratic Republic of Congo | | trimester, 78 in the 3rd trimester | | | <p>than in the 2nd & 3rd trimesters. No significant difference was observed in FT3 ($p=0.78$) and FT4 ($p=0.24$) between the trimesters. Median Tg was significantly higher lower in the 1st trimester ($p=0.01$) than in the 2nd & 3rd trimesters.</p> <p>Data on UIC reported in Habimana et al (2013). All pregnant women did not use iodine supplements.</p> | women, UIC & TPOAb status. | |
| Jaiswal et al, 2014 Bangalore, India | Cross-sectional | N=334 pregnant women in the 1st trimester | UIC, TSH, TT3, FT3, TT4, FT4, TG, TBG, TgAb, TPOAb & TV | Self-reported written questionnaire | <p>Median UIC, TSH, TT3, FT3, TT4, FT4 & Tg in the 1st trimester were 184 $\mu\text{g/L}$, 1.2 mIU/L, 2.2 nmol/L, 5.7 pmol/L, 146.1 nmol/L, 14.3 pmol/L & 6.6 $\mu\text{g/L}$, respectively. Of these, 4% had overt hypothyroidism, 9% had subclinical hypothyroidism & 5% had hypothyroxinaemia.</p> <p>34% of pregnant women used iodine supplements.</p> <p>Maternal age, gestational age, hemoglobin, BMI, consanguinity, parity, maternal education, maternal employment, food</p> | | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|--|---|---|----------------------------|---------------------------|--|---|--|
| | | | | | habits, reason for salt use, seafood intake, egg intake, use of iodine containing multinutrient powders and presence of thyroid antibodies above the cutoff values. | | |
| Joshi et al, 2014 Vadodara, India | Cross-sectional | N=256 pregnant women in the 1st trimester | UIC, TSH, TT4 & FT4 | No assessment | Median UIC, TSH, TT4 & FT4 in the 1st trimester were 297 µg/L, 1.8 mIU/L, 10.24 µg/dL & 10.83 pmol/L, respectively. TSH was negatively correlated with FT4 (p<0.01). No data on the use of iodine supplements. | | Level IV |
| Koukkou et al, 2014a Athens, Greece | Prospective cohort Followed throughout pregnancy | N=47 pregnant women | UIC, TSH, FT3, FT4 & TPOAb | No assessment | Median UICs in the 1st, 2nd & 3rd trimesters were 113, 117 & 122 µg/L, respectively. No significant difference was observed in TSH between the trimesters. Women in the 1st trimester had a significantly higher mean FT3 (p<0.01) and FT4 (p<0.01) than women in the 2nd and 3rd trimesters. No data on the use of iodine supplements. | | Two studies Level III-2 Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|---|--|---|---|---------------------------|---|---|----------------------------|
| Koukkou et al, 2014b Athens & Patras, Greece | Prospective cohort & cross sectional | N=424 pregnant women | UIC, TSH, FT4, Tg & TPOAb | Use of iodized salt | <p>Median UICs in the 1st, 2nd & 3rd trimesters were 130, 125 & 130 µg/L, respectively. Mean TSH was significantly lower in the 1st trimester ($p<0.01$) than in the 2nd & 3rd trimesters. Mean FT4 was significantly lower in the 3rd trimester ($p<0.01$) than in the 1st & 2nd trimesters. Median Tg was significantly lower in the 2nd trimester ($p<0.01$) than in the 1st & 3rd trimester.</p> <p>All pregnant women did not use iodine supplements. Two spot urine samples collected on two different days for the determination of UIC.</p> | | Level IV |
| Kung et al, 2002 Southern China (Hong Kong) | Prospective cohort Followed-up at 1 st & 3 rd trimester & 6wks & 3mths postpartum | N=221 healthy pregnant women, with no history of thyroid dysfunction Borderline sufficient | UI, thyroid function (TSH, FT4, FT3, Tg), TV & nodules (ultrasound) | No assessment | Thyroid nodules were detected in 34 (15.3%) in 1 st trimester, 12 (5.4%) had > 1 nodule. Women with thyroid nodules were older ($P < 0.01$) & had higher gravidity ($P < 0.02$) than those women without thyroid nodules. Patients with thyroid nodules had lower serum TSH values ($P < 0.03$) & higher Tg levels (P | | Level III-2 |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|---|-----------------|---|-----------------------|---|---|---|----------------------------|
| | | | | | <0.05) throughout pregnancy. Appearance of new nodules was detected in 25 (11.3%) women. subjects with new nodule formation had higher UI excretion from 2nd trimester onward (P all < 0.05). No difference in their TSH & Tg levels throughout pregnancy. Fine-needle aspiration on nodules greater than 5 mm in any dimension after delivery (n =21) confirmed the majority having histological features consistent with nodular hyperplasia. No thyroid malignancy was detected. | | |
| Menéndez Torre et al, 2014 Asturias, Spain | Cross-sectional | N=173 pregnant women in the 1st trimester | UIC, TSH, FT4 & TPOAb | Iodine supplements, use of iodised salt & dairy products. | Median UIC, mean TSH & mean FT4 were 197 µg/L, 2.1 mU/L & 1.2 ng/dL, respectively. No difference in TSH and FT4 between iodine supplemented and non-iodine supplemented women. 47% of pregnant women took iodine supplements. | | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|--|--|---|--|---|---|---|----------------------------|
| Meng et al, 2013 Gansu, Shandong, Fujian, Jilin, Anhui & Chongqing provinces, China | Cross-sectional | N=699 pregnant women (trimester of pregnancy not reported) | UIC, TSH, FT4, Tg, TgAb & TPOAb | Household salt samples | Median UIC, TSH, FT4 and Tg were 206 µg/L, 1.7 mU/L, 13.3 pmol/L & 4.9 µg/L, respectively. TSH decreased from ~ UIC 50 to 300 µg/L and increase from UIC 300 to 550 µg/L. No data on the use of iodine supplements. | | Level IV |
| Moleti et al, 2009 Sicily Italy | Prospective cohort Followed up at 12, 18, 24, 30 & 38 wks | N= 220 Pregnant women never tested for thyroid dysfunction Mild ID | FT4, TSH TPO-Ab Tg-Ab (at initial & final follow-up only) | Questionnaire about dietary habits, in particular iodized salt. | Thyroid autoantibodies were detectable in 8.2% women. Overall, the prevalence of hypothyroidism over the course of gestation was 11.8% (26/220), with a RR of hypothyroidism in antibody-positive women of 5.0 (chi (2) 20.02, P<0.0005). Nonetheless, almost 70% hypothyroid women tested negative for thyroid autoantibodies. 15/26 (57.7%) hypothyroid women were identified at presentation, & the remaining 11 at either early (6/11) or | | Level III-2 |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|------------------------------------|--|---|------------------|---|--|---|--|
| | | | | | late (5/11) phases of the 2nd trimester. Isolated hypothyroxinemia was observed in 56/220 (25.4%) women, mostly from the 2nd trimester onwards. | | |
| Moleti et al, 2011 Sicily Italy | Prospective cohort Followed up at 12, 18, 24, 30 & 38 wks | N= 168 women receiving prenatal preparations containing 150 µg of iodine from early pregnancy (150-I group); 105 women who had regularly used (>2 yrs) iodized salt prior to becoming pregnant (I-salt group); 160 women neither taking | TSH, FT3 & FT4 | Questionnaire about dietary habits, in particular iodized salt. | Mean TSH was higher among the 150-I women than in the remaining two groups, & in a high proportion of them, TSH values were found to exceed the upper limit for gestational age. The prevalence of low FT4 in the 150-I women was similar to that observed in the I-salt women & markedly lower than that recorded for the no-I group. | | Note: this is the same study as Moleti et al 2009. |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|-------------------------------------|---|--|--|--|--|--|----------------------------|
| | | iodine supplements nor using iodized salt (no-I group). Mild ID | | | | | |
| Moradi et al, 2013 Tehran, Iran | Cross-sectional | N=584 pregnant women: 162 in the 1st trimester & 422 in the 3rd trimester | UIC, TSH, FT3, TT4, FT4, FTI, T3RU & TPOAb | No assessment | Median UIC, TSH, FT3, TT4 and FT4 were 240 µg/L, 2.2 mIU/L, 30.8 pmol/L, 10.0 µg/dL & 12.4 pmol/L, respectively (only included data from pregnant women negative for TPO-Ab). No data on the use of iodine supplements. | | Level IV |
| Moreno-Reyes et al, 2013 Belgium | National cross-sectional survey Randomly sampled from 55 obstetric clinics | 1311 pregnant women not taking thyroid medication (n=640 & 667 in 1 st & 3 rd trimester respectively) Mild ID | UIC/Cr, TSH, TPO-Ab, TG, FT3, FT4 | Face to face questionnaire for use of iodine-containing supplements, food consumption, | 7.2% had elevated serum TSH & 13.8% of these women were TPO-Ab positive. 4.1% had low serum TSH. 4% of entire population had positive TPO-Ab &/or Tg antibodies. Thyroid disorders (abnormally high or low TSH) or thyroid autoimmunity was present in 18.6% & 12.3% in 1 st & 3 rd trimester | Gestational age, age, ethnicity, seasons, log UIC/Cr | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|---|--|---|---|---------------------------------|--|---|----------------------------|
| | | | | & use of iodized household salt | respectively. Women with adequate iodine (UIC/Cr = 150–249 µg /g) had lower median Tg concentration compared to moderately ID women (UIC/Cr ≤49 µg/g), 19 µg /L & 25 µg /L, respectively. | | |
| Pettigrew-Porter et al, 2011 New Zealand | Cross-sectional | N=170 | UIC (spot urine), TV (ultrasound), FT4 & TSH | Semi-quantitative FFQ | The median UIC of the women was 38 lg / L. 7% of women had goitre. Iodine intake was 48 lg / day. The majority of women had TSH and FT4 concentrations within pregnant reference ranges, suggesting that despite the low UIC observed in these women, thyroid hormone production was not affected. | | Level IV |
| Raverot et al, 2012 Lyon, France | Cross-sectional Iodine intake of general population <100 µg/day | N= 228 healthy pregnant women with no history of thyroid disease from 1 st , 2 nd , 3 rd trimester of pregnancy (n=53, n=107, n=68 | TSH, FT4, anti-TPO, Tg, UIC (spot) in 1 st (6-13 wks), 2 nd (14-27 wks), 3 rd (28-38 wks) trimester of pregnancy | No assessment | The median (range) UIC was 81 (8–832) lg/L, & 77% of pregnant women had a UIC < 150 lg/L. 11% had abnormal TSH or anti-TPO. Median FT4 (pmol/L) was 14.9, 12.6, & 11.5 in the 1st, 2 nd , & 3rd trimesters, respectively. Median Tg in pregnant women was 16.2 lg/L, did not differ across trimesters, & was higher than in the | Maternal age, wk of gestation. | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|--|-----------------|--|--|---------------------------|--|---|--|
| | | respectively). Controls (men & non pregnant women) provided reference intervals of thyroid test | | | control group of non-pregnant adults (11.7 l g/L) ($p = 0.02$). UIC did not predict any of the thyroid function tests. | | |
| Rebagliato et al, 2010 3 areas in Spain (Guipúzcoa, Sabadell, Valencia) | Cross-sectional | N= 1844 pregnant women (gestational age range 8-23 wks) with no diagnosed thyroid pathology Mild ID | FT4 & (TSH) Iodine (spot urine) & questionnaire estimates of iodine intake from diet, iodized salt & supplements | | There was an increased risk of TSH above 3 μ U/mL in women who consumed 200 μ g or more of iodine supplements daily compared with those who consumed less than 100 μ g/day (adjusted OR = 2.5 [95% CI = 1.2 to 5.4]). No association between UI & TSH levels (model 1). Pregnant women from the area with the highest median UI (168 μ g/L) & highest supplement coverage (93%) showed the lowest values of serum FT4. (geometric mean = 10.09 pmol/L [9.98 to 10.19]) (model 2) | Model1: Area, country of origin, education level, parity, gestational age at sample Model 2: Iodine intake from salt, food & | Level IV Increased risk of elevated TSH (reference for pregnancy) in those taking supplements > 200 μ g/day |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|--|---|--|---|---------------------------|---|---|----------------------------|
| | | | | | | supplements | |
| Sahin et al, 2014 Reze, Turkey | Prospective cohort Followed throughout pregnancy & 3 mo postpartum | N= 58 pregnant women Severely iodine deficient area | UIE, TSH, FT3, FT4, TgAb, TPOAb & TV | No assessment | Mean UIE, TSH, FT3 and FT4 in 1st trimester were 14 µg/L, 1.1 mIU/L, 5.1 pmol/L & 14.2 pmol/L, respectively. Only included healthy pregnant women (no nodular thyroid disease). All pregnant women did not use iodine supplements. | | Level III-2 |
| Sang et al, 2012 Tianjin & Haixing, China | Cross-sectional | N=384 (n=174 Tianjin, n= 210 Haixing) with no previous investigation of ID diseases. Tianjin: Iodine sufficient Haixing: Excessive iodine (due to water) | UIC (Morning urine) FT3, FT4, TSH. | | Median UIC of pregnant women with EI intake was higher than those with AI intake (P < 0.001). The prevalence of thyroid disease, especially subclinical hypothyroidism, in pregnant women with excessive iodine intake was significantly higher than in those with adequate iodine intake (P< 0.05). Subclinical hypothyroidism was the most frequent pattern of thyroid disease for pregnant women & those with positive or negative thyroid autoantibodies. Living with high water iodine content & having UIC higher | | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|---------------------------------------|---|--|--|---|---|---|--|
| | | | | | than 250µg/liter are associated risk factors for subclinical hypothyroidism in pregnant women (OR1 = 41.822, OR2 = 6.202; P < 0.05, where OR1 is the OR for living with high water iodine content & hypothyroidism & OR2 is the OR for UIC >250 µg g/liter & hypothyroidism). | | |
| Suarez Rodriguez et al, 2013 Spain | Cross sectional | N=147 women in their 3rd trimester (wk 37) of pregnancy Mild ID | TSH & T4 in mothers at booking. TSH in the babies born to the 140 mothers in the postpartum group | FFQ | Only 10.9% of pregnant women consumed more than 250 µg iodine daily, and 24.4% of them consumed less than 100µg daily. Mean free T4 levels were 9.37pmol/L, and 74 women (54.41%) had levels below the hypothyroxinemia threshold. TSH levels were normal in 135 newborns (96.4%), while 5 (3.6%) had levels higher than 5 µU/mL. | | Level IV |
| Vandevijvere et al, 2013 Belgium | National cross-sectional survey Randomly sampled from 55 obstetric | N=1311 Pregnant women not taking thyroid | Iodine status assessed 1 year after the introduction of bread fortified | General questionnaire completed with practice nurse | The median UIC was 124.1 µg/l and 122.6 µg/g creatinine when corrected for urinary creatinine. The median UIC in the 1st trimester (118.3 µg/l) was lower than that in the 3rd trimester (131.0 µg/l) but | | Note this is the same study as Moreno-Reyes et al 2013 |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|------------------------------|-----------------|---|---|---------------------------|---|---|----------------------------|
| | clinics | medication (n=640 & 667 in 1 st & 3 rd trimester respectively) Mild ID | with iodised salt UIC, iodine intake | | significantly higher than among non-pregnant women (84.8 µg/l). Iodine-containing supplement intake was reported by 60.8 % of the women & 57.4 % of the women took this supplement daily. The risk of iodine deficiency was higher in younger women, in women not taking iodine-containing supplements, with low consumption of milk and dairy drinks and during autumn. Women with a higher BMI had a higher risk of iodine deficiency but the risk was lower in women who reported alcohol consumption. Age, trimester of pregnancy, region, BMI, smoking behavior, alcohol consumption, use of iodised household salt, bread consumption, fish consumption, milk and dairy drink consumption, education level, ethnicity & parity | | |
| Velasco et al, 2013 Spain | Cross-sectional | N= 233 healthy pregnant women (29.7±5.6 years) | TSH, FT4, & FT3, UIC | No assessment | Median maternal UIC was 126.5 µg/L. FT3, but not TSH and free FT4, correlated significantly with the UIC (r=0.17, p=0.013). | | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|---|-----------------|--|----------------------------------|--|---|---|----------------------------|
| | | and in their newborn. Inclusion of women in the study was done within the 24 hours before delivery. | | | The cord blood TSH, FT4, and FT3 correlated positively with the maternal UIC at the time of delivery ($r=0.24$, $p=0.001$; $r=0.16$, $p=0.032$; and $r=0.24$, $p=0.003$, respectively). The cord blood and heel blood TSH correlated positively with the amniotic fluid iodine concentration ($r=0.21$, $p=0.015$ and $r=0.15$, $p=0.036$). The cord blood TSH correlated positively with the cord blood FT4 ($r=0.21$, $p=0.022$) and FT3 ($r=0.32$, $p=0.017$). The maternal TSH correlated with the cord blood TSH ($r=0.22$, $p=0.014$) and with the heel blood TSH ($r=0.13$, $p=0.050$). | | |
| Wang et al, 2014 Yongjing, China | Cross-sectional | N=215 pregnant women: 70 in 1st trimester, 73 in 2nd trimester & 72 in 3rd trimester). | UIC, TSH, FT3, FT4, TgAb & TPOAb | Household salt & drinking water samples. | Median UICs in the 1st, 2nd & 3rd trimesters were 190, 153 & 145 $\mu\text{g/L}$, respectively. Mean TSH in pregnant women in the 2nd trimester was significantly lower ($p<0.05$) than those in the 1st & 3rd trimesters. Mean FT3 in pregnant women in the 3rd trimester was significantly lower ($p<0.05$) than those in | | Level IV |

| First author year, Area | Study design | Population, participants, iodine status of area | Outcome measures | Dietary assessment method | Results | Confounders adjusted for/sensitivity analysis | Study quality and comments |
|-------------------------|--------------|---|------------------|---------------------------|--|---|----------------------------|
| | | | | | the 1st & 2nd trimesters. FT3 decreased significantly with gestational age ($p < 0.05$). No difference was observed in FT4 between trimesters. | | |

Systematic review of RCT

| Author, date | Number of studies included | Search strategy | Studies included | Results of systematic review | |
|-----------------|----------------------------|---|---|--|---------------------------------|
| Zhou et al 2013 | 12 RCTs | Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, Cumulative Index to Nursing and Allied Health Literature and PsycINFO databases. | <p>All RCTs comparing the effect of iodine supplementation with a parallel control group who received no iodine supplementation (or placebo) during pregnancy or the preconceptional period on clinical or biochemical outcomes were eligible for inclusion in the review.</p> <p>Pregnant women or those of childbearing age regardless of iodine status or gestation at trial</p> | <p>No obvious dose-response relation was seen. The effects of iodine supplementation on changes in thyroid hormone concentrations in mothers and infants were not consistent</p> <p>When assessed in mothers, higher thyroxine concentrations were reported in 1 of 5 trials, lower TSH was reported in 1 of 6 trials, and lower thyroglobulin concentrations were reported in 2 of 4 trials in the iodine-supplemented group compared with control group. In infants of iodine-supplemented mothers, significant reductions in cord blood thyroglobulin were observed in 2 of 4 trials, and cord blood thyroxine was increased in 1 of 3 trials. There were no reports of</p> | Level I, with low risk of bias. |

| Author, date | Number of studies included | Search strategy | Studies included | Results of systematic review | |
|--------------|----------------------------|-----------------|---|---|--|
| | | | entry were included. Trials were eligible for inclusion in which women received any form of iodine supplementation, with or without other nutrients, in which the only difference between the treatment and comparison group was the presence or absence of iodine. The primary outcome was the cognitive development of children. <i>Secondary outcomes included pregnancy and birth outcomes, childhood growth and mortality, iodine status, and thyroid function of mothers and infants. The search was restricted to human studies without language restrictions.</i> | <p>significant changes in maternal triiodothyronine/free triiodothyronine or TBG, infant free thyroxine, triiodothyronine, TBG, or TSH between supplemented and control groups.</p> <p>Women in the iodine-supplemented group compared with women in the control group had lower thyroid volumes in 1 of 2 trials that reported this outcome. Two other trials showed that supplementation reduced pregnancy increases in maternal thyroid volume; however, results were analyzed as percentage changes within groups and not based on the intention-to-treat principle. Children of supplemented mothers had lower thyroid volumes than did children of non-supplemented mothers in the 2 trials that reported this outcome.</p> | |

Abbreviations: AI Adequate Intake, BMI Body Mass Index, CI Confidence Interval, EI Excessive Intake, OR Odds ratio, UIC Urinary Iodine Concentration, RR relative risk, TV thyroid volume

¹ FT₃, free triiodothyronine; FT₄, free thyroxine; m, months; MUI, median urinary iodine; MUIE, mean urinary iodine excretion; n, number; No diff, no difference; NR, not reported; P, probability; PP, postpartum; PPTD, postpartum thyroid dysfunction; rT₃, reverse T₃; T₃, triiodothyronine; T₄, thyroxine; TBG, thyroxine-binding globulin; Tg, thyroglobulin; Tg-Ab, thyroglobulin antibodies; TM, trimester; TPO-Ab, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone or thyrotropin; TT₃, total triiodothyronine; TT₄, total thyroxine; UI, urinary iodine; wk(s), week(s); yr(s), year(s)

Table 7:5 Studies related to pregnancy EAR and neurological outcomes in their children (Review Question 3)

Observational studies

| Author, year | Sampling, location, year | Maternal assessment | No. of mother-child pairs | Gestational iodine status | Assessment test method | Child age at testing | Effect | Quality Rating and Comments |
|------------------------|--|---|---------------------------|--|--|----------------------|---|--|
| Bath et al, 2013 | PW participated in Avon Longitudinal Study of Parents and Children. Southwest England in the UK, 1991-1992 & 1999-2001 | One Spot-urine sample in first trimester | 958 | mild-moderate ID; 67% had UICR $\leq 150\mu\text{g/g}$ | Wechsler Intelligence Scale for Children - IQ Neale Analysis of Reading Ability - reading ability | 8y | Gestational UICR of $<150\mu\text{g/g}$ is associated to low child verbal IQ, reading accuracy and reading comprehension vs. gestational UICR $\geq 150\mu\text{g/g}$ | Level III-2 (Birth cohort) Single urine sample only provided in first trimester. Effect of inadequate maternal UIC on child IQ might be attenuated due to potential iodine contamination of some urine samples. This might move iodine value towards $150\mu\text{g/g}$ or more. |
| Ghassabian et al, 2014 | PW enrolled in the Generation R Study (a population-based birth cohort in Rotterdam, Netherlands), | Spot urine samples in the gestation age <18 weeks | 1525 | Median UIC was $230\mu\text{g/L}$ and $297\mu\text{g/g}$; 12% of pregnant women had $\text{UIC} < 150\mu\text{g/g}$. | A validated Dutch test batteries: two subsets of the Snijders-Oomen Niet-verbale intelligentic | 6y | Model 1 (unadjusted): A univariate association was reported between maternal low UIC and children's suboptimum non- | Level III-2 |

| Author, year | Sampling, location, year | Maternal assessment | No. of mother-child pairs | Gestational iodine status | Assessment test method | Child age at testing | Effect | Quality Rating and Comments |
|--------------|--------------------------|---------------------|---------------------------|---------------------------|---|----------------------|--|-----------------------------|
| | 2002-2006 | | | | Test-Revisie & the receptive subtest of the Taaltest voor Kinderren (TvK) | | <p>verbal IQ (unadjusted OR=1.44, 95% CI 1.02-2.02).</p> <p>Model 2 (adjusted for child's sex & age at the time of cognitive assessment, maternal age & maternal education levels): No association between maternal low UIC and children's suboptimum non-verbal IQ (adjusted OR=1.21, 95% CI 0.85-1.73).</p> <p>Model 3 (adjusted for child's sex & age at the time of cognitive assessment, ethnic background, birth order & history of breast feeding at age 6 mo, & parental age</p> | |

| Author, year | Sampling, location, year | Maternal assessment | No. of mother-child pairs | Gestational iodine status | Assessment test method | Child age at testing | Effect | Quality Rating and Comments |
|-------------------|---|----------------------------|---------------------------|---|--|----------------------|---|--|
| | | | | | | | at the time of pregnancy, maternal BMI, maternal history of smoking, maternal IQ, marital status, parental educational levels, maternal psychopathology in pregnancy, maternal folate concentration in early pregnancy, household income & time of urine sampling in pregnancy): No association between maternal low UIC and children's suboptimum non-verbal IQ (adjusted OR=1.33, 95%CI 0.92 to 1.92. | |
| Hynes et al, 2013 | PW attended the Royal Hobart Hospital, Tasmania in Australia, 1999- | One to three urine samples | 228 | mild-moderate ID; 71.1% had UIC<150ug/L; median UIC = | Australian National Assessment Program, NAPLAN and | 9y | Gestational UIC of <150ug/L was associated to poor spelling in children vs. gestational UIC | Level III-2 (Birth cohort) Voluntary iodine fortification program |

| Author, year | Sampling, location, year | Maternal assessment | No. of mother-child pairs | Gestational iodine status | Assessment test method | Child age at testing | Effect | Quality Rating and Comments |
|------------------------|---|---|---------------------------|---|-------------------------------------|----------------------|---|---|
| | 2001 & 2009-2010 | | | 81ug/L | SARIS - literacy; numeracy | | ≥150ug/L. | was implemented during the study. 17% children were born after but within 6 weeks of the fortification program being implemented |
| Julvez et al, 2013 | PW enrolled in the INfancia y Medio Ambiente (INMA) project in Spain, 2004-2008 | TSH & FT4 before the 21st week of gestation | 1761 | Iodine sufficient or mildly iodine deficient (data on UIC were reported in Rebagliato et al (2013) & Murcia et al (2010) | Bayley Scales of Infant Development | 11-23 mo | Low FT4 (<5th percentile) was associated with a decrease of mental scores. No association was observed between TSH and mental or psychomotor scores. | Level III-2 |
| Rebagliato et al, 2013 | PW enrolled to the main public hospital or health center, Sabadell, Asturias and Gipuzkoa in Spain, 2004-2009 | A 100-item SFFQ incl. questions on supplements & salt in 1 st & 3 rd trimester. Spot urine in 1 st trimester | 1519 | mild-moderate ID; UIC ranged from 72ug/L to 212ug/L; median UIC in Gipuzkoa = 169ug/L; in Sabadell = 90ug/L. Median dietary | Bayley Scales of Infant Development | 12-30m | Child development was not associated to dietary iodine intake, iodized salt consumption, high maternal UIC (i.e. 100-149ug/L, 150-249ug/L and ≥250ug/L) vs. UIC<100ug/L, and high supplementary | Level III-2 (Birth cohort) Range of UIC narrow. Good follow-up of infants at 1 yr (89%). Referent group = no supplements or <100ug/day (not directly related to PICO question). Iodine |

| Author, year | Sampling, location, year | Maternal assessment | No. of mother-child pairs | Gestational iodine status | Assessment test method | Child age at testing | Effect | Quality Rating and Comments |
|------------------------------|--|---|---------------------------|--|---|----------------------|--|--|
| | | | | iodine intake = 162ug/day | | | iodine intake (i.e. 100-149ug/day and ≥ 150 ug/day) vs. intake <100ug/day. Maternal supplementation of $\geq 150 \mu\text{g/day}$ iodine related to 1.5-fold increase in odds of a psychomotor score < 85 (95% CI = 0.8, 2.9) and to 1.7-fold increase in odds of a mental score <85 (95% CI = 0.9, 3.0). | supplementation programs differed in geographical regions. Maternal thyroid autoimmunity (thyroid antibodies) not measured. IQ of parents and quality of home environment not measured. |
| Suarez-Rodriguez et al, 2012 | PW attended the University Clinic of Navarra, Pamplona in Spain, 2002-2003 & 2006-2007 | A blood sample A 24-h urine sample in week 37 of gestation | 70 | Moderate ID: median UIC = 87ug/L (Note: 24hr urine sample). 80% had UIC <150ug/L & 56% <50ug/L. For free serum T4, 54% of 140 participants had | McCarthy Scales of Children's Abilities | 38-60m | Suboptimal free T4 concentration (<10 th percentile vs. >10P) in PW was associated with lower general cognitive index, memory and perceptual-manipulative skills | Level III-2 (birth cohort). High level of bias - not all children of the women in the original sample were evaluated (n=70 children of 141 enrolled women). 24hr UIC expressed as ug/L, other studies use |

| Author, year | Sampling, location, year | Maternal assessment | No. of mother-child pairs | Gestational iodine status | Assessment test method | Child age at testing | Effect | Quality Rating and Comments |
|---------------------|---|--|---------------------------|---|--|----------------------|---|---|
| | | | | value <9.5pmol/L. | | | | spot UIC. |
| van Mil et al, 2012 | Convenience sample of PW taking part in an ongoing birth cohort study, named Generation R Study, Rotterdam in Netherland, 2002-2010 | A 293-item SFFQ. Behavior Rating Inventory of Executive Function for Preschoolers (BRIEF-P) A spot urine sample A blood sample | 1123 | Sufficient: median UIC=203ug/L (range: 9.3–1743.5 mg/L) | BRIEF-P (completed by parents or caregivers) | 18-36m & 8-10y | Maternal UIC was directly associated to children inhibition scores and working memory | Level III-2 (Birth cohort). Of 1156 mother-child pairs enrolled in the study, 1123 pairs (97%) completed the BRIEF-P. |

Abbreviation: PW=PW UICR=urinary iodine-to-creatinine ratio; ID=iodine deficiency; UIC=urinary iodine concentration; SFFQ=semiquantitative food frequency questionnaire; h=hour; y=year; m=month T4=throxin 4;

Intervention studies

| Author, year, location | Inclusion criteria | Design and doses | Sample size | Baseline or follow-up gestational iodine status | Assessment test method | Child age at testing | Main effect(s) | Comments |
|------------------------|--------------------------------------|-------------------------------------|---------------------------------|---|------------------------|----------------------|---------------------------------|--|
| Santiago et al, 2013, | Week 10 of pregnancy, and not taking | RCT G1: IS G2: 200ug KI/day & | n = 131 (G1: 38) (G2: 55) | In the 3rd trimester, mean UIC was | Bayley Scales | 6-18m | No significant differences were | Level II. One-third of the women had been |

| Author, year, location | Inclusion criteria | Design and doses | Sample size | Baseline or follow-up gestational iodine status | Assessment test method | Child age at testing | Main effect(s) | Comments |
|--------------------------------|--------------------|--|---|---|--|----------------------|---|---|
| Spain | iodine supplements | recommendation on using IS G3: 300ug KI/day & recommendation on using IS start before 10 week of gestation | (G3:38) | 144ug/L in IS group, 166ug/L in 200ug KI group, and 212ug/L in 300ug KI group | | | observed in child neurological development between groups. | taking IS for ≥1year, and all women in this study appear to have a better iodine status than participants in previous studies. |
| O'Donnell et al, 2002 China | NS | Comparative intervention G1: 400mg oral iodinated oil to PW in 1st or 2nd trimester G2: 400mg oral iodinated oil to PW in the 3rd trimester G3: 200mg oral iodinated oil to children at age 2-3 years | n=44 (G1: 89) (G2: 103) (G3: 80) | The study was done in an area with visible goitre prevalence of 54% and congenital severe hypothyroidism of 2%. | Raven Progressive Matrices Developmental Test of Visual Motor Integration Purdue Pegboard Test Denver Developmental screening Test | 5-7y | No significant differences between groups in Raven test and language delays. Children whose mothers received iodine in the 1st or 2nd trimester in pregnancy (vs. those whose mothers were supplemented later or to | Level II. Provides some evidence that early rather than late I supplementation is beneficial for better psychomotor skills at aged 5 – 7y. Control group was supplementation of children at age 2y, rather than no supplementation as in PICO question. In G1, 23 children who might not receive sufficient iodine from their mother who were supplemented 0.1mg |

| Author, year, location | Inclusion criteria | Design and doses | Sample size | Baseline or follow-up gestational iodine status | Assessment test method | Child age at testing | Main effect(s) | Comments |
|------------------------|--------------------|------------------|-------------|---|------------------------|----------------------|--|---|
| | | | | | | | children received supplementat ion at 2 years) have higher scores in Visual Motor Integration test, and in Purdue Pegboard test. | KI daily for four days each year instead of 400mg iodinated oil. Details refer to Cao et al. (1994). paper. |

Abbreviation: G1=group 1; G2=group 2; G3=group 3; IS=iodised salt; KI=potassium iodide; UIC=urinary iodine concentration; PW:PW

Meta-analysis

| Authors, year, | Aim | Time period of coverage, no. of articles | Inclusion criteria | Exclusion criteria | Main findings | Comments |
|--------------------|---|--|---|--|---|--|
| Bougma et al, 2013 | Using meta-analysis to examine the relationship between iodine and mental | 1980-2011, n=24 (RCT: n=2) (non-RCT intervention: n=8) | 1) Exposure to different iodine levels before pregnancy, during pregnancy or shortly after birth 2) Examine iodine exposure and mental development | 1) Use of non-standardized psychometric tests 2) Sole focus on gross motor milestones 3) Cross-sectional observational designs that compared iodine- | Iodine deficient children had 6.9-10.2 IQ points lower than iodine replete children | Level I Consistent results across study designs. Early pregnancy supplementation has better outcomes than |

| Authors, year, | Aim | Time period of coverage, no. of articles | Inclusion criteria | Exclusion criteria | Main findings | Comments |
|----------------|---|--|--|--|---------------|---|
| | development of children 5 years old and under | (Cohort prospective by maternal I status: n=9) (Cohort prospective by infant I status: n=4) | outcome of children ≤5 years 3) Have placebo, historical control, or iodine sufficient children of similar age as a control | sufficient with iodine-deficient communities 4) Stratification of mothers based on an indicator of thyroid dysfunction and/or antibody status rather than iodine status | | 2 nd and 3 rd trimester, but only 2 RCTs, one in each (early vs late); both small N |

Abbreviation: RCT=randomised controlled trial;

Systematic review of RCT

| Author, date | Number of studies included | Search strategy | Studies included | Results of systematic review |
|------------------|----------------------------|---|--|--|
| Zhou et al, 2013 | 12 RCTs | Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, Cumulative Index to Nursing and Allied Health Literature and PsycINFO databases. | <p>All RCTs comparing the effect of iodine supplementation with a parallel control group who received no iodine supplementation (or placebo) during pregnancy or the preconceptional period on clinical or biochemical outcomes were eligible for inclusion in the review.</p> <p>Pregnant women or those of childbearing age regardless of iodine status or gestation at trial entry were included. Trials were eligible for inclusion in which women received any form of iodine</p> | <p>No obvious dose-response relation was seen. The effects of iodine supplementation on changes in thyroid hormone concentrations in mothers and infants were not consistent</p> <p>When assessed in mothers, higher thyroxine concentrations were reported in 1 of 5 trials, lower TSH was reported in 1 of 6 trials, and lower thyroglobulin concentrations were reported in 2 of 4 trials in the iodine-supplemented group compared with control group. In infants of iodine-supplemented mothers, significant reductions in cord blood</p> |

| Author, date | Number of studies included | Search strategy | Studies included | Results of systematic review |
|--------------|----------------------------|-----------------|--|---|
| | | | <p>supplementation, with or without other nutrients, in which the only difference between the treatment and comparison group was the presence or absence of iodine. The primary outcome was the cognitive development of children.</p> <p><i>Secondary outcomes included pregnancy and birth outcomes, childhood growth and mortality, iodine status, and thyroid function of mothers and infants. The search was restricted to human studies without language restrictions.</i></p> | <p>thyroglobulin were observed in 2 of 4 trials, and cord blood thyroxine was increased in 1 of 3 trials. There were no reports of significant changes in maternal triiodothyronine/free triiodothyronine or TBG, infant free thyroxine, triiodothyronine, TBG, or TSH between supplemented and control groups.</p> <p>Women in the iodine-supplemented group compared with women in the control group had lower thyroid volumes in 1 of 2 trials that reported this outcome. Two other trials showed that supplementation reduced pregnancy increases in maternal thyroid volume; however, results were analyzed as percentage changes within groups and not based on the intention-to-treat principle. Children of supplemented mothers had lower thyroid volumes than did children of non-supplemented mothers in the 2 trials that reported this outcome.</p> |

Abbreviations: AI Adequate Intake, BMI Body Mass Index, CI Confidence Interval, EI Excessive Intake, OR Odds ratio, UIC Urinary Iodine Concentration, RR relative risk, TV thyroid volume

¹ FT₃, free triiodothyronine; FT₄, free thyroxine; m, months; MUI, median urinary iodine; MUIE, mean urinary iodine excretion; n, number; No diff, no difference; NR, not reported; P, probability; PP, postpartum; PPTD, postpartum thyroid dysfunction; rT₃, reverse T₃; T₃, triiodothyronine; T₄, thyroxine; TBG, thyroxine-binding globulin; Tg, thyroglobulin; Tg-Ab, thyroglobulin antibodies; TM, trimester; TPO-Ab, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone or thyrotropin; TT₃, total triiodothyronine; TT₄, total thyroxine; UI, urinary iodine; wk(s), week(s); yr(s), year(s)

Abbreviation: PW=PW UICR=urinary iodine-to-creatinine ratio; ID=iodine deficiency; UIC=urinary iodine concentration; SFFQ=semiquantitative food frequency questionnaire; h=hour; y=year; m=month T4=throxin 4;

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7.3 Appendix 3: Studies relating to UL for Children

Table 7:6 GRADE evaluation of Zimmerman et al (2005) paper used for determination of UL in children

Author(s):

Date:

Question: Iodine intake (urinary Iodine <300mc g/L) for normal thyroid function compared to Iodine intake (urinary iodine >300mc g/L) for abnormal thyroid function (measured by increased thyroid volume/hormone levels) for children 9-13 years

Setting: general population

Bibliography (systematic review):

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|--------------------|-----------------------|---------------|---------------|---------------|---------------|------------------------|--|--|------------------------|-------------------------|----------|------------|
| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Iodine Intake (urinary Iodine <300mcg/L for normal thyroid function) | Iodine Intake (urinary Iodine >300mcg/L for normal thyroid function (measured by increased thyroid volume/hormone levels)) | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | Observational studies | Not serious 1 | Not serious 1 | Not serious 1 | Not serious 1 | Dose response gradient | 1651/3319 (49.7%) | 1668/3319 (50.3%) | OR 1.75 (1.10 to 2.90) | 136 more per 1000 (from | MODERATE | CRITICAL |

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|--------------------|--------------|--------------|---------------|--------------|-------------|----------------------|---|---|-------------------|-----------------------|---------|------------|
| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Iodine Intake (urinary Iodine <300mcg/L for normal thyroid function | Iodine Intake (urinary Iodine >300mcg/L for normal thyroid function (measured by increased thyroid volume/hormone levels) | Relative (95% CI) | Absolute (95% CI) | | |
| | | | | | | | | | | 24 more to 243 more 1 | | |

Table 7:7 Body of Evidence for Provisional UL in children 1-3 years

Review Question 10 *What is the average intake of normal healthy children aged 1-3 years above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels?*

| Component | Rating | Notes |
|----------------------|--------------|--|
| Evidence Base | Poor | 1 Level II (RCT) + 1 Level III-3 + 17 Level IV studies |
| Consistency | Poor | Inconsistent results across studies. Study of Zimmerman et al. (2005) provides best evidence from children across a wide range of intakes in 5 continents and this showed an increase in thyroid volume) at a UI concentration of ~500 µg/L. |
| Clinical impact | Moderate | Health implications of sustained increased thyroid volume and elevated TSH levels in children not well defined. |
| Generalisability | Satisfactory | Most studies from China or Africa, therefore limited generalizability. |
| Applicability | Satisfactory | Probably applicable to Australian and New Zealand healthcare context with some caveats |
| Draft Recommendation | | A Provisional Upper Level (PUL) is set at 280 µg/day because of uncertainty related to evidence for this specific age group and a need to extrapolate values from UL calculated for age 9–13 years using metabolic weight formula. |
| Recommendation | C | Body of evidence provides some support for recommendation(s) but care should be taken in its application. Calculations were based on body weights for 2-3 year old children. |

Table 7:8 Body of Evidence for Provisional UL in children 4-8 years

Review Question 11 *What is the average intake of normal healthy children aged 4-8 years above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels?*

| Component | Rating | Notes |
|----------------------|--------------|--|
| Evidence Base | Poor | 1 Level II (RCT) + 1 Level III-3 + 17 Level IV studies. |
| Consistency | Poor | Inconsistent results across studies. Study of Zimmerman et al. (2005) provides best evidence from children across a wide range of intakes in 5 continents and this showed an increase in thyroid volume) at a UI concentration of ~500 µg/L. |
| Clinical impact | Moderate | Health implications of sustained increased thyroid volume and elevated TSH levels in children not well defined. |
| Generalisability | Satisfactory | Most studies from China or Africa, therefore limited generalizability. |
| Applicability | Satisfactory | Probably applicable to Australian and New Zealand healthcare context with some caveats |
| Draft Recommendation | | A Provisional Upper Level (PUL) is set at 350 µg/day because of uncertainty related to evidence for this specific age group and a need to extrapolate values from UL calculated for age 9–13 years using metabolic weight formula. |
| Recommendation | C | Body of evidence provides some support for recommendation(s) but care should be taken in its application. |

Table 7:9 Body of Evidence for Provisional UL in children 9-13 years

Review Question 12 *What is the average intake of normal healthy children aged 9-13 years above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels?*

| Component | Rating | Notes |
|----------------------|--------------|--|
| Evidence Base | Poor | 1 Level II (RCT) + 1 Level III-3 + 17 Level IV studies. |
| Consistency | Poor | Inconsistent results across studies. Study of Zimmerman et al (2005) provides best evidence from children across a wide range of intakes in 5 continents and this showed an increase in thyroid volume) at a UI concentration of ~500 µg/L. |
| Clinical impact | Moderate | Health implications of sustained increased thyroid volume and elevated TSH levels in children not well defined. |
| Generalisability | Satisfactory | Most studies from China or Africa, therefore limited generalizability. |
| Applicability | Satisfactory | Probably applicable to Australian and New Zealand healthcare context with some caveats |
| Draft Recommendation | | Using data from Zimmermann et al (2005) on thyroid volume in children 6-12 years, an iodine intake in excess of 550 µg/day compared to iodine intake below this level leads to a high thyroid volume. UL for the age group 9-13 years was set at 550 µg/day. |
| Recommendation | C | Body of evidence provides some support for recommendation(s) but care should be taken in its application. |

Table 7:10 Body of Evidence for Provisional UL in children 14-18 years

Review Question 13 *What is the average intake of normal healthy children aged 14-18 years above which adverse effects on thyroid function are observed, as indicated by increased thyroid volume and/or abnormal thyroid hormone levels?*

| Component | Rating | Notes |
|----------------------|--------------|---|
| Evidence Base | Poor | 1 Level II (RCT) + 1 Level III-3 + 17 Level IV studies. |
| Consistency | Poor | Inconsistent results across studies. Study of Zimmerman et al. (2005) provides best evidence from children across a wide range of intakes in 5 continents and this showed an increase in thyroid volume) at a UI concentration of ~500 µg/L. |
| Clinical impact | Moderate | Health implications of sustained increased thyroid volume and elevated TSH levels in children not well defined. |
| Generalisability | Satisfactory | Most studies from China or Africa, therefore limited generalizability. |
| Applicability | Satisfactory | Probably applicable to Australian and New Zealand healthcare context with some caveats |
| Draft Recommendation | | A Provisional Upper Level (PUL) is set at 820 µg/day for males and 750 µg/day for females because of uncertainty related to evidence for this specific age group and a need to extrapolate values from UL calculated for age 9–13 years using metabolic weight formula. |
| Recommendation | C | Body of evidence provides some support for recommendation(s) but care should be taken in its application. |

Table 7:11 Studies relating to Upper Limit in children (Review Questions 10-13)

Observational studies

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|------------------|---|---|-------------|---|------------------------------------|--|---|
| Chen et al, 2012 | Cross-sectional study Purposive sample from two primary schools from Hebei in China, 2010 | 370 (60% B, 40% G) | 7-13 | Blood sample Urine sample | NA | Median UIC was 1032ug/L Prevalence of subclinical hypothyroidism and disease of thyroid gland by UIC level: <200ug/L: 0% and 0%; 200-399ug/L: 13.7% and 16.4%; >400ug/L: 26.9% and 52.4% | Level IV study, high risk of bias. Not a nationally representative sample. Only 6% of subjects has UIC <200ug/L, which cannot be used as a comparative control. |
| Feng, 2010 | Cross-sectional study multistage random sampling was used to select school children from villages at 5 cardinal points from Hebei in China, 2010 | 1209 | 8-12 | Urine sample (n=584) Goiter grading by palpation | Calculated I intake Salt sample | No difference in UIC was found between children with goiter and those without goiter. 225ug/L UIC and 337ug/d estimated I intake in goiter patients (n=55, 9.42% of subjects); 207ug/L UIC and 310ug/d estimated I intake in children without goiter | Level IV study Prevalence of goiter might be underestimated due to the use of palpation vs. ultrasonic scan. |

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|---------------------|---|--|-------------|--|---|---|--|
| | | | | | | (n=529, 90.58%) | |
| Henjum et al, 2010 | Cross-sectional study Random sample from 4 Saharawi refugee camps 2007 | 421 | 6-14 | Thyroid ultrasonic scan Urine sample | Drinking water sample Milk sample from livestock | 16% children had UIC of 100-299ug/L; 28% of 300-499ug/L; 38% of 500-000ug/L. Median [iodine] in drinking water was 108ug/L, and in milk was 595ug/L. Goiter rate based on total thyroid volume-for-body surface area was 86%. | Level IV study. Not relevant to Australia and New Zealand - 21% of subjects were underweight, 24% were stunted, and 9% had low BMI-for-age. Most had UIC indicative of excessive intakes. |
| Hussein et al, 2012 | Cross-sectional study Probability-proportional-to-size sampling method G1: schoolchildren living in the Red Sea | G1: 140 (51% B, 49%G) G2: 140 (51% B, 49%G) | 6-12 | Urine sample Goiter grading by palpation | Fish eating questionnaire Household salt sample | G1: iodine in salt varied from 141 to 361mg/kg; mean UIC was 588ug/L; goiter rate was 17.1% G2: no trace of iodine in salt samples; mean UIC | Level IV study with high risk of bias. G1 and G2 are living in similar geographic areas where seafood is accessible. |

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|----------------------|---|---|-------------|---|--|--|--|
| | region G2: schoolchildren living in the White Nile region, Sudan, 2006 | | | | | was 176ug/L; goiter rate was 1.4% | G1 and G2 are not comparable due to difference in dietary habits - 77.1% of children in G2 consumed fish weekly while only 1.4% in G1 reported fish consumption. |
| Izzeldin et al, 2007 | Cross-sectional study Multistage random sampling method, Red Sea, 2006 | 141 | 6-12 | Urine sample (n=141) Goiter grading by palpation | School salt sample (n=20) | Goiter rate was 17% UIC: 3.5%<100ug/L; 21.3% 100-299ug/L; 75.1% ≥ 300ug/L Iodine content in salt ranged from 154mg/kg to 1272mg/kg | Level IV study with high risk of bias. A pilot study with a small sample size. Goiter rate was only reported in abstract but not in the body of the article |
| Li et al, 2012 | Cross-sectional study Randomly selected schoolchildren from village of 202 towns in 16 districts in China, 2009-2010 | 1594 | 8-10 | Thyroid ultrasonic scan | Drinking water sample (n=1097) Household salt sample (n=4501) | Median UIC is 336ug/L in regions with 150-300ug/L iodine in water, and is 494ug/L in regions with >300ug/L iodine in water. Goiter rate in region with >150ug/L water [iodine] was 8% No obvious relationship between salt intake and | Level IV study with high risk of bias. Goiter rate cannot be compared between areas with different [iodine] in water - goiter rate was not assessed in regions with <150ug/L iodine in water, and goiter rate was not |

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|-----------------|--|--------------------------------------|-------------|--|---|--|---|
| | | | | | | goiter rate. | reported according to the [iodine] in water. Large sample size and national representative sample |
| Lv et al., 2012 | Cross-sectional study Probability-proportional-to-size sampling method to randomly select subjects from 30 villages in Hebei Province, China 2006 | 1259 (49% B; 51%G) | 8-10 | Thyroid ultrasonic scan (n=1259) Urine sample (n=363) | Drinking water sample (n=85) Household salt sample (n=301) | Goiter rate in villages with water iodine of <150ug/L is 10.8%, and in villages with water iodine of >150ug/L is 11%. In villages with water iodine of >150ug/L, median UIC in villages with iodised salt was 443ug/L, which is significantly higher than 350ug/L obtained from villages without iodised salt. 68% subjects had UIC >300ug/L. | Level IV study with high risk of bias. Frequency of seafood consumption was unknown. Only 29% of subject provided a urine sample. |

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|--------------------|--|--|-------------|---|-----------------------------|--|----------|
| Kassim et al, 2014 | Cross-sectional study; stratified, 2-stage, household cluster survey; 3 zones of Somalia; 2009 | 507 of 756 subjects were assessed for the presence of visible goitre (not palpation) | 6-11 | UIC & recognition of visible goitre (not palpation) | Household FFQ & salt sample | Goitre prevalence was higher in children living in Northwest Zone (median UIC: 288 µg/L; goitre prevalence: 1.3) than children living in South Centre Zone (median UIC: 398 µg/L; goitre prevalence: 0.3). It was unknown if goitre cases reported were caused by iodine-induced thyroid dysfunction. | Level IV |
| Kim et al, 2014 | Cross-sectional study; (not reported); high school students in Tuguegarao, Cagayan Valley, Philippines; 2013 | 146 (67M/79F) of 260 were assessed for TV measurement and use of iodised salt. | 12-25 | UIC & TV (by ultrasonography) | Use of iodised salt | Median UIC was 355 µg/L; no significant difference was observed in UIC between iodised salt and non-iodised salt users (p=0.099). Iodised salt users had a significantly lower TV than non-iodised salt users (p=0.032). | Level IV |

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|--------------------|--|---|-------------|---|------------------------|---|----------|
| Medani et al, 2013 | Cross-sectional; multi-stage random sampling; Port Sudan, Sudan; 2006 | 31 of 654 children gave a spot urine sample | 6-12 | UIC & TV (by palpation) | No assessment | Median UIC was 464 µg/L: 77.4% of children had a UIC>300 µg/L. Goitre rate was 35%. | Level IV |
| Meng et al, 2013 | Cross-sectional; 100 children, 100 adults, 50 pregnant women & 50 lactating women were selected from each province; Gansu, Shandong, Fujian, Jilin, Anhui & Chongqing provinces, China; 2009 | 627 (314 M/313F) | 8-10 | UIC, TSH, FT4, Tg, TgAb, TPOAb & TV (ultrasound). | Household salt samples | Median UIC, TSH, FT4 & Tg were 271 µg/L, 2.8 mU/L, 17.7 pmol/L & 5.8 µg/L, respectively. Goitre prevalence was 6.7%. TSH decreased from ~ UIC 50 to 300 µg/L and increase from UIC 300 to 550 µg/L. | Level IV |

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|-------------------|---|--------------------------------------|-------------|---|--|--|---|
| Rossi et al, 2002 | Cross-sectional study Random sample from 21 villages/town in Central Brazil, | 1977 (46% B, 54% G) | 6-14 | Thyroid ultrasonic scan (n=1788) Urine sample (n=1013) | Salt sample (n=1325) | Mean UIC was 360ug/L. 49% >300ug/L Mean thyroid volume by age and sex 3.10cm ³ in boys aged 6-8y; 4.22cm ³ in boys aged 9-14y; 3.19cm ³ in girls aged 6-8y; 4.44cm ³ in girls aged 9-14y | Level IV study with high risk of bias. Sample had exceptional excellent health and nutritional status (80% above the 97th percentile for height and weight, and 7.3% had excessive weight), thus limited generalizability |
| Seal et al, 2006 | Cross-sectional study Cluster sampling in 5 camps and systematic sampling in the remaining 1 camp. Sample from 6 refugee camps in Africa, 2001-2003 | 895 (54% B, 46% G) | 10-19 | Urine sample Recognition of visible goitre (not palpation) | Market and household salt samples (n=11) | Calculated iodine intake was 440ug/d per person Median UIC (goiter rate) in 4 camps was 726ug/L (0.4%); 1074ug/L (1.3%); 1170ug/L (7.1%); 570ug/L (0%) | Level IV study with high risk of bias. Low prevalence of goiter would be attributed to poor assessment method for goiter |
| Shen et al, 2011 | Cross-sectional study random sample from 299 towns in 9 provinces with | 56751 | 8-10 | Urine sample Goiter grading by palpation (n=26575) & thyroid ultrasonic scan | Drinking water sample (n=28857) | Goiter rate increased with increasing median UIC and median water [iodine] respectively. | Level IV study, very large sample size. National representative sample only for those who |

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|------------------|--|---|-------------|---|---|---|--|
| | median water [iodine] of >150ug/L, China, 2005-2006 | | | (n=1413) | | Compared to children with UIC of 100-199ug/L, RR for goitre was 1.56 for those with UIC of 300-399ug/L. | might consume excessive iodine from water. No of children with UIC of 100-199ug/L (not published) might be small as towns with <150ug/L water [iodine] were not included |
| Teng et al, 2006 | Cross-sectional study (convenience sample) from a 5-year cohort study in China, 2004 | 60 of 3018 subjects were children | 8-10 | Urine sample, blood sample, goiter grading by palpation & thyroid ultrasonic scan | Questionnaire elicited personal information, economic status of the family, eating habits, type of salt used, amount of salt ingested per day, and the personal or family history of thyroid diseases | Goiter rate among schoolchildren was not reported | Level IV study, few children. |

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|-----------------|--|--------------------------------------|-------------|---|---|---|--|
| Zimmerman, 2013 | Cross-sectional study Multiethnic sample from 12 countries intake ranging from adequate to excessive | 2512 | 6 to 12 | Measured UIC, TSH, total T4, Tg, and thyroid antibodies. Tg response to both low- and high-iodine intake was examined. Estimated the population cutoff point for iodine deficiency or excess using Tg. Compared thyroid functions within the UIC ranges of 100-199 vs 200-299 µg/L. | Standardized dried blood spots-Tg assay | Compared with iodine-sufficient children, there was a significantly higher prevalence of elevated Tg values in children with iodine deficiency (UIC <100 µg/L) and iodine excess (UIC >300 µg/L). There was no significant change in the prevalence of elevated Tg, TSH, T4, or thyroid antibodies comparing children within the UIC ranges of 100-199 vs 200-299 µg/L. | Level IV study with low risk of bias, Tvol measured by ultrasound, large sample from a range of populations with varying iodine status. Most comprehensive database to date. |

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|------------------------|--|--------------------------------------|-------------|--|---|--|--|
| Zimmermann et al, 2005 | Cross-sectional study Multiethnic sample from 5 continents with iodine intake ranging from adequate to excessive, | 3319 (53% B; 47% G) | 6-12 | Urine sample Thyroid ultrasonic scan | Iodine intake was estimated from median UIC | <p>No significant correlation between UIC and age- and BSA-adjusted Tvol for all locations except coastal Hokkaido (median UIC was <300ug/L in the former locations vs. >700ug/L in the latter). In Coastal Hokkaido, OR for goiter was 1.75 for a 10-fold increase in UIC.</p> <p>Estimated median iodine intake, median UIC, age- and BSA-adjusted thyroid volume: All sites: 241ug/d, 218ug/L, 2.54ml By region: Jona, Switzerland: 120ug/d, 116ug/L, 2.59ml Banama, Bahrain: 183ug/d, 185ug/L, 2.16ml Cape Town, South Africa: 205ug/d, 189ug/L, 2.39ml</p> | <p>Level IV study with low risk of bias.</p> <p>Dose response was assessed and reported.</p> <p>Calculation of sample size was reported. Data from this large international sample had been used to determine a WHO reference values for thyroid volume by ultrasound in iodine sufficient schoolchildren (see Zimmermann (2004) Am J Clin Nutr)</p> |

| Author, year | Study type, Sampling, location, year | Number of subjects Gender: % (No) | Age (years) | Assessment on iodine status or clinical outcomes | Assessment of I intake | Outcomes | Comments |
|--------------|--------------------------------------|--------------------------------------|-------------|--|------------------------|---|----------|
| | | | | | | Lima, Peru: 300ug/d, 253ug/L, 2.42ml Chelsea, MA: 314ug/d, 292ug/L, 2.21ml Central Hokkaido, Japan: 292ug/d, 296ug/L, 2.86ml Coastal Hokkaido, Japan: 241ug/d, 728ug/L, 4.91ml | |

Abbreviation: G1=group 1; G2=group 2; B=boys; G=girls; UIC=urinary iodine concentration; [iodine]=iodine concentration; RR=relative risk; [iodine]=iodine concentration; BSA=body surface area

Table 7:12 Studies relating to Upper Limit in children (Review Questions 10-13)

Intervention studies

| Author, year, location | Inclusion criteria | Design and doses | Sample size | Baseline or follow-up gestational iodine status | Assessment test method | Main effect(s) | Comments |
|------------------------|--|---|--|---|---|--|---|
| Huda et al, 2001 | Children (mean age of 9.8y) studying at one of 10 selected schools in Bangladesh | RCT (4m) G1: placebo G2: 400mg oral iodized poppy seed oil | G1:142 G2: 145 | Baseline median UIC: 2.86umol/L (362ug/L) for G1 & 2.76umol/L (349ug/L) for G2 Follow-up median UIC: 3.31umol/L (419ug/L) for G1 & 6.83umol/L (865ug/L) for G2 | Anthropometry Serum T4, TSH, UIC Cognitive and motor function tests designed for Bangladeshi children | No difference was observed between groups for all cognitive and motor tests | Level II study with low risk of bias. According to the authors, the subjects are moderately iodine-deficient children, but their baseline median UIC are >300ug/L. The authors also claimed that normal median UIC is 7.9umol/L which is 1000ug/L. |
| Li et al, 2012 | Volunteers from urban and rural areas in China | Before and after intervention randomised trial (27 day)G1: 6mg/kg iodised salt; G2: 15mg/kg iodised salt; G3: 24mg/kg | n=1099 G1: 269 G2: 290 G3: 271 G4: 269 | In children aged 7-12y:Baseline median UIC among urban children ranged from 231ug/L to 354ug/L, and ranged from 456ug/L to 519ug/L in rural area | Median UIC | Regardless area of origin, median UIC ranged from 105ug/L to 194ug/L in G1; ranged from 245ug/L to 252ug/L in G3; and ranged from 302ug/L to 336ug/L in G3 | Level III-2 study with high risk of bias. Sample was not randomly selected. Unclear whether participants had thyroid disease. Compliance and amount of salt intake were not reported. |

| Author, year, location | Inclusion criteria | Design and doses | Sample size | Baseline or follow-up gestational iodine status | Assessment test method | Main effect(s) | Comments |
|------------------------|--------------------|---|-------------|---|------------------------|----------------|----------|
| | | iodised salt; G4: 34 mg/kg iodised salt | | | | | |

Abbreviation: y=year; RCT=randomised controlled trial; G1=group 1; G2=group 2; UIC=urinary iodine concentration; T4=thyroxine; TSH=thyroid stimulating hormone

7.4 Appendix 4: Membership of groups and committees involved in the development process

7.4.1 Membership of the Nutrient Reference Values Steering Group

The Steering Group for the project was composed of representatives from the Australian Government Department of Health, and the New Zealand Ministry of Health.

7.4.2 Membership of the Nutrient Reference Values Advisory Committee

Professor Samir Samman (Chair)

Department of Human Nutrition, University of Otago, New Zealand

Ms Janis Baines

Food Standards Australia New Zealand

Associate Professor Marijka Batterham

School of Mathematics and Applied Statistics, University of Wollongong, Australia

Professor Michael Fenech

CSIRO Food & Nutritional Sciences, Adelaide, Australia

Professor Mark Lawrence

School of Exercise and Nutrition Sciences, Deakin University, Australia

Professor Jim Mann

School of Medicine, University of Otago, New Zealand

Professor Murray Skeaff

Department of Human Nutrition, University of Otago, New Zealand

Professor Linda Tapsell

School of Medicine, University of Wollongong, Australia

Emeritus Professor Christine Thomson (until February 2015)

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Professor Lynne Daniels (2013)

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7.4.3 Membership of the Nutrient Reference Values Iodine Expert Working Group

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8 Abbreviations and Glossary

8.1 Abbreviations

| Acronym | Description |
|---------|--|
| ANS | Adult Nutrition Survey |
| BOE | Body of Evidence |
| DoH | Department of Health |
| DRI | Dietary Reference Intakes |
| EAR | Estimated Average Requirement |
| EFSA | European Food Safety Authority |
| EER | Estimated energy requirement |
| EWG | Expert Working Group |
| FAO | Food and Agriculture Organization of the United Nations |
| FNB | Food and Nutrition Board |
| FT3 | Free 3,5,3' tri-iodothyronine |
| FT4 | Free thyroxine |
| GFR | Glomerular Filtration Rate |
| ICCIDD | International Council for the Control of Iodine Deficiency Disorders |
| ID | Iodine deficiency |
| IDD | Iodine deficiency disorders |
| IQ | Intelligence Quotient |
| IOM | Institute of Medicine |
| LOAEL | Lowest-Observed-Adverse-Effect level |
| MoH | Ministry of Health |
| NINS | National Iodine Nutrition Study |
| NHMRC | National Health and Medical Research Council |
| NHS | National Health Survey |
| NRVs | Nutrient Reference Values |
| NZ | New Zealand |
| PICO | Population, Intervention, Comparator, Outcome |
| PUL | Provisional Upper Level of Intake |
| RCT | Randomised controlled trial |

| Acronym | Description |
|----------------|--|
| RDI | Recommended Dietary Intake |
| SDT | Suggested Dietary Target |
| T ₃ | 3,5,3' tri-iodothyronine |
| T ₄ | Thyroxine |
| Tg | Thyroglobulin |
| TgAb | Thyroglobulin antibody |
| TPOAb | Thyroid peroxidase antibody |
| TSH | Thyroid stimulating hormone |
| UIC | Urinary iodine concentration |
| UIE | Urinary iodine excretion |
| UL | Upper Levels of Intake |
| UNU | United Nations University |
| UNICEF | United Nations Children's Fund (formerly United Nations International Children's Emergency Fund) |
| WHO | World Health Organization |

8.2 Glossary

| Term | Description |
|--|---|
| Adequate Intake (AI) | The recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate-used when an RDI or RDA cannot be determined. |
| Acceptable Macronutrient Distribution Range (AMDR) | An estimate of the range of intake for each macronutrient (expressed as percent contribution to energy), which would allow for an adequate intake of all the other nutrients while maximizing good health (applies only to adults and young people aged 14 years and over). |
| Dietary Reference Intakes (DRIs) | A set of four reference values for USA and Canada: Estimated Average Requirements (EAR), Recommended Dietary Allowances (RDA), Adequate Intakes (AI) and Tolerable Upper Intake Levels (UL). |
| Estimated Average Requirement (EAR) | A daily nutrient level estimated to meet the requirements of half of the healthy individuals in a particular life stage and gender group. |
| Estimated energy | The average dietary energy intake that is predicted to maintain energy balance in a healthy adult of a defined age, gender, weight and level of |

| Term | Description |
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| requirement (EER) | physical activity, consistent with good health. For children and for pregnant and lactating women, the EER include needs associated with growth or the secretion of milk at rates consistent with good health. |
| Iodine deficiency disorders (IDD) | A range of health consequences or abnormalities of the body resulting from a prolonged lack or insufficient intake of iodine, ranging from simple goitre to cretinism, which is a condition of severely stunted physical and mental growth. |
| Lowest-Observed-Adverse-Effect level (LOAEL) | The lowest tested dose of a substance that has been reported to cause harmful (adverse) health effects on people or animals. |
| New Zealand Adult Nutrition Survey 2008/09 (ANS) | A nutrition survey carried out by the Ministry of Health to collect the information on food consumption, nutrient intake and biochemical nutrient levels in New Zealand adults aged 15+ years. |
| New Zealand National Children's Nutrition Survey 2002 (CNS) | A nutrition survey carried out by the Ministry of Health to collect food and nutrient information for 3275 school children aged 5–14 years. |
| Nutrient Reference Values (NRVs) | A set of recommendations for Australia and New Zealand for intakes of energy and nutrients aimed at avoiding deficiency and excess/toxicity; Estimated Average Requirements (EAR), Recommended Dietary Intakes (RDI), Adequate Intakes (AI) and Upper Intake Levels (UL). They also include guidance on the dietary patterns needed to reduce the risk of chronic disease. |
| Recommended Dietary Intake (RDI) | The average daily dietary intake level that is sufficient to meet the needs of nearly all (97–98%) healthy individuals in a particular life stage and gender group, including a margin of safety. |
| Suggested Dietary Target (SDT) | A daily average intake for certain nutrients that may help in the prevention of chronic disease (applies only to adults and young people aged 14 years and over). |
| 3,5,3' tri-iodothyronine (T ₃) | One of the thyroid hormones produced by the thyroid gland. |
| Thyroxine (T ₄) | One of the thyroid hormones produced by the thyroid gland. |
| Thyroglobulin (Tg) | A protein in the thyroid gland that can be used as a marker for thyroid disease and thyroid cancer. |
| Thyroid stimulating hormone (TSH) | A hormone, synthesized and secreted by the anterior pituitary gland under the control of TSH, that stimulates activity of the thyroid gland. |

| Term | Description |
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| Upper Levels of Intake (UL) | The highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase. |

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9 References

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