Australian Government
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MINISTRY OF HEALTH
MANATŪ HAUORA

Australian and New Zealand Nutrient Reference Values for Fluoride

A report prepared for the
Australian Government Department of Health and the
New Zealand Ministry of Health

Enquiries

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Disclaimer

This is a technical report to the 2017 NRVs for fluoride: AI and UL for infants and young children (0-8 years). The recommendations apply to the generally healthy population and may not meet the specific nutritional requirements of all individuals. They are not intended to be clinical practice guidelines or guidelines on dental/oral health used by dental and health professionals treating individuals or assessing diets of individuals. This technical report is based on the best information available at the date of compilation.

Council of the National Health and Medical Research Council Approval

Australian Government

National Health and Medical Research Council

Updates to the guideline recommendations for fluoride for 0-8 year olds were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 21 November 2016, under Section 14A of the National Health and Medical Research Council Act 1992. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. Approval of the guideline recommendations will be reviewed for currency after five years.

NHMRC is satisfied that the guideline recommendations are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals/practitioners practising in an Australian and New Zealand health care setting.

Acknowledgments

This report was prepared for the Australian Government Department of Health and the New Zealand Ministry of Health, by the Expert Working Group for Fluoride; Ms Janis Baines, Dr Michael Foley, Emeritus Professor Andrew John Spencer, Professor Marco Peres, Dr Utz Mueller and Associate Professor Loc Do, with research assistance from Dr Judy Cunningham, Mr Emmanuel Gnanamanickam, and Dr Najith Amarasena.

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1 Executive Summary

The Nutrient Reference Values (NRVs) are a set of recommended nutrient intakes used to assess dietary requirements of population groups or, for some NRVs individuals, and are health-based guidance values. The current NRVs for Australia and New Zealand were published in 2006 (NHMRC 2006) after a comprehensive review process commissioned by the Department of Health and Ageing (DoHA) and the New Zealand Ministry of Health (MoH). The National Health and Medical Research Council (NHMRC), which carried out the review, recommended that these recommendations be reviewed every five years. In 2011 DOHA, now the Department of Health (Health), in consultation with the NZ MoH commissioned a scoping study for undertaking a review of the NRVs. This resulted in the development of a Methodological Framework for the review by Nous and a consortium of experts (Department of Health 2015). The Methodological Framework includes criteria to be met in order to trigger a review.

The purpose of this review was to review NRVs for fluoride for infants and young children, by conducting a literature review of relevant literature released since the 2006 NHMRC review and by considering that literature in the context of major international reviews since the landmark US IOM review (1997). NRVs are considered to meet the known nutritional needs of practically all healthy people (NHMRC 2006). In this case the health intent is the prevention of two possible outcomes related to fluoride intake, dental caries and severe dental fluorosis. An additional purpose was to test the Methodological Framework developed for the review of NRVs for nutrients as fluoride had been identified as one of three priority nutrients for review.

Fluoride is naturally present in the food and drink we consume and is considered a normal constituent of the human body. The fluoride concentration in bones and teeth is about 10,000 times that in body fluids and soft tissues (Bergmann and Bergmann 1991; 1995). Nearly 99% of the body's fluoride is bound strongly to calcified tissues. Fluoride in bone appears to exist in both rapidly- and slowly-exchangeable pools.

Fluoride available systemically during tooth development is incorporated into teeth as fluorapatite in tooth enamel. Fluorapatite in tooth enamel alters its crystalline structure, reducing the solubility of enamel to acid dissolution, or demineralisation. At higher fluoride intakes the crystalline structure may be disrupted during tooth development periods, forming porosities which are the basis of dental fluorosis. However, outcomes such as skeletal fluorosis and bone fractures occur only after prolonged exposure to very high fluoride intakes. Fluoride at the surface of enamel can also form calcium fluoride, a more rapidly-exchangeable pool of fluoride to alter the demineralisation-remineralisation balance, which is the dynamic process underlying dental caries. Dental caries is a largely preventable but highly prevalent chronic disease in Australian and New Zealand children and adults.

Australia and New Zealand have pursued public health policy to adjust fluoride intake at the population level with the aim of preventing dental caries without causing moderate or severe dental fluorosis and other adverse effects. It is considered desirable to have a fluoride intake that is sufficient to prevent much dental caries (an Adequate Intake) without exceeding intakes that are associated with moderate or severe dental fluorosis (an Upper

Level of Intake), noting that the AI and UL relate to habitual or chronic intake of fluoride and are applied at the population level, not at an individual level. However, there is evidence that habitual fluoride intakes may exceed recommended levels or established upper levels of intake for children even when water fluoridation levels follow the current target drinking water levels in Australia (0.6-1.1 mg F/L) (NHMRC 2007) and New Zealand (0.7 to 1.0 mg F/L) (MoH 2005) and/or when individuals are exposed to fluoride from other sources[1]. Yet neither country experiences more than the rare occurrence of moderate or severe dental fluorosis. This apparent exceedance of recommended fluoride intake levels without the occurrence of moderate or severe dental fluorosis created the conundrum around NRVs for fluoride to which this report responds.

The current NRVs for fluoride for all age groups were not able to be reviewed in the time allocated for this pilot review. The Expert Working Group (EWG) narrowed the scope of its review to an Adequate Intake (AI) and Upper Level of Intake (UL) for fluoride for infants and young children, as the critical age groups to consider for dental caries and fluorosis. Young children aged 0-8 years of age are considered the critical group for these biomarkers because this is the period of time in which permanent teeth are formed. The EWG noted the term 'Tolerable Upper Level of Intake' was an appropriate way to describe the UL for fluoride that was consistent with use internationally, however, to maintain consistency with the establishment of NRVs for other nutrients in Australia and New Zealand, the term 'Upper Level of Intake' was retained for fluoride.

The EWG conducted several literature reviews. First, eight formal international reports including the landmark US Institute of Medicine (IOM) report on fluoride, published in 1997, and seven others published in the 17 years since the IOM report, were reviewed (IOM 1997, McDonagh et al. 2000, NRC 2006, EPA 2010a,b, SCHER 2011, EFSA 2005, 2013). The focus of this review of reports was the data available upon which to build NRVs and the method adopted. The review of reports revealed the central role that Dean's data of the late 1930s-40s (Dean et al. 1941, 1942; Dean 1942, 1944) had in all these evaluations in estimation of dose-response relationships between critical fluoride concentrations in the water supply and the prevention of dental caries and adverse dental fluorosis.

The end point for dental caries in the Dean studies was the caries experience measured by the Decayed, Missing, and Filled Teeth score among 12–14 year old children while the end point for dental fluorosis was the Dean's Index scores or the Community Fluorosis Index. The most severe dental fluorosis observed had pitting or loss of dental enamel, interpreted as a Dean's Index score of 4 (Dean 1942).

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[1] Drinking water Guidelines in Australia and New Zealand are based on health considerations and state the concentration of fluoride in drinking water should be in the range of 0.7 to 1.0 mg F/L but should not exceed 1.5 mg F/L (NHMRC 2013, MoH 2005). However, in the NHMRC 2007 statement on the safety and efficacy of fluoridation, it is recommended that water in Australia be fluoridated in the range 0.6-1.1 mg/L, depending on climate, to balance the reduction of dental caries and occurrence of dental fluorosis (NHMRC 2007).

Approaches to the derivation of fluoride intakes at critical fluoride concentrations in the water supply were assessed so as to guide the EWG's subsequent determinations.

Literature published in 2005 and onwards was searched and relevant literature identified. No alternative data were identified that could be substituted for Dean's data from the 1930s (Dean et al. 1941, 1942; Dean 1942, 1944) for critical fluoride concentrations in relation to the prevention of dental caries and minimisation of moderate and severe dental fluorosis. The bulk of the relevant literature addressed fluoride intakes in contemporary communities and the prevention of caries or risk of dental fluorosis.

The EWG identified the critical fluoride concentrations in the water supply from Dean's data for the near maximal prevention of dental caries (basis of the AI) and for prevention of severe dental fluorosis (basis of the UL), noting that the consensus is now that moderate fluorosis does not represent an adverse health effect (US EPA 2010b). Near maximal caries prevention was associated with a fluoride concentration of 1.0 mg F/L, while the critical concentration for prevention of severe fluorosis (<0.5% prevalence of severe fluorosis) was 1.9 mg F/L.

Dietary fluoride intake for children at the critical fluoride concentrations was estimated using three sets of data on fluid and food consumption among children: McClure's model diet, the US 1977–78 Nationwide Food Consumption Survey and the Australian 1995 National Nutrition Survey (McClure 1943, EPA 2010a, FSANZ 2014). There was a high level of agreement between the daily fluoride intake estimates. They ranged from approximately 0.04 mg F/kg bw/day at the mean to 0.20 mg F/kg bw/day at the 95th percentile of intake.

The distribution of fluoride intakes for a range of child ages and their associated bodyweights at the critical fluoride concentration of 1.9 mg/L water was determined and the 95th percentile of fluoride intakes used to establish a UL for fluoride. The UL for fluoride was established at 0.20 mg F/kg bw/day for children to avoid severe dental fluorosis. This estimate is higher than the existing UL for fluoride of 0.1 mg F/kg bw/day previously established by the NHMRC in 2006, which was based on the IOM 1997 report (NHMRC 2006). The EWG was satisfied that there was an inconsistency in the estimation of the UL in the IOM report. The EWG noted that the revised UL is higher than the fluoride Reference Dose of 0.08 mg F/kg bw/day established by the EPA in 2010 (EPA 2010a). The EWG considered the EPA's use of the mean dietary fluoride intake, rather than a high percentile fluoride intake, at 1.9 mg F/L in drinking water to estimate fluoride intakes did not provide a robust basis to derive a UL for fluoride.

The average fluoride intake was calculated for a range of children's ages and their associated bodyweights at a fluoride concentration of 1.0 mg F/L in drinking water. The current AI of 0.05 mg F/kg bw/day was reaffirmed to be an intake likely to be associated with appreciably reduced rates of dental caries. An AI has not been established for infants less than 6 months old who were being fed with infant formula. This is in line with the view expressed by the IOM and supported by the American Dental Association's Council on Scientific Affairs statement in 2011 that the preventive effect of fluoride in the first 6 months of life has not been established (IOM 1997, Berg 2011).

The UL for fluoride was compared with estimated total daily fluoride intakes (fluid, food and ingested toothpaste) for Australian and New Zealand children living in areas with 1.0 mg F/L in the water supply. The upper range of the total daily fluoride intake estimates was 0.09 to 0.16 mg F/kg bw/day across different age groups considered, considerably lower than the established UL for fluoride of 0.2 mg F/kg bw/day.

The new reference bodyweight data for Australian and New Zealand populations was used to derive the recommendations on a per day basis from the UL for fluoride of 0.2 mg F/kg bw/day for children aged 4-8 years. The most recent US reference bodyweight 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 (NRC 2005, Appendix B).

Recommendations for the UL for fluoride for children aged 0-8 years

	Age	Mean bodyweight	UL
Infants	0–6 months	6 kg	1.2 mg/day
Infants	7–12 months	9 kg	1.8 mg/day
Children	1–3 years	12 kg	2.4 mg/day
Children	4–8 years	22 kg	4.4 mg/day

The AI for fluoride for children up to 8 years old of 0.05 mg F/kg bw/day is equivalent to the following intakes expressed as mg F/day, using the same reference bodyweight data as for the UL.

Recommendations for the AI for fluoride for children aged 7 months - 8 years

	Age	Mean bodyweight	AI
Infants	0–6 months	6 kg	Not applicable
Infants	7–12 months	9 kg	0.5 mg/day
Children	1–3 years	12 kg	0.6 mg/day
Children	4–8 years	22 kg	1.1 mg/day

The EWG considers there is a moderate degree of certainty in the estimates of the AI and UL for fluoride using the GRADE system, with the strength of the evidence supporting an increase in the usual rating for evidence from observational studies from low to moderate.

These estimates have no implications for current drinking water standards in Australia and New Zealand or for action on fluoride intake from the ingestion of toothpaste.

Future work includes the review of existing ULs and AIs for older children and adults, including pregnant and lactating women.

2 Summary of Recommendations

Fluoride is widespread in nature and a normal part of the human body. It is particularly concentrated in teeth and bone and helps form tooth enamel. Fluoride is ingested from several sources including foods, fluoridated and unfluoridated water, fluoridated toothpastes and some dietary supplements. Both inadequate and excessive fluoride intakes can affect dental health. Inadequate intakes are associated with increased tooth decay (dental caries) and excessive intakes with damage to tooth enamel (dental fluorosis).

NRVs were established for fluoride by NHMRC/New Zealand MOH in 2006 following a review, which drew on an earlier review by the US Institute of Medicine in 1997. NRVs are guides to dietary intakes that help to protect populations and individuals against deficiency disease and, in some cases, against excessive nutrient intakes. In the 2006 review, both the AI and ULs were established for fluoride intake for different age groups, the intent being the prevention of dental caries (AI) and dental fluorosis (UL). The AI and UL relate to habitual intake of fluoride and are used to assess the fluoride intake of populations not individuals.

Recent estimates of dietary fluoride intake in Australia and New Zealand have suggested that the fluoride intake of a substantial proportion of infants and young children may exceed the UL. At the same time, there is no evidence of widespread occurrence of moderate or severe dental fluorosis. This suggests that the existing UL needs reconsideration.

This report examines evidence from the 1997 Institute of Medicine review and seven other major reviews of fluoride released since the 1997 review and from a comprehensive literature review of post-2005 scientific literature on fluoride intakes and oral health. From this examination of relevant evidence, a UL and an AI for fluoride were determined for children up to 8 years of age.

As this report was a pilot for future NRV reviews, it was limited to considering children up to 8 years of age, the critical age group to consider for dental caries and fluorosis because this is the period of time in which permanent teeth are formed.

Dental fluorosis was chosen as the key measure of excess fluoride intake and dental caries as the measure of fluoride adequacy. These measures are consistent with those used in other major reviews. These reviews showed the central role of observational data collected in the US in the late 1930s-40s for estimating dose-response relationships between the presence of dental caries or dental fluorosis and the concentration of fluoride in the water supply. The literature review did not find any more recent data, observational or experimental, that could replace it.

Based on this US data, the report identifies the critical fluoride concentrations in the water supply for optimising prevention of dental caries and for minimising severe dental fluorosis: 1.0 mg fluoride/L and 1.9 mg fluoride/L respectively. From these values, together with nationally representative data on water and food consumption and bodyweight data for Australian and New Zealand populations, **the UL for fluoride for infants and children up to 8 years old was estimated to be 0.2 mg fluoride/kg bodyweight/day. The AI was reaffirmed to be 0.05 mg F/kg bodyweight/day**. New reference bodyweight data for Australian and New Zealand children aged 4 years and above were used to determine new values for the AI and UL expressed in mg F/day; the most recent US reference bodyweight data were used for infants and children aged 1-3 years as no Australian and New Zealand data were available for these age groups.

The EWG considers there is a Moderate degree of certainty in the estimates of the AI and UL, using the GRADE system (see Appendix 1). Strengths of the evidence include the large number of children included in the US observational study, the wide range of drinking water fluoride concentrations reported, the clear dose-response relationships found and the absence of potential confounding factors that are present in later studies from the use of fluoridated water supplies, and toothpaste, supplements and dental treatments containing fluoride. These issues support the rating up of the strength of the evidence from the usual Low, for evidence from observational studies, to Moderate. Although data for food and fluid consumption and bodyweights were not directly available from the US study and had to be drawn from other sources, the three sources of information used for this purpose provided consistent results and had good precision.

The EWG strongly recommends the adoption of these revised NRVs for the UL and AI for fluoride for Australian and New Zealand children aged up to 8 years.

These estimates have no implications for current drinking water standards in Australia and New Zealand or for action on fluoride intake from ingestion of toothpaste.

Recommended future work includes the review of existing ULs and AIs for older children and adults, including pregnant and lactating women.

3 Introduction

NRVs are a set of recommended nutrient intakes designed to assist dietitians and other health professionals assess the dietary requirements of population groups or, for some NRVs individuals. Public health nutritionists, researchers, educators, 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 (Health) 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 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.

3.1 Scoping study

In 2011, Health 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, Health 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.

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 method applied or evidence. Fluoride, iodine and sodium were identified in the scoping study as priority nutrients for review.

3.2 Methodological Framework

In 2013, the Nous Group was contracted to develop the Methodological Framework to outline the overarching principles, methodologies, and approaches to ensure consistency of application and transparency in the NRV reviews across all nutrients. The Methodological Framework was developed through multiple rounds of consultations with technical experts and relevant stakeholders in Australia and New Zealand.

The Methodological Framework is designed for application across a range of nutrients and provides high level guidance that should not be impacted by characteristics unique to specific nutrients.

3.3 Review process

This review was funded by the Department of Health and the NZ MoH. The recommendations have been developed by independent experts, and the funding bodies have not influenced the content of the recommendations. A Steering Group is overseeing the review process and is responsible for all strategic and funding decisions for the review. It consists of representatives from both funding agencies, Health 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.

The Steering Group 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 advice from the Advisory Committee determined that fluoride, iodine and sodium are priority nutrients and first to be reviewed, with the purpose being to pilot the Methodological Framework.

The Steering Group (with the advice of the Advisory Committee), established a group of experts to conduct this fluoride review. The Fluoride 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 fluoride NRV guidelines can be found at Section 7.

Given the purpose of the review was to pilot the application of the Methodological Framework, and given time and resource constraints, the Fluoride EWG narrowed the scope of its review to an AI and UL for fluoride for infants and young children, as the critical age groups to consider for dental caries and fluorosis. Young children aged 0-8 years of age are considered the critical group for these biomarkers because this is the period of time in which permanent teeth are formed. Where a NRV has not been reviewed, the value from the 2006 NRVs for Australia and New Zealand stand.

The review process complies with the 2011 NHMRC Procedures and requirements for meeting the *2011 NHMRC standard for clinical practice guidelines*.

The suite of NRV terms outlined in the 2006 document (NHMRC 2006), adapted from the US/Canadian Dietary Reference Intakes (DRIs), were considered to remain applicable for the NRV reviews with no change of name to the reference indicators (NHMRC 2006, Department of Health 2013).

In line with the Methodological Framework, the following criteria are triggers for nutrient reviews:

- Changes to and/or developments in NRVs in comparable countries – changes have been made to recommendations for specific nutrients in comparable Organisation for Economic Cooperation and Development countries.

- Emergence of new evidence – the emergence of significant new evidence suggests the current NRV may be inappropriate for the population.
- Public health priority – fortification or widespread supplement use (due to the perceived need for a particular nutrient by the public) may require a review of nutrient recommendations.
- Methodological rigour – there are concerns regarding the strength and/or consistency of the method applied and evidence underpinning the current nutrient recommendations.

Future reviews will be undertaken in accordance with the Methodological Framework.

3.4 Public consultation

A draft report of the NRV for fluoride was submitted to the Advisory Committee in mid-2015 and was approved for public consultation.

The draft NRV review report for fluoride was released for public consultation from 30 October 2015 to 11 December 2015. Public consultation is a requirement for this review under the National Health and Medical Research Council Act (1992).

For more information on the public consultation process and on submissions received please refer to the Review of NRVs for Fluoride Public Consultation Report.

NRV terms

EAR Estimated Average Requirement

A daily nutrient level estimated to meet the requirements of half the healthy individuals in a sex[2] and particular life stage group.

RDI Recommended Dietary Intake

The average daily intake level[3] that is sufficient to meet the requirements of nearly all (97–98%) healthy individuals in a sex and particular life stage 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, sex, 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 average daily nutrient intake level likely to pose no adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases.

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 AI of all the other nutrients while 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.

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[2] Given NRVs are based on biological characteristics, the term 'sex' rather than 'gender' has been used to be consistent with recent government guidelines on the use of the term 'sex' and 'gender': the *Standard for Sex and Gender Variables 2016* and the *Australian Government Guidelines on the Recognition of Sex and Gender 2015.* The NRV definitions in the *Methodological Framework for the Review of NRVs 2015* currently uses the term 'gender'.

[3] The term average daily nutrient intake refers to the usual intake for a population, or individual (RDI only), typically derived from two or more days of data.

3.5 Summary of 2006 NRVs for fluoride

The 2006 NHMRC Australian and New Zealand recommendations for fluoride were for AIs and ULs for all age groups, and were based on the values from the 1997 Institute of Medicine (IOM) Report. The AI of 0.05 mg/kg bw/day and UL of 0.1 mg/kg bw/day were extrapolated to different age groups (except infants ≤6 months of age) using bodyweights for the US population used in the 1997 IOM report (IOM 1997). The current NRVs for fluoride are summarised in Table 3.1. The AI was set in relation to the prevention of dental caries and the UL to the prevention of dental fluorosis.

Table 3.1: Overview of NRVs for fluoride (NHMRC 2006)

Age group	AI* mg/day	UL# mg/day	Comments
Infants 0–6 months	0.01	0.7	AI assumed 780 mL breast milk per day and concentration of 0.013 mg/L (IOM 1997)
Infants 7–12 months	0.5	0.9	
Children 1–3 years	0.7	1.3	
Children 4–8 years	1.0	2.2	
Children 9–13 years boys, girls	2.0	10.0	
Adolescents 14–18 years boys, girls	3.0	10.0	
Adults 19–70 years male	4.0	10.0	
Adults 19–70 years female	3.0	10.0	
Adults 14–50 years Pregnancy	3.0	10.0	No evidence that requirements are higher in pregnancy than those of nonpregnant women
Adults 14–50 years lactation	3.0	10.0	Fluoride concentration in breast milk low and fairly insensitive to fluoride concentration in drinking water, requirements same as for nonpregnant women (Esala et al. 1982, Spak et al. 1982, Ekstrand et al. 1984)

*AIs for older infants and children based on AI of 0.05 mg.kg bw/day and standard bodyweights for US children for 7–12 month infants of 9 kg; children 1–3 yrs old 13 kg; children 4–8 yrs old 22 kg; children 9–13 yrs old 40 kg; boys 14–18 yrs old 64 kg; girls aged 14–18 yrs old 57 kg; adult males 76 kg, adult females 61 kg (NHMRC 2006, IOM 1997).

#Based on Dean's 1942 study on fluoride and dental health (Dean 1942); UL for older children and adults derived from NOAEL of 10 mg/day, which was based on data on relationship between fluoride intake and skeletal fluorosis (NHMRC 2006, IOM 1997).

3.6 Triggers and rationale for review

The Australian Drinking Water Guidelines and New Zealand Drinking Water Standards both recommend water fluoridation levels in the range of 0.7–1.0 mg F/L with a maximum level in both countries of 1.5 mg/L (NHMRC 2013, NZ MOH 2005). However, it is noted that in the NHMRC 2007 statement on the safety and efficacy of fluoridation, it is recommended that water be fluoridated in the range 0.6-1.1 mg/L, depending on climate, to balance the reduction of dental caries and occurrence of dental fluorosis (NHMRC 2007).

There is Australian, New Zealand and international evidence that estimated fluoride intakes for a sizeable minority of the population who consume drinking water at optimal levels of fluoridation (1.0 mg F/L) are above the UL for fluoride (0.1 mg/kg bw/day) (FSANZ 2009). Yet neither country experiences more than the rare occurrence of moderate or severe dental fluorosis. This apparent exceedance of recommended fluoride intake levels without the occurrence of adverse dental fluorosis created the conundrum around NRVs for fluoride to which this report responds.

This situation met the criteria for triggering a review of NRVs for nutrients and called for a re-evaluation of the data which underpins the current UL for fluoride. As part of this review an evaluation of the AI was also included for completeness. As this report was a pilot for testing the Methodological Framework, which was to be undertaken within a given timeframe, it was limited to considering children up to 8 years of age, the critical age group to consider for dental caries and fluorosis.

3.7 Background information - fluoride

Fluoride is naturally present in the food and drink we consume and is considered to be a normal constituent of the human body. The fluoride concentration in bones and teeth is about 10,000 times that in body fluids and soft tissues (Bergmann and Bergmann 1991; 1995). Nearly 99% of the body's fluoride is bound strongly to calcified tissues. Fluoride in bone appears to exist in both rapidly- and slowly-exchangeable pools.

Fluoride available systemically during tooth development is incorporated into teeth as fluorapatite in tooth enamel. Fluorapatite in tooth enamel alters its crystalline structure, reducing the solubility of enamel to acid dissolution, or demineralisation. At higher fluoride intakes the crystalline structure may be disrupted forming porosities which are the basis of dental fluorosis. Outcomes of fluoride intake on bone have been considered, especially among adults. However, outcomes such as skeletal fluorosis and bone fractures occur only after prolonged exposure to very high fluoride intakes.

Fluoride at the surface of enamel can also form calcium fluoride, a more rapidly-exchangeable pool of fluoride to alter the demineralisation-remineralisation balance which is the dynamic process underlying dental caries. Dental caries is a largely preventable but highly prevalent chronic disease in Australian and New Zealand children and adults.

Australia and New Zealand have pursued public health policy to adjust fluoride intake at the population level with the aim of preventing dental caries without causing moderate or severe dental fluorosis with adverse effects. It is considered desirable to have a fluoride intake that is sufficient to prevent much dental caries (an AI) without exceeding intakes that are associated with severe dental fluorosis (a UL), noting that these NRVs relate to habitual or chronic intake of fluoride.

3.8 Target Users

The NRV values are designed to assist dietitians and other health professionals assess the dietary requirements of the population. Public health nutritionists, food legislators and the food industry will also use these recommendations for preventive health strategies, dietary modelling and/or food labelling and food formulation.

Users need to be aware that the NRVs examined here (AI and UL):

- apply to the generally well population of children aged 7 months to 8 years (AI) and children 0 to 8 years (UL);
- are not intended to be clinical practice guidelines or guidelines on dental/oral health used by dental and health professionals treating individuals; and
- are not intended for assessing the diets of individuals.

4 Scope and Purpose

The purpose of this review was to discuss and derive NRVs for fluoride (UL and AI) for infants and young children, by conducting a comprehensive literature review of relevant literature released since the 2006 NHMRC review and by considering recent international reviews in this context. NRVs are considered to meet the known nutritional needs of practically all healthy people (NHMRC 2006). In this case the health intent is the prevention of two possible outcomes related to fluoride intake; dental caries (AI) and severe dental fluorosis (UL). An additional purpose was to test the Methodological Framework developed for the review of health-based guidance values for nutrients (NRVs) as fluoride had been identified as one of three priority nutrients for review.Based on this consideration, the review determined the critical fluoride concentration in drinking water to minimise both dental caries and severe dental fluorosis. From this, using nationally representative data for fluid and food consumption and bodyweight data for Australian and New Zealand populations, a UL and an AI for fluoride, expressed in mg F/bw/day, were derived. Finally, recommendations for revised UL and AI values, expressed in mg F/day for different age groups, were determined. The EWG noted the term 'Tolerable Upper Level of Intake' was an appropriate way to describe the UL for fluoride that was consistent with use internationally, however, to maintain consistency with the establishment of NRVs for other nutrients in Australia and New Zealand, the term 'Upper Level of Intake' was retained for fluoride.

This report is restricted to discussion and derivation of relevant NRVs for fluoride (UL and AI) for infants and young children up to 8 years of age, who were determined to be the two critical groups for reconsideration and therefore a priority to assess. Time and resources available for the task restricted the scope of the work to be undertaken and included in this report by the EWG; at this time it was not possible to assess AIs or ULs for older children or adults.

The Evidence Review in Section 5 set out the review process and findings, with further detail provided in Supporting Documents 1-4. The recommendations for the UL and AI for fluoride in infants and young children are set out in Section 6.

No issues specific to Aboriginal and Torres Strait Islander people in Australia or to Maori and Pacific Islander people in New Zealand have been identified in this report. No other potentially more sensitive subgroups of children were identified when evaluating the evidence base for the establishment of NRVs for fluoride.

5 Evidence Review (Technical report)

5.1 Fluoride intake estimates in infants and young children

5.1.1 Australia and New Zealand

There is Australian, New Zealand and international evidence that estimated fluoride intakes for a sizeable minority of the population who consume drinking water at optimal levels of fluoridation (1.0 mg F/L) are above the UL for fluoride of 0.1 mg/kg bw/day (FSANZ 2009, NHMRC 2013, NZ MOH 2005). Yet neither country experiences more than the rare occurrence of moderate or severe dental fluorosis. This apparent exceedance of recommended fluoride intake levels without the occurrence of adverse dental fluorosis created the conundrum around NRVs for fluoride to which this Evidence Review responds.

Food Standards Australia New Zealand (FSANZ), when considering the voluntary addition of fluoride to packaged water in 2009, found that infants and children under the age of 8 years consuming fluoridated water were the group most likely to exceed the UL for fluoride of 0.1 mg/kg bw/day as set by NHMRC in 2006 (FSANZ 2009, NHMRC 2006). All infants fed exclusively with infant formula made with nonfluoridated or fluoridated water had estimated fluoride intakes that exceeded the UL. For infants aged 6–12 months consumption of fluoridated water on top of dietary fluoride sources, including infant formula, increased estimated fluoride intake over the UL. Some 22% of 2–3 year old Australian children and 5% of 4–8 year old Australian children had estimated fluoride intakes that exceeded the UL when assuming that all water consumed was fluoridated at the maximum level of 1.0 mg F/L (FSANZ 2009).

Cressey et al. in 2010 updated the estimates for fluoride intake in New Zealand (Cressey et al. 2010) using analytical data for the fluoride content of foods from the NZ Total Diet Survey in 1990/91, which analysed fluoride content of foods and used a simulated typical diet to estimate intake. Cressey found that for many the estimated mean fluoride intake was below the AI of 0.05 mg/kg bw/day for optimal caries protection. All groups, except 6–12 month old infants living in fluoridated areas, and assuming use of high fluoride toothpaste had estimated fluoride intakes below the UL (0.1 mg/kg bw/day). While infants consuming formula prepared with fluoride-free (deionised) water had intakes well below the UL, a sizeable proportions of infants, assuming use of water with fluoride concentrations of 0.7 or 1.0 mg F/L, had estimated fluoride intakes that exceeded the UL (30% and 90% respectively).

Clifford et al. in 2009 studied fluoride intake from infant formula available in Australia and found that infant formula powders contained lower average levels of fluoride in 2006-07 (0.07 mg/kg) than that reported by Silva and Reynolds in 1996 (0.24 mg/kg), a decade earlier (Clifford et al. 2009, Silva and Reynolds 1996). Using this new information and recommended fluid intakes, fluoride exposure for infants were recalculated by FSANZ for this review. When infant formula was reconstituted with water containing no fluoride, the UL was not exceeded. However, when some formulas were reconstituted with fluoridated water, the UL of 0.1 mg/kg bw/day was exceeded, especially for 0-3 month old infants (FSANZ 2014).

Supporting Document 1 provides more detail on fluoride intake estimates for Australian and New Zealand infants and young children.

5.1.2 International

A number of studies have compared estimated fluoride intake against long-standing recommendations of fluoride intake. These recommendations were based on an average fluoride intake estimated by McClure (1943) of 0.05 mg/kg bw/day for children with 1.0 mg F/L in the water supply, also expressed as a range from 0.05–0.07 mg/kg bw/day. This is often referred to as the recommended 'optimal' dose range, terminology that reportedly emerged as a recommendation from Farkas and Farkas and later was accepted by Ophaug et al. (Farkas and Farkas 1974, Ophaug et al. 1980).

Erdal and Buchanan studied the estimated average daily intake of fluoride in the United States of America, via all applicable exposure pathways contributing to dental fluorosis risk for infants and children living in hypothetical fluoridated and nonfluoridated communities (Erdal and Buchanan 2005). They also estimated hazard quotients and indices for exposure conditions representative of central tendency exposure (CTE) and reasonable maximum exposure (RME). For infants <1 year of age in areas of water fluoridation (1.0 mg F/L), the cumulative daily fluoride intake was estimated to be 0.11 and 0.20 mg/kg bw/day for the CTE and RME scenarios respectively. In older children (3–5 years of age) under the same conditions, the CTE and RME fluoride intake was estimated as being 0.06 and 0.23 mg/kg bw/day, respectively. In infants the major source of fluoride was infant formula and the fluoridated water used to reconstitute it. In older children the main source was inadvertent ingestion of toothpaste fluoridated at 1000 mg F/kg.

Reporting that their estimates were in good agreement with measurement-based estimates, Erdal and Buchanan found that CTE estimates were within the recommended range for dental caries prevention, but the RME estimates were above the Tolerable Upper Intake Limit established by the US Environmental Protection Agency at that time (recommended safe threshold of 0.06 mg/kg bw/day; lower bound value 0.05 mg/kg bw/day, upper bound value 0.07 mg/kg bw/day). This suggested some children were at risk of adverse dental fluorosis (Erdal and Buchanan 2005).

The Iowa Fluoride study (Hong et al. 2006, Warren et al. 2009) examined fluoride intake across the first 36 months of life and its association with any dental fluorosis (including very mild changes to only a fraction of the surface of key teeth). Hong et al. reported that fluorosis prevalence was related to elevated fluoride intake when averaged over the first 3 years of life, but was even more strongly related to fluoride intake that was elevated for all of the first 3 years of life. However, Warren et al. reported on the considerable overlap in the fluoride intake of children in the Iowa Fluoride study with and without dental fluorosis with up to 20% of children with fluoride intakes above the recommended level of 0.05 mg/kg bw/day, some by several times this level, where severe dental fluorosis was not observed.

Colombian research reported in 2005 examined the total fluoride intake of children aged 22–35 months in four Columbian cities. Franco et al. used the duplicate plate method and recovery of toothpaste used in tooth brushing. Toothpaste accounted for approximately 70%

of fluoride intake, followed by food (24%) and beverages (<6%) (Franco et al. 2005a). Mean daily fluoride intake was higher in children from high socioeconomic status backgrounds in several cities. Many children had total fluoride intakes above the recommended range (i.e. above 0.05–0.07 mg/kg bw/day). A related paper by Franco et al. included a focus on fluoridated table salt. It concluded that preschool children residing in Columbian urban areas were ingesting amounts of fluoride above the upper bound of the EPA recommended safe threshold (0.07 mg/kg bw/day) (Franco et al. 2005b).

Fluoride intake from toothpaste and diet in 1–3 year old Brazilian children was reported by de Almeida et al. in 2007. Among low numbers of children in fluoridated and nonfluoridated areas, fluoride intake was monitored by direct measurement of fluoride dispensed and recovered during tooth brushing and the duplicate plate method for foods. Fluoride intake was above the upper bound of the EPA recommended safe threshold for dental fluorosis (>0.07 mg/kg bw/day). Toothpaste was responsible for an average of 81.5% of daily fluoride intake (de Almeida et al. 2007).

This research in Brazil was followed-up by Miziara et al. in 2009 who studied fluoride intake among 2–6 year old children in a fluoridated community using a food frequency approach and estimated fluoride intake from fluoridated toothpaste. Among the children evaluated, 31.2% were estimated to have an intake of fluoride above the safe threshold for dental fluorosis (>0.07 mg/kg bw/day) (Miziara et al. 2009).

Nohno et al. in 2011 studied the fluoride intake of Japanese infants from infant formula. Each infant formula powder was reconstituted with distilled water or water with 0.13 mg F/L and fluoride intake estimated from model diets. The potential fluoride intake of an infant depended on the fluoride level of the water used to reconstitute the formula. Risk of fluorosis was deemed to be low as most Japanese water supplies are low in fluoride. However, there was a possibility of exceeding the Tolerable Upper Intake Level referred to in their paper, especially for infants within the first 5 months of life (Nohno et al. 2011).

The same approach was pursued by Siew et al. in US based research (Siew et al. 2009). They determined the concentrations of fluoride in formula and estimated the fluoride intake of infants consuming predominantly formula against various concentrations of fluoridated water. They based consumption volumes on published recommendations. They concluded that some infants between birth and 6 months of age, who consume powdered and liquid concentrate formula, reconstituted with water containing 1.0 mg F/L, were likely to exceed the UL for fluoride established by the IOM (0.1 mg/kg bw/day).

Sohn et al. examined fluid intakes of 1–10 year olds in the USA via a 24-hour recall diet survey as part of the third National Health and Nutrition Examination Survey 1988–94 (Sohn et al. 2009). The amount of fluoride ingested from fluids was estimated from several assumptions about the concentration of fluoride in drinking water and beverages. The estimated fluoride intake at the 75th percentile (0.05 mg/kg bw/day or more) and 90th percentile (0.07 mg/kg bw/day or more) held across all age groups. Some children were ingesting significantly more fluoride than others depending on sociodemographic factors and fluid consumption patterns. Sohn et al. called for additional research on fluoride ingestion and its impact on dental fluorosis.

More recent published information on fluoride intake explores the ingestion of fluoridated toothpaste by 4-6 year olds by Zohoori et al. (Zohoori et al. 2012). The fluoride intake of 4–6 year olds from fluoridated toothpaste was studied in the Newcastle area of the UK. The research involved a low number of subjects. While the average amount of fluoridated toothpaste used per brushing was more than twice the recommended amount (0.25 g), only one child (out of 61) had a daily fluoride intake that exceeded the UL of 0.1 mg/kg bw/day for their age group (from toothpaste alone).

In a subsequent publication by Zohoori et al., fluoride intake was estimated for infants 1–12 months old living in fluoridated and nonfluoridated areas of the UK via a 3-day food diary coupled with analysis of the fluoride content of foods and drinks consumed (Zohoori et al. 2014). Total daily fluoride intake was estimated from diet, plus fluoride supplements and fluoridated toothpaste where used. The conclusion was that infants living in fluoridated areas may receive a fluoride intake from diet only of more than the recommended range of 0.05-0.07 mg F/kg bw/day.

5.2 Selection of Biomarkers for fluoride

The Working Group considered a range of biomarkers for fluoride, selecting dental caries and fluorosis as the biomarkers to use for the NRV review for infants and young children. The evidence to support this decision is given below and in Supporting Document 2. A summary of other biomarkers considered as part of the scoping process but not used in this NRV review is given below.

5.2.1 Dental caries

Dental caries is the result of an interaction of biological and environmental processes (Holst et al. 2001). The biological process is defined by the demineralisation and destruction of dental hard tissues by acidic by-products from bacterial fermentation of dietary carbohydrates, mainly sucrose (Selwitz et al. 2007). The environmental process is a combination of behaviour, contextual and societal factors (Holst et al. 2001). The aetiology of dental caries is complex and involves different levels of determinants from social structure, so-called distal determinants, to intermediate determinants such as behaviours and dental care utilisation, which in turn affects more proximal determinants, such as dental biofilm, fluoride exposure and saliva flow and composition. Caries is a dynamic process of demineralisation and remineralisation of the tooth tissues but the majority of the lesions, particularly in permanent teeth, progress slowly through enamel to dentine (Mejare et al. 1998) and can be seen in the crown of the teeth in the primary and permanent dentition and root surfaces of teeth in the permanent dentition.

Dental caries is a major public health problem worldwide; it is one of the most prevalent preventable chronic diseases (Vos et al. 2012), and the most common chronic childhood disease in most industrialised countries, affecting 60–90% of schoolchildren (Petersen 2003). Despite improvement in the last decades in developed countries, recent studies showed that caries in the primary dentition is increasing in the USA, UK, Canada, Australia, Norway and the Netherlands (Gao et al. 2010).

Along with its high prevalence and financial burden for society, dental caries is the main cause of toothache in children (Boeira et al. 2012) and it is the main reason for tooth extraction, resulting in tooth loss, among adults. The experience of pain, chewing difficulties, restriction of some foods and problems with smiling and communication due to damaged teeth, have an important impact on people's lives and wellbeing (Petersen et al. 2005).

The measurement of dental caries has largely remained unchanged since the 1930s. While Dean and colleagues used slightly different nomenclature, they were essentially recording the prevalence of caries in the permanent dentition (i.e. one or more teeth with caries experience) among children 12–14 years old and the number of teeth with decay (D), missing because of caries (M), or filled (F). The nomenclature of the DMF Teeth Index has been settled since the late 1930s (Klein et al. 1938). Rules for the observation of decay in a tooth and the recording of teeth missing due to caries have been available from the World Health Organization (WHO 2013). Since the 1960s and onwards refinements to these basic measures were introduced. These have included varying the unit of observation including individual tooth surfaces and more recently observing decay at earlier thresholds than cavitation or dentine involvement. This report has stayed with the decayed, missing (due to caries) and filled primary (dmft) and permanent (DMFT) teeth indices as that provides continuity with the key data to establish a dose-response relationship between fluoride and caries.

A summary of the known prevalence and extent of dental caries in the Australian and New Zealand child populations is given in Table 5.1 below. The data presented in Table 5.1 were derived from oral health surveys all conducted in the 2000 decade. Approximately half of all children in Australia aged 5–6 years old and in New Zealand aged 5–11 years old have experience of caries in the primary dentition and have one to two teeth on average with caries experience. A lower proportion of 12 year olds, approximately 30%, have experience of caries in the permanent dentition and the average number of teeth with caries experience is below one tooth. Both the prevalence and experience (dmft or DMFT) are strongly age-related and show variation across sites in Australia, between the two countries and between areas that have fluoridated water or not.

Table 5.1: Summary of data for dental caries in Australian and New Zealand children

Year	dmft/DMFT	% Caries free	Region	Age (years)	Fluoridation (mg/L water)	Study
2010-12	dmfs: 2.75 (2.16-3.34) dmfs: 4.31 (3.79-4.84) DMFS: 0.82 (0.65-0.99) DMFS: 1.51 (1.31-1.71)	63.1 (59.2-66.4)* 52.3 (48.7-55.9)* 70.6 (67.2-73.9)* 60.7 (57.8-63.5)*	Queensland	5-8 5-8 9-14 9-14	F area Non-F area F area Non-F area	Do and Spencer 2015 Do et al. 2015
2009	dmft: 2.13 (2.08–2.18) DMFT: 1.05 (1.01–1.08)	53.7 54.9	Australia, National (excluding NSW, VIC)	5–6 12	NS NS	Ha et al. 2013
2007	dmft: 1.88 (1.78–1.99) DMFT 0.95 (0.85–1.05)	50.2 69.4	Australia, National (excluding Vic)	5–6 12	NS NS	Meija et al. 2012
2007	dmft :1.40 (1.22–1.58) dmft: 2.62 (1.89–3.36) DMFT: 0.71 (0.63–0.79) DMFT: 0.98 (0.75–1.21)	63.2 (60.0–66.3) 45.9 (35.0–56.7) 63.2 (63.7–69.4) 45.9 (48.8–64.0)	NSW	5–6 5–6 11–12 11-12	F area Non-F area F area Non-F area	COHS NSW 2009
2005	dmft 2.27 DMFT 1.11	na	Australia, National (excluding NSW)	6 12	NS NS	Meija et al. 2012
2003	dmft 0.63 (0.37–0.88) dmft 0.95 (0.57–1.32) DMFT 0.33 (0.13–0.54)	75 61 79	NSW	6 8 11	F area	Evans et al. 2009
2009	dmft : 0.8 (0.3–1.2) dmft: 1.9 (1.5–2.3) DMFT: 0.5 (0.3–0.6)	79.7 (71.7–87.7) 51.0 (53.2–58.8) 7.5 (71.4–	NZ, National	2–4 5-11 5-11 5–17	NS NS NS Non-F areas	NZ MoH 2010

Year	dmft/DMFT	% Caries free	Region	Age (years)	Fluoridation (mg/L water)	Study
	dmft+DMFT 2.4 (2.0–2.8) dmft+DMFT 1.5 (1.1–1.9)	83.5)		5-17	F areas	

Notes: F area = fluoridated area 0.8–0.85 mg F/L, NF area = nonfluoridated area <0.2–0.3 mg F/L.
NS = not specified.
Dmfs/DMFS = decayed, missing (due to caries), filled surfaces (s/S)

The dose-response relationship between fluoride concentration in water supplies and dental caries was established by Dean and colleagues in the 21 Cities Study (Dean et al. 1941, 1942)[4]. The current NRVs for fluoride established in Australia and New Zealand and elsewhere for infants and children were based on the IOM recommendations, which were derived from this pivotal study (IOM 1997, NHMRC 2006, EPA 2010a, b; EFSA 2013). The value of Dean's study is that it was undertaken before water fluoridation programs, fluoridated toothpaste and dental treatment with fluoride products were available so it is possible to explore the relationship between dental caries and the natural level of fluoride in tap water without these confounding factors. Further research followed on from Dean's original study on dental caries and water fluoridation. Important reports include Galagan and Vermillian (1957), Eklund and Striffler (1980), Heller et al. (1997) and several systematic reviews - the York Review (McDonagh et al. 2000, Griffin et al. 2007, Rugg-Gunn and Do 2012 and Iheozor-Ejiofor et al. 2015). A number of more recent scientific articles on dental caries and water fluoridation in Australia were also available (Do et al. 2015, Do and Spencer 2015). A number of reports onward from the landmark IOM report in 1997 also provide overviews of the dose-response relationship: the EPA review in 2006 and 2010 (EPA 2006, 2010a, b) and the EC Scientific Committee on Health and Environmental Risk Review in 2011 (SCHER 2011), as well as research specific to Australia and New Zealand. Further details on the research on the link between dental caries and fluoride levels in water supplies is summarised in Supporting Document 2 and details from these reports are also summarised in Supporting Document 3.

5.2.2 Fluorosis

The dose-response of fluoride in water supplies and oral health is also inseparable from dental fluorosis. The origin of a dose-response relation between fluoride in water supplies and oral health was initially focused on dental fluorosis, not dental caries. Dental fluorosis is a developmental condition or defect of the enamel layer of teeth. It is characterised by white flecks or white, wavy lines (opacities) on the enamel of teeth. As the severity of dental fluorosis increases, the white lines may coalesce to form cloudy patches involving steadily

[4] Dean et al studied 26 cities in US in total; 21 cities were selected as suitable for the fluoride and dental caries research, a slightly different list of 22 cities was selected for the fluoride and fluorosis research.

more of the tooth surface. At severe levels, the whole surface may be involved in opacities and pitting; chipping or loss of enamel structure may occur.

There are set rules for the observation of dental fluorosis that attempt to separate out enamel opacities that are fluorotic in origin from those that are nonfluorotic. The best known set of criteria for a differential diagnosis of fluorotic opacities is that of Russell (Russell 1961) which were more widely promulgated by Horowitz in 1986 (Horowitz 1986). These involve the area of a tooth surface affected, the shape of the lesions, their demarcation from the surrounding unaffected parts of the tooth surface, the colour of the affected areas, and the pattern of teeth affected in the whole mouth. An essential aspect to documenting dental fluorosis is the application of these criteria while examining a person, and/or the application of these sort of criteria via algorithms used in analysis. Once a differential diagnosis of fluorosis is made, various scoring systems are available to rate the severity of the fluorotic changes. The best known of these is Dean's Index (Classification System) for Dental Fluorosis (Dean 1942), and the subsequent summary measure from this, the Community Fluorosis Index (Dean 1942, 1944).

In more recent times new indices have become widely used including the Thylstrup and Fejerskov Index (Thylstrup and Fejerskov 1978), the Tooth Surface Index of Fluorosis (Horowitz et al. 1984) and the Fluorosis Risk Index (Pendrys 1990). Each of these indices has different emphases which make comparison between them and with the Dean's Index subtly complex. For instance, Dean's Index classifies an individual by the second most severe observation of fluorosis at the tooth-level in the mouth, the Thylstrup and Fejerskov Index is a dry tooth index that scores the most severe presentation of fluorosis, the Tooth Surface Fluorosis Index is a wet tooth index meant to reflect what one would see in everyday activity, while the Fluorosis Risk Index divides the tooth surface into thirds and can capture very early stages of fluorosis and indications of the timing of the risk exposure. Any examination of dental fluorosis runs into the strong historical background using Dean's Index and the more recent domination of the Thylstrup and Fejerskov Index, especially in Australian oral epidemiology.

A different path to observations on dental fluorosis is that of the Developmental Defects of Enamel recording system which firstly records all defects of enamel at an examination and then separates out presumed fluorotic opacities from other enamel defects like demarcated, hyperplastic defects and combinations of these, on the basis of fluorotic defects being diffuse on affected surfaces and the distribution of affected teeth being symmetrical, but not always of the same severity. The Developmental Defects of Enamel (DDE) had its origin in New Zealand and has been widely used in oral epidemiological surveys (FDI, 1982; Clarkson and O'Mullane 1989).

A population-based study in the state of NSW in 2007 examined dental fluorosis in children using the TF Index (NSW CDHS 2007). A total of 5017 children aged 8–12 years were examined for fluorosis. The prevalence of moderate/severe dental fluorosis (TF score 4 or 5) was 0.3% (14 cases). Among those, two cases were considered as having a TF score of 5 (severe dental fluorosis – the health adverse end point). The prevalence of this adverse end point in the NSW child population was, therefore, 0.04%.

Studies in Western Australia and South Australia using the TF Index did not observe any cases of moderate to severe dental fluorosis (Riordan 2002; Do and Spencer 2007a) (see Table 5.2).

The NZ National Oral Health Survey 2009 (NZ MOH 2010a) reported no cases of severe fluorosis using the Dean Index, while the prevalence of moderate fluorosis was 2.0%.

A study in NSW in 2003 (Bal et al. 2015) reported dental fluorosis using Dean Index. Some 1% was observed to have moderate dental fluorosis while some 0.135% (4 cases) reportedly had severe dental fluorosis.

Further information on dental fluorosis and fluoride levels in water supplies, fluorosis measurement and reports of the prevalence of fluorosis in Australian and New Zealand populations and other countries is given in Supporting Document 2.

Table 5.2: Summary of data for the prevalence of any dental fluorosis (Prevalence TF1+ or Deans's Index 1+) in Australia and New Zealand

Year	*Nonfluoridated water area* Town/city	*Nonfluoridated water area* Prevalence (%)	*Fluoridated water area* Town/city	*Fluoridated water area* Prevalence (%)	Study
1989	Bunbury	33.0	Perth	40.2	Riordan 1991 Age: 12 years
2000	Bunbury	10.8	Perth	22.2	Riordan 2002 Age: 10 years
1994–1995	Rural South Australia	30.3	Adelaide	48.7	Spencer and Do 2007 Age: 7–15 years
2003	-	-	Blue Mountains, NSW	39.0+	Bal et al. 2015
2004/2005	Mt Gambier, Bordertown, Kingscote	15.0	Adelaide	29.5	Do and Spencer 2007a
2007	Various areas in NSW	16.8	Various areas in NSW	25.1	COHS NSW 2009*
2009	Various areas in NZ	20.4+	Various areas in NZ	14.9+	NZ MoH 2010 Age: 8–30 years

+ Using Dean's Index
* Whole population-based study samples

5.2.3 Other potential biomarkers

Several further biomarkers for fluoride and health were assessed for relevance to the NRV review, however, none were considered appropriate for use in the derivation of ULs for infants and young children. The EWG considered these in the light of the latest national reviews conducted in Australia (NHMRC 2007) and New Zealand (Royal Society of New Zealand 2014) and additional scientific reports.

Osteoporosis, osteosarcoma, pineal gland physiology, Intelligence Quotient and delayed permanent tooth eruption were considered by the EWG as potential biomarkers with outcomes summarised briefly below.

The EWG was not in a position to evaluate any published data on the genotoxic potential of fluoride in the timeframe for this pilot review as the literature available did not meet the criteria set for considering human data only. It was noted that there are international guidelines for testing chemicals in the food supply, including their potential to damage DNA, utilising a variety of well–validated biomarkers, such as chromosomal aberrations and micronuclei (OECD 2014). The EWG acknowledged there is a body of literature that mainly relates to in vitro studies or studies in rats of the impact of fluoride on cell function that can be deduced by exploring studies that have investigated effects on gene expression. There is a lack of in vivo data on DNA damage indices in humans with varying fluoride exposures, which is a knowledge gap.

Osteoporosis and bone fractures: This is considered potentially relevant as a biomarker for adults but not for infants or young children. A large number of studies have investigated possible associations between the levels of fluoride in drinking water and the risk of fractures of the hip and other bones. An association is biologically plausible, since very high levels of fluoride are known to affect bone density and strength, but may also reduce bone flexibility. However, research indicates that water fluoridation at levels aimed at dental caries prevention has been equivocal with small variation around the 'no effect' finding. It has been concluded that fluoride at levels associated with water fluoridation has no clear effect on hip fracture risk in adults (McDonagh et al. 2000, Nasman et al. 2013). A recent report from the longitudinal Iowa Fluoride study found no significant relationship between daily fluoride intake and adolescents' bone density (Levy et al. 2014).

Osteosarcoma: This is not considered suitable as a biomarker. A number of studies have investigated links between the level of fluoridation and osteosarcoma, an often-fatal bone cancer most commonly diagnosed in adolescents. An association between fluoride and osteosarcoma is biologically plausible, since bones readily take up much of the fluoride ingested; children/adolescents are often diagnosed around the time of the pubertal growth spurt, when osteoblastic activity is particularly high. While there has been one recent report of an association of osteosarcoma in males with earlier exposure to fluoridated water (Bassin et al. 2006), most available scientific evidence strongly suggests that community water fluoridation is not associated with osteosarcoma (Douglass and Joshipura 2006, Kim et al. 2011, Levy and Leclerc 2012, Blakey et al. 2014).

Pineal gland: This is not considered suitable as a biomarker. Concerns have been expressed about possible harmful effects of fluoride on the pineal gland (Luke 2001). The pineal gland lies near the centre of the brain, but outside the blood–brain barrier that restricts the passage of fluoride into the central nervous system. Luke studied the accumulation of fluoride in the pineal gland of older adult cadavers. Fluoride deposition was linked to calcium levels, but was considered a normal process of ageing. While there has been speculation that such fluoride deposition may be related to brain function, the EWG considered that insufficient evidence existed to determine any possible links between this deposition in the pineal gland function and human health.

Intelligence Quotient (IQ): This is not considered suitable as a biomarker. A recent meta-analysis of a number of studies dating back to the 1980s, almost all from China, concluded that naturally occurring fluoride levels in drinking water mainly in the range of 2-11 mg/L may reduce children's IQs by almost 7 points (Choi et al. 2012). However, the interpretation of this systematic review was cautioned by the authors given the lack of individual-level measures on exposure, neurobehavioural performance and covariates that would adjust for educational resources of families and communities, as well as other possible contaminants from low quality coal. Even stronger criticism has been made by Borman and Fyfe (2013). The outcomes of the Chinese studies have not been confirmed in countries practising community water fluoridation. Recently Broadbent, using data from the Dunedin Birth Cohort study, found no support for the assertion that fluoride exposure was related to IQ (Broadbent et al. 2015).

Delayed permanent tooth eruption: This is not considered suitable as a biomarker. Delayed eruption of the permanent teeth has been raised as a growth and development consequence of fluoride intake. However, a counter argument is that fluoride intake reduces caries in the primary dentition and the early loss of affected teeth. It is therefore not surprising that the literature is equivocal on delayed eruption. The latest reports do not support any significant delay in the eruption of the permanent teeth (Jolaoso et al. 2014). Hence delayed eruption was not considered to be suitable as a biomarker.

Hypothyroidism: In 2015 Peckham et al. reported an ecological study (an observational study in which data are analysed at a population or group level), which was claimed to show that after limited adjustment for demographic differences, there is a slightly higher prevalence of hypothyroidism (which can result from a number of different diseases) in four areas of England that have higher concentrations of fluoride in drinking water (Peckham et al. 2015). However, several investigators have cast considerable doubt on the reliability of the conclusion because of the seriously flawed method used in the study (Newton et al. 2015, Grimes 2015, Warren and Saraiva 2015, Foley 2015). These considerations led the EWG to discount this study.

Attention Deficit Hyperactivity Disorder (ADHD): Although there is no a priori knowledge to link drinking water fluoridation with ADHD an epidemiological study based on an ecological design was published in 2015 that compared the prevalence of ADHD in all US states with water fluoridation to those without (Malin and Till 2015). The investigators used State-based self-diagnosed ADHD prevalence estimates (2003, 2007, 2011) and fluoridation prevalence (for years 1992, 2000, 2002, 2004, 2006, and 2008) from the Centers for Disease Control and Prevention website. The authors concluded that there was an association between ADHD prevalence and fluoridation and hence fluoridated water may be an environmental risk factor. Despite acknowledging that ADHD results from interactions between genetic and environmental factors, the only potential confounder considered by authors was median household income as a proxy for socio-economic status. The authors did not consider the possibility that a correlation does not equate to causation but nevertheless concluded that fluoridated water may be an environmental risk factor for ADHD. The EWG did not agree with this conclusion and noted that causation cannot be established with cross sectional or observational studies of this type. Hence ADHD was not considered to be suitable as a biomarker.

Kidney dysfunction: Chronic kidney disease is well recognised in Australia and New Zealand with a higher prevalence amongst Māori and Australian aboriginal people, and numbers increasing due to the increasing prevalence of hypertension and diabetes. Since fluoride is excreted though the kidneys, blood fluoride concentrations are typically elevated in patients with end-stage kidney disease, and this group may be considered to be at increased risk of excess fluoride exposure. However, to date no adverse effects of exposure to fluoridated drinking water in people with impaired kidney function has been documented. In their position statement Kidney Health Australia cautions that only limited studies addressing this issue are available, but advises that "There is no evidence that consumption of optimally fluoridated drinking water increases the risk of developing chronic kidney disease", and "There is no evidence that consumption of optimally fluoridated drinking water poses any health risks for people with chronic kidney disease." (Kidney Health Australia 2011).

5.3 Selection of evidence

The NHMRC prepared its latest report on dietary reference values for fluoride and other nutrients for Australians and New Zealanders in 2005. Accordingly, the task of the EWG was to review any new evidence on fluoride and its related nutritional reference data since 2005. However, considering the range of information that can be gathered through reviewing the pertinent literature across the last two decades, the EWG agreed that the following major publications on fluoride alongside their related bibliographies, would be relevant and useful in the context of the current report and should be reviewed in detail:

1. Institute of Medicine - Dietary Reference Intakes for Ca, P, Mg, Vitamin D and Fluoride (IOM 1997)
2. The NHS Centre for Reviews and Dissemination at the University of York - The York Review: A systematic review of water fluoridation (McDonagh et al. 2000)
3. European Food Safety Authority (EFSA 2005): Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Fluoride
4. National Research Council (NRC 2006) - Fluoride in drinking water: A scientific review of EPA's standards
5. US Environment Protection Agency (EPA 2010a and b) - Fluoride: Exposure and Relative Source Contribution (RSC), Analysis and Dose-response analysis for non-cancer effects
6. Scientific Committee on Health and Environment Risk (SCHER 2011) - Opinion on critical review of any new evidence on the hazard profile, health effects and human exposure to fluoride and the fluoridating agents of drinking water

7. European Food Safety Authority (EFSA 2013): Scientific opinion on dietary reference values (DRV) for fluoride.

5.3.1 Review of major reports

Detailed comments on the reports reviewed are given in Supporting Document 3, including the overview, methods, findings/estimates and a comment on strengths, weaknesses and inconsistencies of these reports. A summary of the outcomes of the review is given in Table 5.3 below.

In brief, the UL of 0.1 mg F/kg bw/day established by the IOM in 1997 has been adopted by many agencies without further considering its derivation, in particular, the conversion of a fluoride concentration in reticulated water into a fluoride intake for children. This step is essential because Dean's 22 city dental fluorosis prevalence data did not provide any details about water consumption or bodyweights of the children. The EWG noted that the best available dose-response data for derivation of a UL was still the Dean's study which was conducted over 70 years ago.

There are a number of other methodological issues to be considered when establishing a UL or Reference Dose (RfD; established by EPA) that are apparent from the review of the above reports. These include:

- the selection of an appropriate end point or outcome i.e. severity of dental fluorosis considered to be adverse
- the acceptability of a threshold prevalence of the end point
- the identification of suitable data which establishes a clear dose-response relationship between fluoride intake and the prevalence of the end point
- the application of either a deterministic NOAEL and LOAEL analysis or a statistical Benchmark Dose analysis to a suitable dose-response relationship.

These issues are discussed further in Section 5.5.

Table 5.3: Summary of previous reports

Report	Overview	Method	Findings/estimates	Comments
Food and Nutrition Board, IOM (IOM 1997)	IOM reassessed the DRI for calcium and related nutrients including fluoride.	AI was the reference value for fluoride and was based on the average intake of dietary fluoride in fluoridated communities where maximum caries protective effect and minimum risk for adverse effects was present. UL was based on NOAEL in the Dean study with a Uncertainty Factor of 1 and a conversion to a dietary F intake.	AI: 0.01 mg/day for 0–6 months was based on fluoride content in human milk and for all other age groups including pregnant and lactating females was based on estimated mean of 0.05 mg/kg bw/day for optimally fluoridated drinking water at 1.0 mg/L. UL for children below 8 years (critical end point: moderate fluorosis of ≤ 5% prevalence) was calculated to be 0.1 mg/kg bw/day. UL for older children (>8 yrs) and adults (critical end point skeletal fluorosis) =10 mg F/day.	USA only. No specific search or assessment strategy available. The derivation of the UL of 0.10 mg/kg bw/day is consistent with drinking water at the optimal fluoride concentration for dental caries but appears to be inconsistent with the reported NOAEL of 1.9 mg F/L for less than a 5% prevalence of moderate dental fluorosis.
York review – (McDonagh et al. 2000)	Systematic review on the efficacy and safety of water fluoridation.	An extensive review from 1930s to 2000 based on 25 databases including Medline and Embase. Inclusion criteria were based on 3 levels of evidence on handling the risk of bias and study validity was assessed using NHSCRD checklist. Meta-analysis and meta-regression were performed where appropriate.	None of the studies yield highest level of evidence (Level A). Level B (moderate quality) evidence suggested that caries prevalence decreases with water fluoridation while discontinuation of fluoridation increases caries prevalence. Numbers needed to treat (NNT) for fluoridated water was 6. All but one study provided Level C (lowest quality) evidence for dose-response relationship between level of water fluoridation and dental fluorosis. No conclusive evidence for association between fluoride and bone	A clear search strategy extended to non-English articles, studies restricted to ‘before’ and ‘after’ studies, excluding cross-sectional studies. Extensive and independent review process transparent to public. Scoring system used for validity assessment of studies was not sensitive enough to detect how well

Report	Overview	Method	Findings/estimates	Comments
			fractures, cancers or other adverse effects. Evidence for caries preventive effect of fluoride should be considered along with increasing prevalence of fluorosis.	studies were carried out.
EFSA (EFSA 2005)	EFSA reviewed UL for fluoride in regard to adverse health effects.	No search strategy available in report.	Critical endpoints for children aged 1–8 years and older children and adults were occurrence of moderate fluorosis and bone fracture, respectively. No UL was established for infants less than 1 year. UL for 1–3 year olds: 1.5 mg/day and 4–8 year olds: 2.5 mg/day (based on an intake of 0.1 mg F/kg bw/day). UL for 9–14 year olds: 5 mg/day and for ages 15 or more (including pregnant and lactating women): 7 mg/day.	Absence of a search strategy in the report. No estimates for AI.
US National Research Council (NRC) (2006)	NRC re-evaluated the adequacy of the Maximum Containment Level Goal (MCLG) and Secondary Maximum Containment Level (SMCL) for fluoride.	Research articles, position papers and unpublished data available after 1993 NRC report was reviewed. A general weight-of-evidence approach, assessing multiple lines of evidence from in vitro assays, animal research and human studies to suggest a human health risk, was used. Toxicity endpoints considered for assessing the adequacy of MCLG and SMCL were severe enamel fluorosis, skeletal fluorosis and bone fractures.	The overall prevalence of severe enamel fluorosis was about 10% among children in the USA where water fluoride concentrations were at or near the MCLG of 4 mg/L and hence the MCLG was not adequate to protect children from this condition. Based on the available evidence it was concluded that the MCLG of 4 mg/L should be lowered to stop children from developing severe enamel fluorosis. The prevalence of severe enamel fluorosis is almost zero and the prevalence of cosmetically significant dental fluorosis was within the acceptable level, at fluoride	A specific search strategy was not available.

Report	Overview	Method	Findings/estimates	Comments
			concentrations below 2 mg/L (SMCL).	
US EPA -Fluoride: Exposure and RSC Analysis - (EPA 2010a)	Office of Water (OW) was assigned the task of quantifying exposure and RSC analysis of fluoride.	Peer-reviewed and published data from the USA and Canada for public and consumer water systems were used.	Drinking water contributed to total fluoride intake of 40% in 1–10 year olds, 60% in those aged above 14 years to 70% in infants aged 6–11 months. Food and beverages in combination account for about 45% of total fluoride intake in 4–11 year old children while toothpaste accounts for 20–25% of total fluoride intake in children aged between 1–4 years. The risk for severe dental fluorosis is greater for children living in areas where fluoride content in water is close to the MCL (4 mg/L).	Restricted to the USA and Canada.
US EPA -Fluoride: Dose-response analysis for noncancer effects (EPA 2010b)	US EPA reassessed dose-response of fluoride on dental fluorosis.	Dean (1942) study was selected and a Benchmark Dose (BMD) analysis was performed for a 0.5% prevalence of severe fluorosis.	BMD: 2.14 mg/L BMDL: 1.87 mg/L RfD considering only the contribution from drinking water: 0.07 mg F/kg bw/day Overall RfD (water + food): 0.08 mg/kg bw/day No data to support dose-response analysis of skeletal effects of fluoride.	The RfD was determined by considering the central tendency estimate (i.e. the 50^{th} percentile (median) or mean of the lognormal distribution) of fluoride intakes with drinking water fluoridated at 1.9 mg/L for each age group. This estimate was then adjusted upwards to be greater than the AI value of 0.05 mg F/kg bw/day by arbitrarily selecting 0.07 mg F/kg bw/day as the RfD. A further 0.01 mg/kg bw/day was also added for the

Report	Overview	Method	Findings/estimates	Comments
				likely contribution of fluoride from food to arrive at the final RfD value of 0.08 mg F/kg bw/day.
ECSCHER 2010	EC requested SCHER to provide scientific opinion for new evidence on fluoride.	Journal articles including reviews and reports in particular the ones published after 2005 were reviewed. Public was informed to provide relevant information online. Assessment of the information was done by weight-of-evidence approach developed by the EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).	Early enamel (very mild/mild) fluorosis in children is associated with daily intake of fluoride in both fluoridated and non-fluoridated areas for which a threshold cannot be determined. Insufficient evidence to support an association between fluoride and bone fractures and other adverse effects including carcinogenicity and neurotoxicity. There has been no new evidence to change the established values for UL by EFSA in 2005. Fluoride intake in adults and children aged above 12 years was below the UL in most areas except where fluoride level in water exceeded 3 mg/L and with a high water consumption.	No specific search strategy. Weight-of-evidence approach.
EFSA 2013	EFSA was requested by EC to provide a scientific opinion on DRV for fluoride.	Search strategy information is not available in report – a narrative review.	No consistent evidence to show that biomarkers can be used to establish intake of fluoride or set DRV. Considering the beneficial effects of fluoride in caries prevention, establishing an AI is more appropriate. Based on the available evidence AI for fluoride from all sources should be 0.05 mg/kg bw/day for both children and adults including pregnant and lactating women.	A broad range of material has been reviewed. Narrative nature of review. Basis of AI and UL values not reviewed. Adopted IOM AI and UL values.

5.3.2 Review of new literature

5.3.2.1 Research questions

This report focuses on answering two questions of interest in reviewing the NRVs for fluoride in Australia and New Zealand.

1. What is the recommended UL for fluoride intake among children up to 8 years of age?
2. What is the recommended AI for fluoride among children up to 8 years of age?

However, the PICO models extended beyond these two main questions to include the health outcomes of interest; dental caries and dental fluorosis (see Section 3.5.3.2).

McDonagh et al. (2000) in their systematic review of water fluoridation examined a range of potential adverse outcomes of fluoride and concluded that the evidence for dental fluorosis was strongest, with all other outcomes such as bone fractures and bone development and studies inconclusive based on available evidence. The NRC 2006 report called for more research into the relationship between fluoride intake and skeletal fluorosis and subsequently the US EPA 2010 dose-response analysis concluded that there was insufficient evidence to support a dose-response relationship between skeletal fluorosis or fractures and fluoride intake. Hence dental fluorosis was chosen by the EWG as the outcome of interest in answering the first research question. A summary of other potential adverse outcomes is in Section 5.2.3.

Dental caries was selected as the outcome of interest (biomarker) in answering the second research question.

5.3.2.2 Literature Search

A comprehensive literature search rather than a full systematic review was undertaken in December 2013–February 2014 to assist with the nominated task of estimating an AI and UL for fluoride for young children and to address the two questions outlined above. Although the task of the EWG was to review any new evidence on fluoride and its related nutritional reference data since the 2006 NHMRC report was published, the EWG reviewed the bibliographies of the major international reports on fluoride noting that some of the critical papers were published prior to 2005 (summary of major reports in Section 5.3.1, Supporting Document 3).

The literature review was conducted specifically to confirm that there was no new post-2005 data that could be used to estimate the AI and UL as it appeared from the more recent international major review reports that this was the case. All the eight international major reports had relied on Dean's data (as revealed by the review of these reports, see 5.3.1 and Supporting Document 3). As Dean's data are old (late 1930s- 1940s), but still apparently the best for the nominated task it was not considered appropriate to apply the same quality criteria to Dean's data as one would for a newly identified study. The Dean study was therefore not expected to meet the criteria for the literature search for studies undertaken from 2005 onwards. However, the EWG considered the strengths and weaknesses of Dean's data for the nominated task in this report (section 6.2).

The databases that were searched included the Cochrane Library, PubMed, Embase, Ovid Medline, Dentistry and Oral Sciences Source (DOSS), Web of Science, Toxline and the ANZ Reference centre. References of key reports that were identified in the review of reports were also searched for any relevant papers. The PICO model as shown in Box 5.1 was used to develop the search strategy for the two questions. The search strategy and generic search terms were agreed by the reviewers and EWG members.

Box 5.1: PICO model

Population	Infants and children up to 8 years of age
Intervention	Fluoride intake from all sources of potential intake
Comparator	None
Outcome	Dental Fluorosis/Dental Caries

The overall search terms and search strategy are shown in Boxes 5.2 and 5.3. Variations of the search terms were used in different databases as appropriate to their structure (for example, Medical Subject Headings terms were used in PubMed). Supporting Document 4 contains details of search terms used for specific databases.

Results were restricted to articles published from 2005 and onwards, papers or studies on humans and where full texts were available in English. Other inclusion and exclusion criteria were directly related to the study question - studies were to include information on fluoride intake, ingestion, bioavailability etc. from all sources, have information on children up to 8 years of age, and look at dental fluorosis and/or dental caries as the end point. The intention was to assess the quality of the final search results using the GRADE criteria for Assessment of Quality and ranking of evidence (Guyatt et al. 2011).

Box 5.2: Search strategy and search terms for Question 1

Exposure OR intake OR Excret* OR Diet* OR concentration* OR ingesti* OR content OR Bio* marker* OR bio* availabilit*

OR

Adequate Intake OR AI OR Upper Limit OR UL OR Upper Intake Level OR UI OR NRV* OR Nutritional reference value* OR Dietary Reference Intake OR DRI OR Dietary Reference value* OR DRV OR Average Requirement* OR AR OR *Maximum Contaminant Level* OR *MCL* OR *observed adverse effect level* OR *OAEL* OR Estimated Average requirement*

AND

Fluorid* OR Fluoros

AND

Child* OR Infan*

AND

Australia OR New Zealand OR Europe* OR EU OR United States* OR USA OR America* OR Canad* OR UK OR United Kingdom OR OECD

Box 5.3: Search strategy and search terms for question 2

Exposure OR intake OR Excret* OR Diet* OR concentration* OR ingesti* OR content OR Bio* marker* OR bio* availabilit*

OR

Adequate Intake OR AI OR Upper Limit OR UL OR Upper Intake Level OR UI OR NRV* OR Nutritional reference value* OR Dietary Reference Intake OR DRI OR Dietary Reference value* OR DRV OR Average Requirement* OR AR OR *Maximum Contaminant Level* OR *MCL* OR *observed adverse effect level* OR *OAEL* OR Estimated Average requirement*

AND

Fluorid*

AND

"Dental caries" OR "Tooth Decay"

AND

Child* OR Infan*

AND

Australia OR New Zealand OR Europe* OR EU OR United States* OR USA OR America* OR Canad* OR UK OR United Kingdom OR OECD

The literature search was restricted to the countries detailed in boxes 1-3 based on the findings of the eight major review reports, although international evidence was included from some other countries (see section 5.1.2). The literature search was updated in December 2014 using the same search terms. A summary of results of the search is in Section 5.3.3 below, including the PRISMA diagram for the outcomes for each of two research questions. A more detailed description of outcomes of the comprehensive literature search is given in Supporting Document 4.

A small number of more recent references were added to the review report following the public consultation in October - November 2015 to address specific issues raised. None of these new references were relevant to the establishment of the AI for UL for fluoride for young children.

5.3.3 Literature review results

The comprehensive literature search was completed in February 2014 and updated in December 2014 to identify any major new studies relevant to this report (new records retrieved from the Cochrane database 7, PubMed 4 and ANZ Reference Centre 14). No additional articles were identified in the searches using the PICO criteria. These studies were not included in the PRISMA diagrams.

The more recent references added to the review report following the public consultation in October - November 2015 to address specific issues raised were not added to the PRISMA diagrams as none were relevant to the establishment of the AI for UL for fluoride for young children.

5.3.3.1 Fluoride and Fluorosis

For the question on fluoride intake and fluorosis, to inform the establishment of a UL, a total of 401 citations were identified across all databases searched, after elimination of duplicates. These 401 citations were title sifted and 47 were then sifted by abstract; 16 citations were found eligible for full text review. The searches were conducted by one reviewer and subsequently reviewed and updated by another reviewer. The 47 abstracts and 16 papers were read by two reviewers independently. One paper was found to meet all the inclusion criteria (Hong et al. 2006), with the remaining papers either not reporting estimates of fluoride intake from all sources, and/or not reporting fluorosis prevalence. All remaining 15 papers were noted to have substantial background information to include in the report though they did not meet all inclusion criteria to use as evidence for the NRV review. Figure 5.1 sets out the literature search results in PRISMA format up until February 2014.As part of the Iowa Fluoride study, Hong et al. (2006) reported the prevalence of fluorosis by fluoride intake levels over the first 3 years of life in 628 participants. They noticed a dose-response effect with increasing intake of fluoride (low: <0.04 mg/kg/bw, moderate: 0.04–0.06 mg/kg/bw, high: >0.06 mg/kg/bw). Only 1.3% of children were found to have severe fluorosis (FRI score 3). Apparently duration of fluoride intake alongside its long-term cumulative effect was associated with increased risk for any fluorosis. However, the authors cautioned about the limited robustness and generalizability of their findings due to various reasons including the convenience nature of sampling that biased towards high social strata, a high rate of loss to follow-up (>80%), incomplete and non-verified intake data based on self-reported questionnaires, not controlling for potential risk factors in fluorosis development, and not assessing daily fluctuation of fluoride ingestion. The quality of this observational study was rated as Low due to the high probability of bias arising from sampling and loss to follow-up, and hence it as not used in the derivation of the UL. Nevertheless, its findings did not conflict with those of other studies, in finding a dose-response relationship between fluoride intake and prevalence of fluorosis.

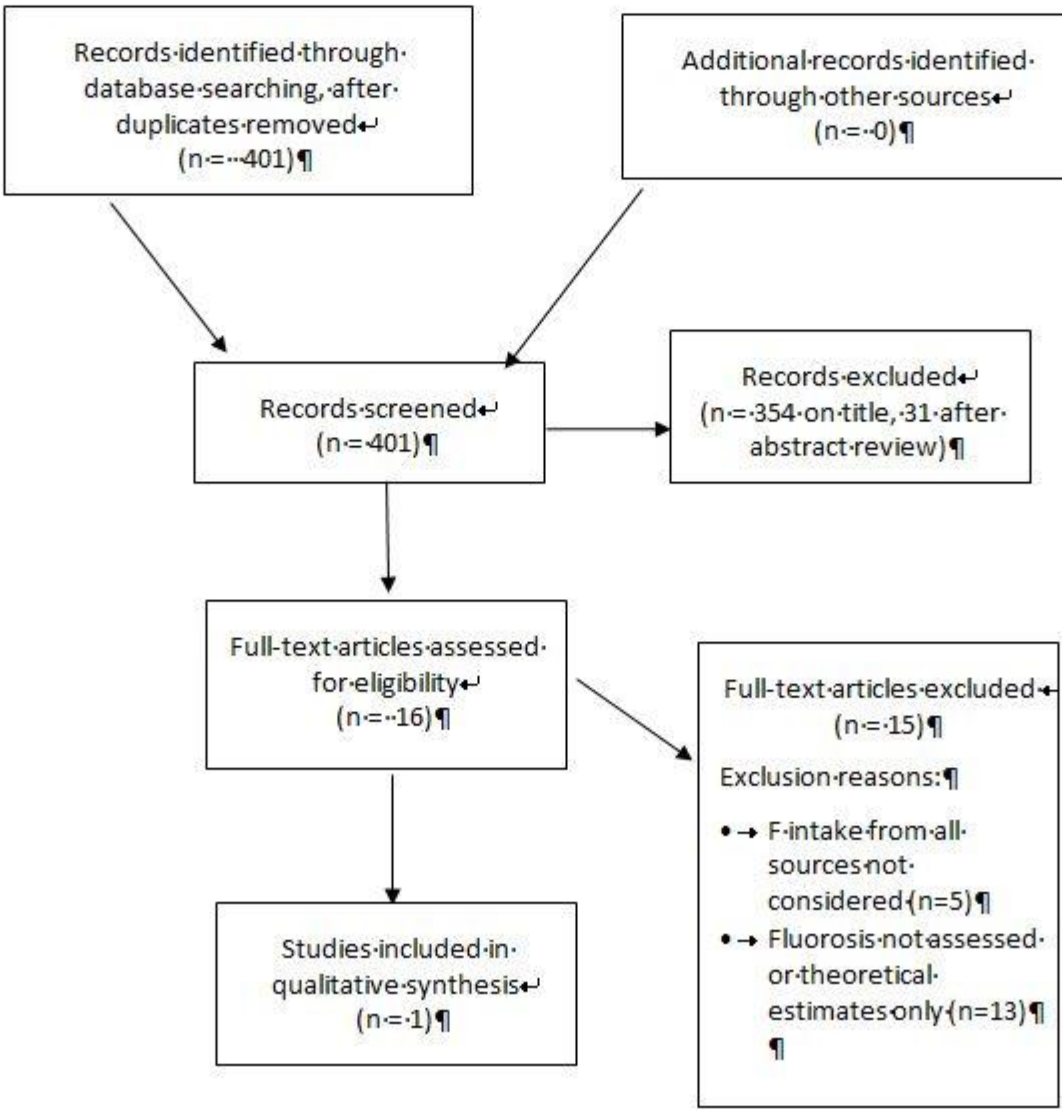

Figure 5.1: PRISMA diagram of literature search findings, fluoride intake and fluorosis (up to February 2014)

5.3.3.2 Fluoride and dental caries

For the research question on fluoride intake and dental caries, to inform the review of the AI, 576 citations were identified and title sifted across all databases, after eliminating duplicates. Thirty-three of these citations were then retained for sifting by abstract and six citations were found eligible for full text review. These six papers were read by two reviewers independently. Two papers were finally found to meet all the inclusion criteria having applied the exclusion criteria (Warren et al. 2009, Kirkeskov et al. 2010). Figure 5.2 sets out the literature search results in PRISMA format up until February 2014.

Data from the Iowa Fluoride study was used by Warren et al. to estimate the optimal level of fluoride intake that would be necessary to prevent any fluorosis or caries among children. However, the authors concluded that recommendation of an optimum level of fluoride intake was not possible because of the individual variability of fluoride exposure in those children without either fluorosis or caries. As this observational study did not contain sufficient data for a full dose-response analysis of fluoride intake and dental caries, it was not suitable to replace Dean's data.

Health registry data was used by Kirkeskov et al. to study the association between varying fluoride concentration occurring naturally in drinking water and dental caries for over 40,000 children in Denmark aged 5 years old at two time points (1989, 1999). The authors found a 20% reduction in dental caries at the lowest concentration of fluoride in drinking water of 0.125-0.25 mg F/L, and a 50% reduction at highest level of fluoride of 1 mg F/L in comparison with dental caries a the very low fluoride concentration (<0.10 mg F/L), after adjusting for gender and family income. Although an inverse relation was confirmed between fluoride exposure through drinking water and dental caries, the study did not provide prevalence rates of caries at different levels of drinking water fluoridation. In addition, bias may have arisen through the use of multiple outcome assessors who were likely to be aware of the fluoride status of the regions' water supply. Therefore the quality of this observational study was rated as Low, for the purposes of this assessment, and the paper was not used for the derivation of an AI.

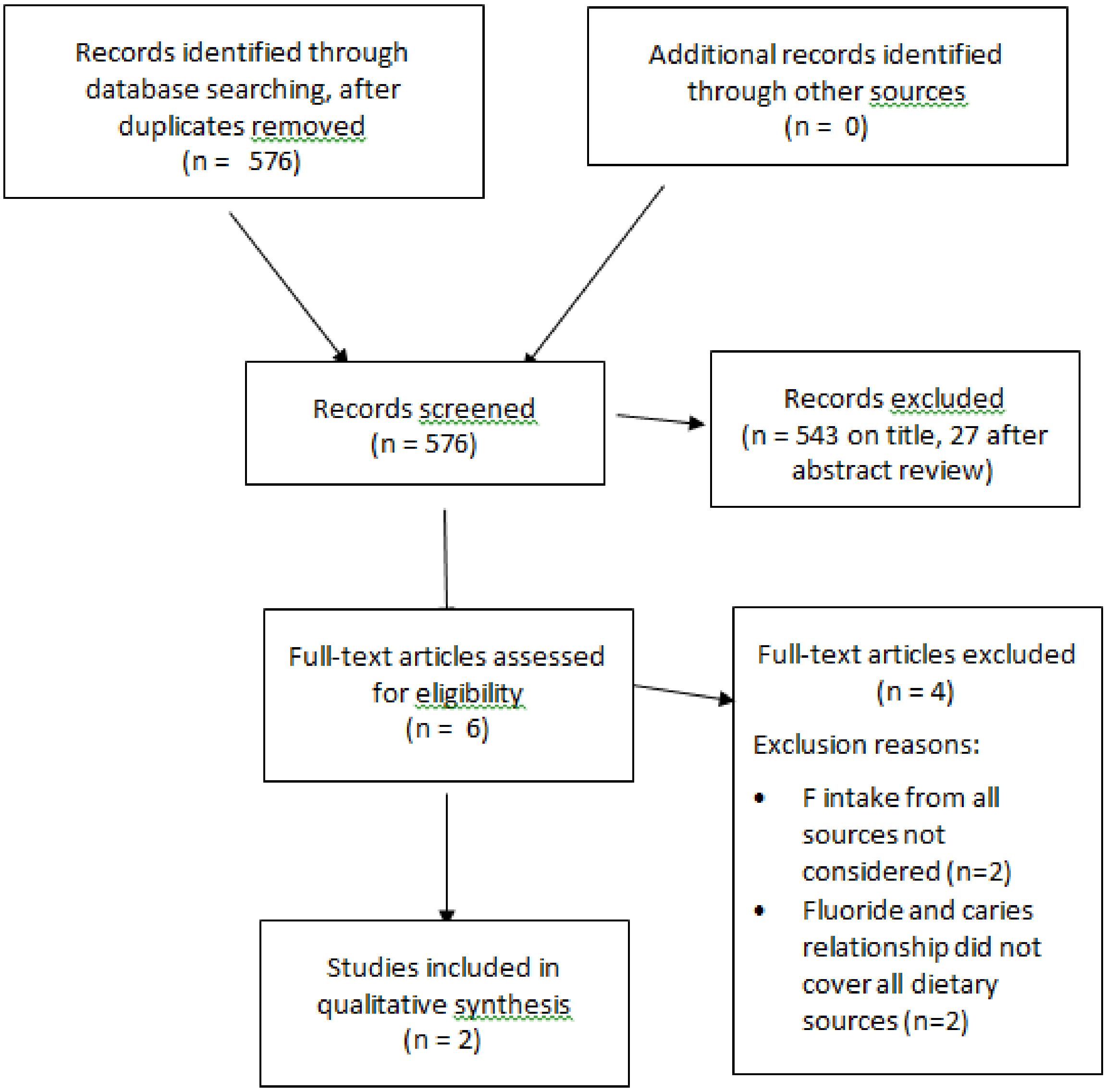

Figure 5.2: PRISMA diagram of literature search findings, fluoride intake and dental caries (up to February 2014)

5.3.3.3 Miscellaneous studies

There were a number of other studies focusing on fluoride supplement use (Hamasha et al. 2005), fluoride content in beverages (Fojo et al. 2013) as well as private wells (Graves et al. 2009) and the relationship between fluoride intake and fluid consumption pattern (Sohn et al. 2009). In general, excessive fluoride content/intake from these sources was not reported in these studies despite Sohn and colleagues raising some concerns about socioeconomically disadvantaged children being at a higher risk of ingesting more fluoride than their counterparts from high social background.

Two studies made more generic statements about the process of reviewing NRVs. Bergman et al., in reviewing the new evidence on Dietary Reference Intakes for fluoride along with calcium, phosphorus, magnesium and vitamin D from the IOM reports (IOM 1997), pointed out that defining AIs and establishing individual and synergistic activities of these nutrients would be rather complicated and therefore reviewing DRIs for these nutrients could be an arduous task (Bergman et al. 2009). Verkerk criticised the conventional model for its oversimplified two-tailed risk approach that may not consider beneficial effects of exceeding a certain threshold and suggested a new model with overlapping risks and benefits for risk/benefit analysis (Verkerk 2010). These issues were not explored further in this review.

5.4 Assumptions and limitations

In this pilot review, resources were insufficient to undertake a complete review of all literature on fluoride intakes and dental caries or dental fluorosis. Although eight major reports published from 1997 onwards were included in the review, only literature published since the time of the NRV review in 2005 (NHMRC 2006) was searched and reviewed as the NRV review was intended to be an update of the 2006 recommendations. The eight major reports and the 2005 review by NHMRC included a comprehensive review of the literature available at the time they were undertaken and together were considered to provide an excellent historical overview of research on fluoride intakes in relation to dental caries and dental fluorosis. The 2006 NRVs for fluoride were based on those cited in the IOM 1997 report, which was evaluated.

Therefore, a key assumption is that previous literature searches were complete and comprehensive.

As noted earlier, this pilot review was restricted to infants and young children up to 8 years of age, as these were identified as the key groups for assessment of adequacy and excess of fluoride intakes. Therefore, the literature search was restricted to this age group, potentially missing some key publications in the area that focused on older children and adults. One exception were the critical papers by Dean et al, as they were cited in all the eight major reports as the basis of derivation of reference values for fluoride (Dean's studies in the late 1930s –early 1940s assessed children aged 8-14 years because fluorosis may not be fully evident before this age). Similarly, the review focused largely on evidence emerging from developed countries with similar socioeconomic and dietary patterns to those found in Australia and New Zealand, potentially missing evidence arising from studies in developing countries. Some studies from countries such as Brazil, Columbia and Japan were included in the review of evidence. However, the EWG did not consider that any pivotal evidence related to the research questions was overlooked in this review process.

The review did not update, in a comprehensive way, literature relating to fluoride and health outcomes other than dental caries and dental fluorosis, as outlined in Section 5.2.3.

5.5 Review of evidence - Derivation of UL and AI

The studies by Dean from the 1930s and 1940s provide the best data for establishing the AI and UL due to the clear dose-response relationship observed between dental caries and fluorosis and concentration of fluoride in drinking water, but did not include estimates of total dietary fluoride intake among participants. In order to derive values for the UL and AI, for the purposes of establishing NRVs, it was necessary to:

- identify the critical concentrations of fluoride in drinking water that are associated with minimisation of dental caries and severe fluorosis
- predict the range of total fluoride intakes among participants in Dean's US studies at various levels of naturally fluoridated drinking water by estimating the intake of fluoride, on a bodyweight basis (mg/kg bw/day) from a number of studies, including relevant ones for Australian and New Zealand populations, associated with these critical concentrations
- assign observed levels of dental fluorosis to the higher levels of fluoride intake in each city in the Dean study taking account of the considerable overlap in distributions of fluoride intake at differing concentrations of water fluoridation
- establish an AI and UL on a bodyweight basis (mg/kg bw/day) based on the available evidence outlined above
- express these values as a total amount per day (mg/day), based on appropriate data for the bodyweight of infants and young children.

5.5.1 Dose-response assessment to establish a UL

5.5.1.1 Selection of an end point

The selection of the end point in terms of dental fluorosis needs to reflect a consensus that it represents an adverse effect to the individual and community. Over time the end point selected for establishing a UL has shifted from moderate fluorosis (e.g. the IOM 1997) to severe fluorosis (e.g. the US EPA 2010b). The reasons for this shift are multiple, varying from analytic issues cited by the US EPA (2010b) to division of opinion among experts as to whether moderate fluorosis is aesthetically displeasing but not adverse to health (NRC 2006). Further, there is also a growing body of research that comments on thresholds of dental fluorosis regarded as having an effect on aesthetics (Chankanka et al. 2009). This reflects the changed community perception of what is aesthetically objectionable. Further, anterior teeth with very mild and mild fluorosis (Dean's labels) are associated with child self-reported and parent–reported ratings of better oral health and improved oral health related quality of life than teeth with no dental fluorosis (Do and Spencer 2007b). An extension of this research showed that very mild and mild fluorosis (TF Index scores 1, 2 & 3) diminishes with time and did not have a negative impact on perceptions of oral health (Do et al. 2016). Nair et al. (2016) have reported similar perceptions among Asians who only regarded severe fluorosis (TF Index 4 or 5) as aesthetically less pleasing. As a result, very mild, mild or moderate dental fluorosis is no longer regarded as an adverse effect. The probability of them occurring can no longer be regarded as a risk.

There is a clear consensus that severe fluorosis, i.e. fluorosis which involves loss of enamel structure, is an adverse effect. The notion of an adverse effect is justified on the basis of potentially 'weakened' tooth enamel which may be more prone to dental caries and the expectation that anterior teeth with such enamel defects will be perceived to be an aesthetic concern. This is difficult to confirm as very few cases of severe fluorosis are encountered in population surveys in countries like Australia and New Zealand (see Section 5.2.2 and Supporting Document 2).

5.5.1.2 Specification of the threshold prevalence

When aesthetically objectionable (Dean's Index - Moderate) fluorosis was the end point, the threshold tolerance for its prevalence was no more than 5%. This was the basis of the IOM UL (IOM 1997), and that has been replicated in a number of the subsequent reports that adopted the IOM value. The US EPA (EPA 2010b) report explicitly moved to a severe fluorosis end point (Dean's Index - Severe) for which the threshold prevalence was set at 0.5%. Such severe fluorosis is extremely rare in Australia and New Zealand and there should also be some caution about the diagnostic accuracy of such rare observations and case-specific investigation of the likely causation. It should be noted that the change in end point and threshold does not alter the NOAEL or LOAEL interpretation from Dean's 22 cities data (Chankanka et al. 2009, Dean 1942).

5.5.1.3 Available data to establish the dose-response relationship with dental fluorosis

The reports reviewed in Section 5.3.1 concur that the 'best' data available to estimate the dose-response relationship between fluoride ingestion and severe fluorosis is Dean's 22 cities data from the US in the late 1930s. Dean and colleagues studied the prevalence of dental fluorosis and the concentration of fluoride in local water supplies. Four aspects of Dean's data support their use. First, the study involves a large number of children (n=5824) aged predominantly between 12 and 14 years old, who were continuous residents of the communities studied. Second, the concentration-response relationship shows a clear increasing prevalence of severe fluorosis with increasing fluoride concentration in the drinking water. Third, the observations were made before the availability of fluoride from the ingestion of toothpaste and fluoride supplements, or from the use of fluoride products in clinical preventive dentistry. Fourth, Dean and his colleagues were studying dental fluorosis in naturally fluoridated cities. Effort was made to include cities with a wide range of fluoride concentrations in their water supply. Hence both very low and very high fluoride concentrations were involved.

However, these same data have a number of limitations. First, some uncertainty has been expressed about the accuracy of the measurement of fluoride concentrations of the water supplies using the technology available at the end of the 1930s. However, the 2010 US EPA report, while acknowledging possible inaccuracy of the chemical method of determining the fluoride concentrations, validates them against later data. Second, there were a limited number of observations for cities with fluoride concentrations between 0.7 and 1.2 mg F/L, the range which would subsequently become crucial to water fluoridation programs in the US. Third, and more importantly, there were no data collected on water consumption and fluoride levels in foods consumed by children in the 22 cities at the time of the study. Therefore water consumption and dietary intakes of foods needed to convert any concentration of fluoride in water to an estimate of total fluoride intake were based on data from separate places and times in the EPA report (EPA 2010b).

5.5.1.4 Analysis of critical fluoride concentrations

The determination of a No observed adverse effect level (NOAEL) and Lowest observed adverse effect level (LOAEL) from the available data from Dean's 22 cities can be made on the basis of tabulated data of fluoride concentration (Table 5.4), and the prevalence of severe fluorosis in each city with the cities ranked by fluoride concentration.

An alternative strategy was used by the US EPA whereby they applied a Benchmark Dose (BMD) analysis to Dean's data. Assigning a 0.5% prevalence of severe dental fluorosis in children as an acceptable end point, several mathematical models which simulated the relationship with a fluoride concentration in drinking water were tested for goodness-of-fit. The best fit, as judged by the smallest Akaike Information Criterion value, was observed with the dichotomous Hill model. Using this model, the BMD was calculated to be 2.14 mg F/L and the BMDL (lower 95% confidence limit of the BMD) was 1.87 mg F/L. As expected the calculated BMD and BMDL corresponded well to a LOAEL of 2.2 mg F/L for a 0.7% prevalence of severe fluorosis (Clovis, NM) and a NOAEL of 1.9 mg F/L (Galesburg, IL), respectively.

5.5.1.5 Uncertainty factor

The Dean (1942) study examined the extent of fluorosis in the permanent teeth of a large number (n=5824) of children primarily in the age range of 12 to 14 years. In the cities having fluoride in their drinking water at relevant concentrations for the purpose of deriving a BMDL/BMD or NOAEL/LOAEL (i.e. 1.9–2.6 mg/L), the number of randomly selected children whose teeth were examined was large (Table 5.4). As the severity of dental fluorosis is related to the timing, duration and dose of fluoride intake, this study considered the effects of cumulative exposure on tooth maturation. Therefore, the uncertainty in the relationship of fluoride concentration in drinking water and the extent of fluorosis is considered to be low in this study. Accordingly, an uncertainty factor of 1 is considered appropriate because the data includes the most sensitive end point in the most vulnerable subpopulation in humans. The BMDL or NOAEL of 1.9 mg F/L for a 0.5% prevalence of severe dental fluorosis is divided by an uncertainty factor of 1 to establish a robust basis to derive a UL for adverse dental fluorosis in young children through to eight years of age.

Table 5.4: Percent distribution of fluorosis in populations studied by Dean (1942), sorted by concentration of fluoride in community-specific drinking water supplies

Town	No	Age (yrs)	F (mg/L)	*Dean's Index** 0	*Dean's Index** 0.5	*Dean's Index** 1	*Dean's Index** 2	*Dean's Index** 3	*Dean's Index** 4
Waukegan, IL	423	12–14	0.0	97.9	1.9	0.2	0.0	0.0	0.0
Michigan City, IN	236	12–14	0.1	97.5	2.5	0.0	0.0	0.0	0.0
Zanesville, OH	459	12–14	0.2	85.4	13.1	1.5	0.0	0.0	0.0
Lima, OH	454	12–14	0.3	84.1	13.7	2.2	0.0	0.0	0.0
Marion, OH	263	12–14	0.4	57.4	36.5	5.3	0.8	0.0	0.0
Elgin, IL	403	12–14	0.5	60.5	35.3	3.5	0.7	0.0	0.0
Pueblo, CO	614	12–14	0.6	72.3	21.2	6.2	0.3	0.0	0.0
Kewanee, IL	123	12–14	0.9	52.8	35.0	10.6	1.6	0.0	0.0
Aurora, IL	633	12–14	1.2	53.2	31.8	13.9	1.1	0.0	0.0
Joliet, IL	447	12–14	1.3	40.5	34.2	22.2	3.1	0.0	0.0
Elmhurst, IL	170	12–14	1.8	28.2	31.8	30.0	8.8	1.2	0.0
Galesburg, IL	273	12–14	1.9	25.3	27.1	40.3	6.2	1.1	0.0
Clovis, NM	138	9–11	2.2	13.0	16.0	23.9	35.4	11.0	0.7
Colorado Springs, CO	404	12–14	2.6	6.4	19.8	42.1	21.3	8.9	1.5
Plainview, TX	97	9–12	2.9	4.1	8.3	34.0	26.8	23.7	3.1
Amarillo, TX	289	9–12	3.9	3.1	6.6	15.2	28.0	33.9	13.2
Conway, SC	59	9–11	4.0	5.1	6.7	20.4	32.2	23.7	11.9
Lubbock, TX	189	9–12	4.4	1.1	1.1	12.2	21.7	46.0	17.9
Post, TX	38	~8–11	5.7	0.0	0.0	0.0	10.5	50.0	39.5
Chetopa, KS	65	~7–17	7.6	0.0	0.0	9.2	21.5	10.8	58.5
Ankeny, IA	21	~6–17	8.0	0.0	0.0	0.0	9.5	47.6	42.8
Bauxite, AK	26	14–19	14.1	0.0	0.0	3.9	3.9	38.5	53.8

SOURCE: US EPA (2010b) and modified from Dean (1942). *Dean's Index 3= moderate, 4= severe fluorosis

5.5.2 Dietary Fluoride Intake estimates for the Dean study

Since the Dean study does not provide any details on water or food consumption, an indirect approach was used by both the IOM (IOM 1997) and US EPA (EPA 2010b) to estimate the range of fluoride intakes for each age group. Though not explicitly stated it seems that the IOM used the food and water intake estimates (Table 5.5) reported by McClure with fluoridated water at 1.0 mg F/L (McClure 1943). The results cited in Table 8–1 of the IOM report show a range of daily dietary fluoride intakes for children aged between 1 and 9 years of between 0.02 and 0.10 mg F/kg bw that were the same as reported by McClure.

Using the same dietary model as specified by McClure but assuming water to be fluoridated at 1.9 mg F/L (level at which the NOAEL or BMDL was derived), the EWG estimated that the range of fluoride intakes coming from dietary sources was between 0.04 and 0.19 mg F/kg bw/day for children aged between 1 and 9 years (Table 5.6).

Table 5.5: Summary of estimated daily fluoride intakes with 1 mg F/L in water with dry substances of food (adapted from McClure 1943)

Age in years	Bodyweight kg	Tapwater consumption[ǂ] mL/day	Drinking water mg F/day	Intakes from food[ł] mg F/day	Dietary F intakes mg F/day	Daily dietary F intakes mg F/kg bw/day
1–3	8–16	300–396	0.390–0.560	0.027–0.265	0.417–0.825	0.03–0.10
4–6	13–24	400–528	0.520–0.745	0.036–0.360	0.556–1.105	0.02–0.08
7–9	16–35	500–660	0.650–0.930	0.045–0.450	0.695–1.380	0.02–0.07

ǂ Range between 25% and 33% of total daily water requirement - estimated to be 1 ml per calorie of energy in the daily diet.

ł Contains between 0.1 and 1 mg F/kg

Table 5.6: Summary of estimated daily fluoride intakes with 1.9 mg F/L in water with dry substances of food (adapted from McClure 1943)

Age in years	Bodyweight kg	Tapwater consumption[ǂ] mL/day	Drinking water mg F/day	Intakes from food[ł] mg F/day	Dietary F intakes mg F/day	Daily dietary F intakes mg F/kgbw/day
1–3	8–16	300–396	0.741–1.064	0.051–0.503	0.792–1.567	0.05–0.19
4–6	13–24	400–528	0.988–1.455	0.068–0.684	1.056–2.139	0.04–0.16
7–9	16–35	500–660	1.235–1.767	0.086–0.855	1.321–2.622	0.04–0.16

ǂ Range between 25% and 33% of total daily water requirement - estimated to be 1 ml per calorie of energy in the daily diet.

ł Contains between 0.19 and 1.9 mg F/kg.

The IOM reported that for water fluoridated at 2 mg F/L the fluoride intakes were likely to lie between 0.08 and 0.12 mg F/kg bw/day but provided no data or reference to support this estimate. The EWG noted that if the community exposure for water fluoridated at 1 mg/L ranged between 0.02 and 0.10 mg F/kg bw/day it is difficult to reconcile a range of only 0.08 to 0.12 mg F/kg bw/day at twice the concentration of fluoride in drinking water.

In contrast to the IOM, the EPA did not use the McClure's 1943 model dietary fluoride intake estimate but was unable to identify any other data which could provide a better estimate of average bodyweights and water intakes for children during the time when the Dean data were collected (Dean 1942). Consequently the US EPA considered the results of the first comprehensive US Nationwide Food Consumption Survey (NFCS) from 1977–1978, which gave bodyweight and drinking water intakes from direct and indirect information, to be a suitable surrogate (Ershow and Cantor 1989). The daily fluoride intakes, calculated from approximately 20,000 study participants using 3-day self-reported data, are shown in Table 5.7 (0.06–0.20 mg F/kg bw) and are in good agreement with the estimates using the dietary model proposed by McClure (Table 5.6), especially in relation to the upper range of intakes for 1–6 year old children, noting the range presented in Table 5.7 for tap water consumption is from the mean to the 95th percentile of consumption.

Table 5.7: Summary of estimated daily fluoride intakes with 1.9 mg F/L in water (adapted from EPA 2010b)

Age in Years	Mean bodyweight kg	Tapwater consumption[ǂ] mL/day	Drinking water mg F/day	Intake from food mg F/day	Total F intakes mg F/day	Daily dietary F intakes mg F/kg bw/day
1–3	14	646–1419	1.23–2.70	0.14	1.37–2.84	0.10–0.20
4–6	21	742–1520	1.40–2.89	0.21	1.61–3.10	0.08–0.15
7–10	32	787–1556	1.49–2.96	0.32	1.81–3.28	0.06–0.10

ǂ Range between mean and 95th percentile of water consumption levels

Using Australian dietary data for children aged between 2–3 and 4–8 years old from the 1995 National Nutrition Survey (NNS) to calculate likely total fluoride intakes with fluoridated drinking water at 1.9 mg F/L (Table 5.8) there was also a very good agreement with the upper range of total fluoride intake estimates expressed per kilogram of bodyweight obtained by the US EPA (Table 5.7) and the McClure model diet (Table 5.6) at equivalent fluoride concentrations. The mean intakes at the bottom end of the range in Table 5.8 are given for comparison with the data reported by the US EPA (Table 5.7) only but were not used in the derivation of the UL in this assessment.

It is important to note that each set of estimates cannot be directly compared as age groups differ and the method of estimating water and food intakes differ. For example, the range presented in Tables 5.8 and 5.7 for tap water consumption is from the mean to the 95th percentile, which differs from data presented in Tables 5.5 and 5.6, where the range of consumption recorded is presented.

In selecting a high percentile to represent a 'high consumer of fluoride, the EWG recognised there will be a wide distribution of food and water consumption within any population. There are several options that can be considered to reduce the uncertainty in these data; one is to choose a lower percentile to represent a high consumer (eg 90th rather than 95th percentile); another is to apply a statistical adjustment to account for within-person variation. For the Australian estimates, the 'habitual' dietary intake of fluoride for a population group from food and water was estimated using a statistical approach that took within person variation into account and used individual records from the 1995 NNS, where a 10% subset had two days of records. Some of the uncertainty in food and water consumption records were accounted for as the adjustment brings the tails of the distribution in compared with a distribution of intakes based on one day of records (FSANZ 2009). In this instance the 95th fluoride intakes was then selected to represent the high consumer. For the US EPA report, three days of data per respondent from their national survey were available to estimate habitual intakes, with the mean and 95th percentile amounts reported for tap water consumption.

Further details are given on the fluoride intake estimates in Supporting Document 1.

Table 5.8: Summary of estimated daily fluoride intakes with 1.9 mg F/L in water (derived from Australian food consumption data from the 1995 NNS by FSANZ in 2014)

Age in years	Bodyweight kg	Tapwater consumption‡ mL/day	Drinking water mg F/day	Dietary F intakes* mg F/day	Daily dietary F intakes mg F/kg bw/day
2–3	16	559–1250	1.30–2.87	1.6–3.0	0.10–0.19
4–8	24	642–1520	1.68–3.48	1.9–3.5	0.08–0.15

‡ Range between mean and 95th percentile of water consumption levels

* Range between mean and 95th percentile of fluoride intakes, food and drinking water combined, Fluoride concentration used in tap water and where tap water is used in recipes (eg tea, coffee, cordials, cooked rice/pasta, soups etc)

Due to time and resource restraints for this review, the modelling of fluoride intakes at different levels of water fluoridation was not able to be updated to include the 2007 Australian National Children's Nutrition and Physical Activity Survey (ANCNPAS) data or the 2011-12 National Nutrition and Physical Activity Survey (NNPAS) component of the 2011-13 Australian Health Survey. However estimates of water and fluid consumption were derived from the 2007 ANCNPAS and the 2002 New Zealand Children's National Survey for comparison with the 1995 NNS and overseas data and fluoride intakes were estimated for young children in the 23rd Australian Total Diet Study using the 2007 children's data (see Supporting Document 1).

5.5.3 Upper Level of Intake (UL)

While the Dean study which relates the prevalence and severity of fluorosis with a fluoride concentration in drinking water is robust and reliable, it does pose some difficulty in determining individual fluoride intake due to the absence of water consumption data and bodyweights of the children. The Dean data show that all consumers in communities with drinking water with a fluoride concentration of 1.9 mg/L or less had no evidence of severe dental fluorosis, while for communities where drinking water fluoride concentration was 2.2 mg F/L the prevalence of severe fluorosis was 0.7%. In the absence of any specific information about the individual total fluoride intakes of those children who had severe dental fluorosis with drinking water at 2.2 mg F/L, the EWG assumed that their fluoride intake would be greater than the highest fluoride intake values for all children at 1.9 mg F/L. This assumption seems reasonable because it has been shown that fluoride water concentrations in the Dean study data are predictive of more severe fluorosis levels in teeth using a CATMOD (Categorical Model) statistical procedure (EPA 2010b).

Hence a UL for fluoride can be established at the upper range of fluoride intake (in mg/kg bw/day) for young children (1-3 years) when drinking water fluoride concentration is 1.9 mg F/L (the level below which there is no evidence of severe dental fluorosis). These young children will have the highest fluoride intakes on a bodyweight basis, compared to older children, and so by selecting the upper range of estimated fluoride intakes for this group it is likely that the rest of the population will have intakes below this UL.

Since the Dean study was undertaken before non-dietary sources of fluoride were available, the EWG calculated the likely total fluoride intakes from the diet with 1.9 mg F/L fluoridated water by using three different population estimates. These were, the model diet proposed by McClure (1943), the US 1977–78 NFCS and the Australian 1995 National Nutrition Survey data. There was reasonably good agreement among the total fluoride intake estimates for children aged 1–8 years in that reported intakes were of a similar range of values. They ranged from approximately 0.04 mg F/kg bw/day at the mean to 0.20 mg F/kg bw/day at the 95^{th} percentile. Hence the maximum intake level of 0.20 mg F/kg bw/day appears to be the threshold beyond which severe enamel fluorosis is likely to appear in some children. A UL for fluoride was established at 0.20 mg/kg bw/day.

The difference between the proposed UL of 0.20 mg/kg bw/day and the Reference Dose (RfD) value of 0.08 mg/kg bw/day established by the US EPA warrants comment (EPA 2010b). The US EPA adopted the conventional approach of selecting a mean intake concentration at the BMDL to derive an RfD even though water intake data and bodyweights for the children was not available. They soon recognised the difficulty of applying this conventional approach to Dean's fluorosis data when it became apparent that the RfD for a substantial proportion of children was *at or lower* than the identified beneficial dose (AI) of 0.05 mg/kg bw/day. In order to avoid the conflict where the AI and RfD would have the same numerical value, the US EPA arbitrarily adjusted the RfD to be 0.02 mg/kg bw/day higher than the AI value of 0.05 mg/kg bw/day. An additional 0.01 mg/kg bw/day was also added to account for the fluoride derived from food. The primary cause of this problem was the absence of matched individual water intake and dental fluorosis data in Dean's study that would have enabled a direct individual dose-response relationship to be determined.

The EWG noted that in the US NFCS, water consumption for children at the 95th percentile was slightly more than double the mean consumption level. This observation meant that at least 85% of children residing in Clovis, NM community and drinking water containing fluoride at a concentration of 2.2 mg/L would not have fluoride intakes greater than children residing in the Galesburg, IL community where the drinking water fluoride concentration was 1.9 mg/L (Table 5.4). As a result the EWG reasoned that using a *mean* fluoride intake at the BMDL (1.9 mg F/L - rounded) would not provide a robust basis to derive a UL for fluoride when the full range of fluoride intakes also included most intakes at the effect dose (BMD – 2.14 mg F/L) for 0.5% prevalence of severe enamel fluorosis. Hence the EWG did not take the same approach as the US EPA, and instead used the upper range of fluoride intakes at the BMDL to derive a UL for fluoride.

5.5.4 Adequate Intake

While fluoride has been classified by some as essential to human health, others have classified it as important to human health. The distinction between these classifications is whether the criterion of involvement in metabolic pathways needs to be satisfied. For fluoride a key nutrient reference value will be an AI for children, including infants. An estimated average requirement (EAR) and hence a recommended dietary intake (RDI) could not be determined based on the evidence available. The AI is based on estimated mean (average) fluoride intakes that have been shown to minimise caries in a population without causing unwanted side effects such as severe dental fluorosis.

A curvilinear dose-response relationship between fluoride concentration in water supplies and dental caries was established by Dean and colleagues in the 21 cities study (for details see Supporting Document 2). Additional studies in other countries (for example Kirkeskov et al. 2010) have confirmed this relationship that results in an approximate reduction in caries prevalence of 50% at around 1 mg F/L relative to negligible fluoride in drinking water. Increasing the water fluoride concentration from 1 mg F/L to around 2 mg F/L reduces the caries prevalence by no more than an additional 10%. Hence the fluoride concentration in drinking water resulting in near maximal caries prevention is widely regarded to be around 1 mg F/L.

The IOM reported that in seven U.S. and Canadian studies published from 1943 to 1988, dietary fluoride intakes by children aged between 3 months and 9 years ranged from 0.4 to 1.38 mg F/day in areas where the drinking water fluoride concentration ranged between 0.7 and 1.1 mg F/L (IOM 1997). However, only one of these studies involved children over 2 years old. A comprehensive survey of water consumption by infants and children in the US was reported in the 1977–1978 NFCS (Ershow and Cantor 1989). These water consumption data for adults and children were shown to be log-normally distributed with children aged between 1 and <11 years having a median daily tapwater consumption of 620 mL/day and a mean consumption of 701 mL/day (Roseberry and Burmaster 1992). In tabulating the NFCS data Roseberry and Burmaster weighted the data that were originally collected in 1977–78 to better represent the US age group distribution. However, they adapted the age distributions patterns of the US in 1988. A summary of unweighted NFCS tap water consumption amounts for children in specified different age groups is shown in Table 5.9. At a fluoride concentration of 1 mg F/L in tap water the average fluoride intake was 0.046 mg/kg bw/day, 0.037 mg/kg bw/day and 0.026 mg/kg bw/day for children aged 1–3, 4–6 and 7–10 years respectively. The contribution of fluoride in food to the overall fluoride intake during the time of the Dean study was estimated to be an additional 0.01 mg F/kg bw/day (McClure 1943). So the range of average daily total fluoride intakes from the diet was estimated to be 0.04–0.06 mg/kg bw/day (rounded) for children aged between 1 and 10 years.

Warren et al. in 2009 reported that the estimated fluoride intake for children in the Iowa Fluoride study with no dental caries history and no fluorosis at age 9 years was at, or below, 0.05 mg F/kg bw/day (Warren et al. 2009).

Table 5.9: Summary of Daily Tap Water Consumption in US during 1977–78 (Ershow and Cantor 1989)

Age (years)	Mean bodyweight (kg)	Mean (mL)	75th percentile (mL)	90th percentile (mL)	95th percentile (mL)
0.5–0.9	9.2	328	480	688	764
1–3	14.1	646	820	1162	1419
4–6	20.3	742	972	1302	1520
7–10	30.6	787	1016	1338	1556

Infants have unique nutritional needs, necessitating the exclusive feeding of human (‘breast’) milk or milk substitutes to at least three months, and more commonly through to four to six months of age. Infants who are fed breast milk typically receive little, if any, other fluid. Consequently, breast milk fed infants will receive no more fluoride than what is present in breast milk. After 6 months most infants and children receive fluoride in their diet from water.

Based on studies reported by the IOM, in particular the 1989 study by Ershow and Cantor described above for children aged 1-10 years, and Warren et al. in 2009, the current AI of 0.05 mg/kg bw/day seems to be a reasonable fluoride intake estimate to appreciably reduce the prevalence of caries in a population for infants aged 6 months and over and young children (1-10 years old).

5.5.5 Current fluoride intake in Australia and New Zealand

In order to examine current fluoride intakes against the proposed AI of 0.05 mg/kg bw/day and UL of 0.20 mg/kg bw/day the EWG tabulated the estimated intakes for each age group (Table 5.10). In their calculations, the EWG assumed that all packaged water and reticulated water was fluoridated at 1.0 mg F/L. In 2009 permission was given in the Australia New Zealand Food Standard Code to add fluoride to bottled water on a voluntary basis at levels up to 1.0 mg/L (FSANZ 2009). However, in the 1995 NNS, consumption of bottled water was limited and information from the 2007 ANCNPAS indicates less than 5% of children under 8 years of age reported consuming bottled water, so an assumption that all bottled water consumed was fluoridated was considered unlikely to impact on estimated total fluoride intakes for this age group. The range of concentrations of fluoride in Australian and New Zealand reticulated water supplies is expected to be between 0.6 and 1.1 mg/L and 0.7 and 1.0 mg F/L respectively (NHMRC 2007, NZ MOH 2005). The fluoride intake estimates for Australian population groups aged 2 years and above were derived using food consumption data from the 1995 Australian National Nutrition Survey (Table 5.10).

For New Zealand children, Cressey et al. estimated that for 5–6 year olds drinking fluoridated water at 1.0 mg F/L the mean dietary fluoride intake was 0.84 mg F/day, and 1.74 mg F/day for the 95th percentile intake estimate (Cressey et al. 2010). For 7–10 year old New Zealand children, the dietary fluoride estimates at the mean and 95th percentile intakes were 0.99 and 1.80 mg F/day respectively. Although the age groups do not align, there was reasonably good agreement with updated daily fluoride dietary intake estimates for Australian children aged 4–8 years, where mean and 90th percentile intakes when water is fluoridated at 1.0 mg/L were 1.2 mg F/day and 1.9 mg F/day respectively (see Table 9 in Supporting Document 1).

For infants (3 months solely formula fed; 9 month olds in Australia; 6–12 month olds in New Zealand), model diets were used to update estimated dietary intakes of fluoride (Table 5.10, Table 7 in Supporting Document 1). For 3-month old formula fed infants, fluoride intakes were estimated to be 0.8 mg F/day when water was assumed to be fluoridated at 1.0 mg/L (FSANZ 2014). Cressey et al., based on slightly different assumptions on infant formula consumption, estimated a similar mean fluoride intake for a 6-12 month old infant fed formula and complementary foods, where formula was assumed to be prepared with water fluoridated at 1.0 mg F/L (0.71 mg F/day, see Table 6 in Supporting Document 1) (Cressey at al. 2010).

5.5.5.1 Estimated fluoride intakes from toothpaste

In Australia, guidelines have been published that children should use a ‘pea sized’ amount of toothpaste, assumed to be 0.5 g (ARCPOH 2006). Similar guidelines exist in New Zealand (NZ Ministry of Health 2009). In New Zealand a thin smear of toothpaste is recommended to be increased to a pea sized amount for children 6 years and over. The key difference is that Australia emphasises the use of low fluoride toothpaste (400-550 mg F/kg) and accepts regular fluoride toothpaste (1000 mg F/kg) use as an exception for children of elevated risk of caries, whereas New Zealand emphasises regular fluoride toothpaste for children, with low fluoride toothpaste as the exception for children at elevated risk of dental fluorosis.

Both countries follow a set of tooth brushing practices that will reduce fluoride intake from toothpaste. These include ages at which to commence use of toothpaste, parental supervision, small-headed tooth brushes, spitting out and not rinsing or swallowing. If these guidelines are followed the fluoride exposure from toothpaste for young children (<6 years) is likely to be in the range of 0.1–0.3 mg F/day assuming that half or all of the toothpaste is swallowed.

British children aged 30 months were reported to have an average of 0.36 g toothpaste applied to the brush of which 0.27 g (72%) was swallowed (Bentley et al. 1999). Similarly, in a study of Irish and Dutch children, the mean amounts of toothpaste used were 0.35 g for children aged between 1.5–2.5 years and 0.44 g for children aged between 2.5–3.5 years (Van Loveren et al. 2004). In Brazilian children aged between three and four years (mean bodyweight =18.8 kg) the mean amount of toothpaste used was reported to be slightly higher at 0.55 g (Oliveira et al. 2013). The estimated ingested amount of total soluble fluoride (TSF) was reported to be 0.039 mg F/kg bw/day because the TSF of adult and children’s toothpaste was determined to be around 1000 mg F/kg. One study by Erdal and Buchanan estimated US children aged 3-5 years obtained a mean of 0.015 mg F/kg bw/day (one brush per day and 0.26 g/brush) and a maximum exposure of 0.13 mg F/kg bw/day (3 brushes per day and 0.77 g/brushing) from toothpaste at a concentration of 1000 mg F/kg. A maximum exposure estimate (RME) was not reported in other studies (Erdal and Buchanan 2005).

Based on these data the EWG allocated an additional estimate amount of 0.04 mg F/kg bw/day for young children (2–4 years) from toothpaste to estimated dietary fluoride intakes for those children who may swallow the most toothpaste. Although it is anticipated that older children (>4 years) would consume appreciably less in proportion to their bodyweight, the same fluoride intake from toothpaste was assumed.

Table 5.10: Summary of estimated total daily fluoride intakes assuming 1.0 mg F/L drinking water and toothpaste use (Australian Data – Adapted from Tables 4-9 in Supporting Document 1)

Age (years)	Bodyweight kg	Tap water consumption ǂ mL/day	Fluoride from total water consumption ǂ mg F/day	Total fluoride intakes* mg F/day	Total fluoride intakes mg F/kg bw/day
0.25	6.5	-	–	Mean 0.80 95th centile 0.96	0.12 0.15
0.75	9	-	–	Mean 1.23 95th centile 1.47	0.14 0.16
2–3	16	559–1250	0.68–1.51	Mean 1.0 95th centile 1.8	0.06 0.11
4–8	24	642–1520	0.88–1.83	Mean 1.2 95th centile 2.1	0.05 0.09

ǂ Range between mean and 95th percentile of water consumption levels (from Tables 4, 5 in Supporting Document 1, applying a concentration of 1.0 mg /F/L to total water consumption)

* Includes toothpaste intake for children 2–8 yrs (additional 0.04 mg F/kg bw/day)

**. See Tables 7-9 in Supporting Document 1 for intake calculations

Table 5.10 shows that the upper range of fluoride intake estimates were from 0.09 to 0.16 mg/kg bw/day across the different age groups considered, which is considerably lower than the proposed UL of 0.2 mg/kg bw/day. This result is consistent with the observation that there is currently a very low prevalence (<0.04%) of severe dental fluorosis among the Australian population (Section 5.2.2). Although this calculation was not undertaken for the New Zealand population, due to lack of data from children under 5 years of age, a similar outcome is expected (information is available for older New Zealand children in Supporting Document 1).

6 Guideline recommendations

6.1 Revised NRVs

6.1.1 Upper Level of Intake (UL)

The estimated UL for fluoride, based on the end point of enamel pitting or loss as manifest in severe dental fluorosis, is 0.20 mg F/kg bw/day for children during the period from newborn to 8 years of age (GRADE rating - Moderate). Beyond the period when the enamel forms on permanent teeth, the ingestion of fluoride does not cause further developmental changes to teeth. To extrapolate to different ages of children, standard bodyweights are applied. Those reported in the 2006 NRV document (NHMRC 2006) were derived from the original 1997 IOM report. However, these bodyweights were revised by IOM in 2005 using a different method to derive them based on ideal bodyweights at median body mass index in the normal range and known height-for-age rather than actual bodyweights as had been used in the 1997 report (IOM 1997, NRC 2005). The following recommendations for the UL can be made, based on the revised IOM bodyweights for infants and children 1-3 years, in the absence of updated values for the Australian (ABS 2014) and New Zealand populations for these age groups, and new ideal bodyweights for Australian New Zealand children aged 4-8 years, rounded up to the nearest whole number.

Table 6.1: Recommendations for the UL for children aged 0-8 years

	Age	**Mean bodyweight**	**UL**
Infants	0–6 months	6 kg	1.2 mg/day
Infants	7–12 months	9 kg	1.8 mg/day
Children	1–3 yrs	12 kg	2.4 mg/day
Children	4–8 yrs	22 kg	4.4 mg/day

This recommendation for ULs for infants and young children has no impact on current drinking water guideline levels or for action on fluoride intakes from the ingestion of toothpaste.

Since the low intake of fluoride by breastfed infants during this stage of life does not appear to increase the risk of dental caries, fluoride from human milk is considered adequate in early life. The EWG consideration of a UL for 0—6 month old children was built around both an interpretation of the time of Dean et al’s collection of data on fluoride levels in water supplies and fluorosis and caries and also an assessment of contemporary evidence around fluorosis and caries development associated with breast and infant formula feeding (see section 5.5.3).

Dean et al. collected data on 12—14 year olds who were infants and children in the mid-1920s. It is unknown what proportion of these infants and children would have been fed with infant formula but it was assumed by the EWG that most would have been breast fed at least between 0—6 months of age. Fluoride levels in breast milk from mothers who consume drinking water at 1 mg F/L is reported to be around 10 ng/g (Dabeka et al. 1986). Infants (6-months) who received this milk would be exposed to about 0.008 mg/day (~0.001 mg/kg bw). It follows that fluoride intake over 0—6 months probably played a small role in the resulting dose-response relationship between fluoride in water supplies and fluorosis or caries in children.

In establishing the UL on the basis of Dean et al.'s data it was judged as prudent to extrapolate the information on fluoride levels and the occurrence of severe fluorosis back into the 0—6 month-age group. The purpose of the UL is to provide protection from what is regarded as an adverse effect, severe fluorosis, and the best information available indicates that the UL should be estimated on the basis of 0.2 mg F/kg bw/day.

The EWG reviewed contemporary evidence on fluoride intake among infants 0—6 months old and both dental fluorosis and dental caries. As breast milk is low in fluoride the focus across this age range is on fluoride intake among infant formula fed children. The issue then becomes a consideration of the nature of the infant formula and what is used in its reconstitution.

The use of infant formula and its reconstitution with fluoridated water has been associated with dental fluorosis (but not at the severity used as a threshold to establish an UL) (Hujoel et al. 2009; Berg et al. 2011). This supports the EWG decision to establish a UL for 0—6 month old infants. However, the EWG considered this as a prudent measure as the evidence of the specific intake across this age from bottle feeding with infant formula reconstituted with fluoridated tap water and dental fluorosis is not strong. There are several issues. There is considerable risk of misclassification as individual children have varied patterns of the timing and extent of bottle feeding, introduction of other fluids and solids, even the commencement of oral hygiene and the use of toothpaste that creates multiple and often concurrent exposures to fluoride. This is accentuated by the use of time periods in characterising infant formula use which do not directly fit with the 0-6 months age range. Further, the potential for correlations between fluoride intake at early and later periods of a child's life leads to analytical problems in dis-entangling associations for a specific period (Levy et al 2010). A recent Australian study of children examined at age 8-13 years found that infant formula use for more than 6 months was associated with higher prevalence of very mild to mild fluorosis for infants who had lived in non-fluoridated areas compared to infants in those areas who did not consume infant formula; however there was no significant difference in fluorosis in fluoridated areas. Overall, children in fluoridated areas had a higher prevalence of very mild to mild fluorosis but lower caries experience than those in non-fluoridated areas (Do et al 2012).

Guidance is given in the Australia New Zealand Food Standards Code for labelling infant formula products in relation to fluoride content. Labelling is required if the fluoride concentration is more than 17 μg/100 kJ in powdered or concentrated product prior to reconstitution or more than 0.15 mg/100 mL in ready to drink formula products. In these cases, a statement is required to the effect that consumption of the formula has the potential to cause dental fluorosis plus a statement recommending that the risk of dental fluorosis should be discussed with a medical practitioner or other health professional (Standard 2.9.1 Infant formula products section 23, FSANZ 2016).

6.1.2 Adequate Intake

A reduction in the prevalence and severity of dental caries associated with communities having fluoridated water (approx. 1 mg F/L) has been confirmed by numerous epidemiological studies conducted in several countries throughout the world (Murray et al. 1991, McDonagh et al. 2000, Rugg-Gunn and Do 2012). The average daily dietary intake of fluoride under conditions that results in near maximal caries prevention is approximately 0.05 mg/kg bw/day (Table 5.5).

The EWG recognised that infants are not necessarily exclusively breastfed in the first six months of life and may consume infant formula as well as solid foods; however food consumption data are not available to model estimated fluoride intakes for this age group. For older infants fed infant formula that has been prepared using tap water fluoridated at 1 mg/L, the estimated mean fluoride intake is 1.2 mg F/ day for 9–month old infants in Australia and 0.79 mg F/day for 6-12 month infants in New Zealand (Table 5.10 Australia only, Table 7 in Supporting Document 1). It is important to note that these two estimates of fluoride intake differ substantially because of differences in assumptions around formula consumption amounts, energy requirements and the proportion of energy coming from complementary foods. In general the average daily dietary fluoride intakes by children with fluoridated drinking water at 1.0 mg F/L increases across older ages but declines when expressed as a proportion of bodyweight (Table 5.10).

These same issues identified previously in regard to infant formula and fluorosis also apply to the examination of the evidence on fluoride intake across the 0—6 month-age group and dental caries. A recent systematic review of breastfeeding and infant formula feeding with dental caries found some 10 studies but the results were equivocal (Tham et al 2015). The majority of the studies found no association between feeding with infant formula and caries. The conclusion of the review was that the risks [benefit] of breast feeding/formula feeding with infant formula and dental caries could not be readily determined. This review did not include a recent Australian study which found that the prevalence of dental caries and fluorosis in children aged 8-13 years varied with their reported infant feeding experiences during the first year of life (Do et al 2012). In this study infants who had been fed formula reconstituted with nonfluoridated water had a higher prevalence of caries than infants fed formula reconstituted with fluoridated water; however effects of feeding patterns in the first 6 months of life were not distinguished from the period from 6-12 months of age.

Overall, these findings support the view of the American Dental Association's Council on Scientific Affairs which stated in 2011 that the preventive effect of fluoride intake in the first 6 months of life has not been established (Berg et al 2011). This also reiterates the view expressed by the US Institute of Medicine in 1997 (IOM 1997). Therefore, the prudent approach adopted by the EWG was not to establish an AI for 0—6 month old infants.

The following recommendations for the AI can be made, based on the revised IOM bodyweights for infants and children 1-3 years, in the absence of updated values for the Australian (ABS 2014) and New Zealand populations for this age group, and new bodyweights for Australian and New Zealand children aged 4-8 years, rounded up to the nearest whole number.

Table 6.2: Recommendations for the AI for children aged 6 months - 8 years

	Age	Mean bodyweight	AI
Infants	0–6 months	6 kg	Not applicable
Infants	7–12 months	9 kg	0.5 mg/day
Children	1–3 years	12 kg	0.6 mg/day
Children	4–8 years	22 kg	1.1 mg/day

This recommendation for the AI for infants and young children has no implications for current drinking water standards in Australia and New Zealand or for action on fluoride intake from ingestion of toothpaste.

The withdrawal of an AI for infants aged 0-6 months of age means there is no reference point for this age group, which may impact manufacturers of breast milk substitutes intended for this age group.

6.1.3 Applicability

The recommendations apply to the generally well population of children aged 7 months to 8 years (AI) and children aged 0-8 years (UL) and are not intended to be guidelines on dental/oral health or clinical practice guidelines used by dental and health professionals treating individuals.

The NRVs for fluoride are health based guidance values designed to be used as reference standards by dietitians and other health professionals working in different settings when developing clinical practice guidelines, assessing dietary requirements of populations and as the basis for public health policy initiatives. They can provide a benchmark for activities that involve monitoring and assessing population fluoride intake and fluoride levels in the food supply.

Public health professionals and food legislators may use the NRVs to undertake dietary modelling, risk assessments and/or set food standards, including food labelling standards. The food industry may refer to the NRVs in relation to food formulation.

6.2 Validity of Recommendations

Andrews et al describe the GRADE approach to classifying the strengths and weaknesses of recommendations for systematic reviews and practice guidelines (Andrews et al., 2013). As the EWG did not undertake a systematic review of the literature and NRVs are health-based guidance values not clinical practice guidelines, the approach was not implemented fully.

However, a rating was given to the recommendations for NRVs for fluoride by the EWG, based on consideration of the strengths and weakness of the underlying evidence presented in the relevant studies for the AI (Dean 1942) and for the UL (Dean 1942), taking account of the age of the studies and standard of reporting at that time. The summary of findings is at Appendix 1.

Although Dean's studies in the US in the late 1930s and early 1940s were observational in design, they have several features that supported their use. This included the large number of children studied and the wide range of drinking water fluoride concentrations observed, the clear dose-response relationships shown between fluoride in water and prevalence of dental caries and dental fluorosis and the absence of potential confounding factors from the use of fluoridated water supplies and toothpaste, supplements and dental treatments containing fluoride. For these reasons, the EWG considered there was a high degree of certainty in the estimated critical fluoride concentration in the water supply for each of these endpoints.

No recent data were identified that were of comparable quality and covered the same range of fluoride intakes as Dean's studies. Nevertheless, none of the recent studies contained findings that would challenge the validity of Dean's data. It is unlikely that a comparable set of data will become available in the future because of the now widespread use of water fluoridation, fluoridated toothpaste and other topical fluoride treatments. It is also unlikely, for ethical reasons, that experimental studies such as randomised clinical trials will become available in the future to allow refinement of these estimates.

However, to estimate an AI and UL from Dean's data required use of data for food and fluid consumption and bodyweights drawn from other sources. Although the results from three different sources provided consistent results, because of this need to use indirect data, the EWG considered that the overall evidence base for the relationship between fluoride intakes and both dental caries and fluorosis was Moderate, using the GRADE system.

The EWG also noted that the revised UL is consistent with the very low rates of moderate or severe dental fluorosis observed in Australia and New Zealand, as intake estimates indicated only a very small proportion of children were likely to have fluoride intakes above the proposed UL when drinking water was assumed to be at 1.0 mg F/L. From the model diets for infants, the UL was not exceeded, assuming the 95^{th} percentile of fluoride intakes and a median weight child. No children aged 2-3 years and 0.1% children aged 4-8 years (1 child out of 977) in Australia were estimated to have fluoride intakes that exceeded the UL.

The EWG strongly recommends the adoption of these revised NRVs for the UL and AI for fluoride for Australian and New Zealand children aged up to 8 years.

6.3 Further research

Information on population bodyweights for infants and children under the age of 4 years, to be used in the extrapolation of derived NRVs to all age groups, was not available for Australian and New Zealand populations, resulting in the use of the revised IOM values for the American population (NRC 2005). The availability of Australian and New Zealand bodyweight data for these age groups could be assessed and, if appropriate, the data reviewed prior to future nutrient reviews. Agreed reference bodyweights for Australian and New Zealand populations should be included in the final Methodological Framework for NRV Reviews with information on how to use the values for extrapolation of NRVs.

For the future, the work remaining is to review the AI and ULs for fluoride for older children and adults, including pregnant and lactating women as part of the NHMRC NRV review program. Where an AI or UL has not been reviewed, the values from the 2006 NRVs for Australia and New Zealand stand. Although the most robust data identified in this and previous international assessments to derive a UL for fluoride was that from the Dean studies in the US undertaken in the late 1930-early 1940s, it may be beneficial in the future to pool more recent information from different research groups to determine what can be learnt from the totality of information on oral health and associated factors. In this assessment the UL has been derived based on a critical end point for severe fluorosis, however, further research could be undertaken with consumers on the aesthetics of moderate fluorosis, as it remains contentious in some jurisdictions as to whether it is of importance or not.

To better estimate fluoride intakes in the future, it would be desirable to update the fluoride food and water content data sets prior to starting this work so that these data can be combined with the most recent food consumption data for the Australian and New Zealand populations for use in future reviews (2002 NZ children’s NNS, 2008/09 NZ adults NNS, 2011-13 Australian Health Survey for ages 2 years and over). In addition, comprehensive research on fluoride intake from toothpaste in infants and children in Australian and New Zealand populations would improve the accuracy of estimates of fluoride intakes from this source.

7 Membership of groups and committees involved in the development process

7.1 Membership of the Nutrient Reference Values Steering Group

The Steering Group for the project is composed of representatives from the Australian Government Department of Health, and the New Zealand Ministry of Health and makes decisions relating to the strategic, technical and funding elements of the project. Membership is held by the following positions:

Australian Government Department of Health:

- Assistant Secretary - Preventive Health Policy Branch, Population Health and Sport Division.
- Director – Food and Nutrition Policy Section, Population Health and Sport Division.

New Zealand Ministry of Health:

- Director/Deputy Director of Public Health, Protection Regulation and Assurance Business Unit
- Team Leader & Senior Advisor (Nutrition), Clinical Leadership, Protection and Regulation Business Unit.

7.2 Membership of the Nutrient Reference Values Advisory Committee

The NRV Advisory Committee includes members with technical expertise in the areas of micronutrients, toxicology, nutrition risk assessment, public health, end user needs, research, chronic disease, and nutrition. The role of the Advisory Committee is to provide advice to the Steering Group on the nutrient priorities for review, appointments and to support the nutrient specific Expert Working Groups. Membership of the Advisory Committee is outlined below.

Professor Samir Samman (Chair)

Head of the Department of Human Nutrition, University of Otago

Expertise: micronutrients, biomarkers and the role they play in informing nutritional status and disease risk in humans. Professor Samman's interest in micronutrients has involved him in a range of national and international committees including the US National Institutes of Health and UN International Atomic Energy Agency committees that considered nutrient biomarkers.

Role: Chair the Advisory Committee meetings and provide expert reference and advice to the Steering Group and guidance to the Expert Working Groups on the development of the reports including on micronutrient research components, and responses to methodological and independent expert reviews**.**

Ms Janis Baines

Manager, Food Data Analysis Section, Food Standards Australia New Zealand

Expertise: nutrition; chemistry; food regulation; nutrient risk assessment including dietary exposure assessment methods and nutrient fortification assessments; NRV end-use; and food composition. Ms Baines has been an expert member (and chair) of a number of Joint FAO/WHO expert committees in relation to dietary exposure assessment methods for food chemicals, including nutrients.

Role: contribute expert advice to the Steering Group and guidance to the Expert Working Groups on the development of the reports, including on end user needs and dietary exposure assessment aspects. Chair of the Fluoride Expert Working Group.

Associate Professor Marijka Batterham

Director of Statistical Consulting Service in Informatics, University of Wollongong

Expertise: statistics and nutrition research. Dr Batterham is an accredited statistician and advanced accredited practising dietitian. Dr Batterham is the Director of the Statistical Consulting Service in Informatics and works across the University of Wollongong to assist students and staff members with the statistical design and analysis of their research.

Role: contribute expert advice to the Steering Group and guidance to the Expert Working Groups on the development of the reports, including on nutrition research and statistical elements.

Professor Michael Fenech (until March 2016)

Professor, CSIRO Food & Nutritional Sciences

Expertise: micronutrients, genetic toxicology, genome health, nutrition research. Dr Fenech has written reviews relating to biomarkers of genome damage relevant to cancer risk and the role of folate and B12 in prevention of DNA damage.

Role: ***contribute expert advice to the Steering Group and guidance to the Expert*** Working Groups on the development of the reports, including on nutrition research elements.

Professor Mark Lawrence

Professor, School of Exercise and Nutrition Sciences, Deakin University

Expertise: public health, food and nutrition policy, and food systems. Professor Lawrence is a technical adviser to the World Health Organisation, a member of the FSANZ Public Health Dialogue and a member of the 2013 Australian Dietary Guidelines Working Committee.

Role: contribute expert advice to the Steering Group and guidance to the Expert Working Groups on the development of the reports, including on public health and end user needs.

Professor Jim Mann

Professor in Human Nutrition and Medicine, University of Otago and Consultant Physician (Endocrinology), Dunedin Hospital

Expertise: nutrition epidemiology; research and public health; chronic disease; endocrinology; and medicine. Professor Mann is the Director of Edgar Diabetes and Obesity Research and the WHO Collaborating Centre for Human Nutrition; the Principal Investigator for the Riddet Institute at Massey University; and has chaired several WHO/FAO Expert Advisory Groups and Scientific Update Groups.

Role: contribute expert advice to the Steering Group and guidance to the Expert Working Groups on the development of the reports, including on nutritional epidemiology, public health and chronic disease elements.

Professor Murray Skeaff

Professor in Human Nutrition, University of Otago

Expertise: nutritional epidemiology and nutrition research. Professor Skeaff is a member of the FSANZ Health Claims Scientific Advisory Group, the New Zealand Heart Foundation's Scientific Advisory Committee and has been a member of the technical advisory groups for the Eating and Health Activity Guidelines and a number of FAO/WHO nutrition expert groups.

Role: contribute expert advice to the Steering Group and guidance to the Expert Working Groups on the development of the reports, including on nutritional epidemiology and research elements.

Professor Linda Tapsell AM

Senior Professor, School of Medicine, University of Wollongong

Expertise: nutrition and dietetics, nutrition research translation, evidence based review and guideline development. Professor Tapsell is a member of the FSANZ Health Claims Scientific Advisory Group, the 2013 Australian Dietary Guidelines Working Committee and several international science advisory committees. Professor Tapsell worked in health services before becoming an academic.

Role: contribute expert advice to the Steering Group and guidance to the Expert Working Groups on the development of the reports, including on nutrition research, evidence based guideline development aspects, and end-user needs. Chair of the Sodium Expert Working Group.

Associate Professor Sheila Skeaff (proxy member from March 2015)

Professor, Department of Human Nutrition, University of Otago

Expertise: nutrition research. Associate Professor Skeaff's expertise is in trace element research with a particular emphasis on iodine. Associate Professor Skeaff is particularly interested in assessing the iodine status of vulnerable groups of the population including children and pregnant women**.** Associate Professor Skeaff is the current President of the Nutrition Society of New Zealand.

Role: contribute expert advice to the Steering Group and guidance to the Expert Working Groups on the development of the reports, including on nutrition research. Deputy Chair of the Iodine Expert Working Group.

Emeritus Professor Christine Thomson (until February 2015)

Professor, Department of Human Nutrition, University of Otago

Expertise: nutrition research and public health**.** Professor Thomson's research involved studies of the nutritional importance of selenium and iodine for New Zealand residents, which has gained international recognition. This research identified a re-emergence of mild iodine deficiency in New Zealand.

Role: contribute expert advice to the Steering Group and guidance to the Expert Working Groups on the development of the reports, including on nutrition research and public health elements. Chair of the Iodine Expert Working Group until February 2015.

Professor Lynne Daniels (2013)

Head of School, Exercise & Nutrition Sciences, Queensland University of Technology

Expertise: nutrition research. Professor Daniels was appointed to a newly established capacity building research chair within the Institute Health and Biomedical Innovation. Professor Daniels research interests include nutrition and feeding in infancy and early childhood, childhood obesity, selenium status of infants and nutrition assessment and support of older adults.

Role: contribute expert advice to the Steering Group and guidance to the Expert Working Groups on the development of the reports, including on nutrition research elements.

7.3 Membership of the Nutrient Reference Values Fluoride Expert Working Group

The Fluoride Expert Working Group is responsible for examining scientific evidence and establishing nutrient values for fluoride. Membership of the Fluoride Expert Working Group is outlined below.

Ms Janis Baines (Chair)

Manager, Food Data Analysis Section, Food Standards Australia New Zealand

Expertise: nutrition; chemistry; food regulation; nutrient risk assessment including dietary exposure assessment methods and nutrient fortification assessments; NRV end-use; and food composition. Ms Baines has been an expert member (and chair) of a number of Joint FAO/WHO expert committees in relation to dietary exposure assessment methods for food chemicals, including nutrients.

Role: Chair EWG meetings, report on progress in Advisory Group meetings, contribute to the development of the report, including on end user needs and dietary exposure assessment aspects. I***n conjunction with the EWG and Advisory Committee, develop responses to the public consultation and methodological and independent expert reviews.***

Dr Michael Foley

Director, Brisbane Dental Hospital, Queensland

Expertise: dentistry, epidemiology and public health. Dr Foley graduated with a bachelor of Dental Science and holds Masters degrees in epidemiology and public health, and lectures at the University of Queensland and Griffith University Schools of Dentistry.

Role: contribute to the development of the report, including advise on population dental health and fluoride NRV end-use.

Emeritus Professor Andrew John Spencer

Emeritus Professor, Australian Research Centre for Population Oral Health, School of Dentistry, the University of Adelaide

Expertise: dentistry; child and preventive dentistry; oral health policy and dental health care; and research in population strategies for prevention of oral diseases. Professor Spencer has had a long involvement in informing policy on oral and dental care in Australia. He was the Deputy Chair of the 2012 National Advisory Council on Dental Health to the Australian Government's Minister to Health.

Role: contribute to the development of the report, including advise on population dental health elements.

Professor Marco Peres

Professor in Population Oral Health and Director of the Australian Research Centre for Population Oral Health, School of Dentistry, the University of Adelaide

Expertise: population oral health research; oral health surveillance; use of fluorides; inequalities in oral health; life course epidemiology and the relationship between oral health and general health. Professor Peres is the coordinator of the 2016-18 National Study of Adult Oral health and is International Dental Association for Dental Research Global Oral health Inequities Research Network counsellor for Asia and Pacific region.

Role: contribute to the development of the report, including advise on population dental health elements.

Dr Utz Mueller

Principal Toxicologist and Manager Risk Assessment – Chemical Safety and Nutrition Section, Food Standards Australia New Zealand

Expertise: toxicology and risk assessment for food additives, processing aids, nutritive substances and food contaminants. Dr Mueller is a member of the Joint FAO/WHO Expert Committee on Food Additives and has served as rapporteur on the WHO (toxicology) panel. Dr Mueller has extensive experience in reviewing the toxicological data which underpins the development of NRVs.

Role: contribute to development of the report, including advise on toxicological frameworks and tools for use in undertaking risk analysis and on end-user needs.

<u>Observers</u>

Associate Professor Loc Do

Principal Research Fellow, Australian Research Centre for Population Oral Health, School of Dentistry, the University of Adelaide

Expertise: dentist and oral epidemiology with special interest in social and clinical oral epidemiology. Professor Do is a member of various committees of the International Association of Dental Research. He has been the recipient of several international and national awards for his work.

Role: observer for experience and future succession planning.

<u>Fluoride Research Assistants</u>

Dr Judy Cunningham

Consultant

Expertise: scientific editor; risk assessment, dietary exposure assessment methods, food technology, food composition.

Role: update the systematic literature review and edit draft reports for consideration by the EWG.

Mr Emmanuel Gnanamanickam

Australian Research Centre for Population Oral Health, School of Dentistry, the University of Adelaide

Expertise: population oral health research.

Role: undertake the comprehensive literature review process and develop draft reports for consideration by the EWG.

Dr Najith Amarasena

Australian Research Centre for Population Oral Health, School of Dentistry, the University of Adelaide

Expertise: population oral health research.

Role: undertake the comprehensive literature review process and develop draft reports for consideration by the EWG.

Administrative Assistants

Ms Rose Thomas

Australian Research Centre for Population Oral Health, School of Dentistry, the University of Adelaide

Expertise: population oral health research.

Declarations of interest process

Declarations of interest were made by all members of the Advisory Committee and EWGs during the review process in accordance with the requirements of the *National Health and Medical Research Council Act 1992.* A record of interests was made publicly available on Health's website to ensure transparency. See NRV Advisory Committee Membership and NRV's Fluoride Expert Working Group Membership.

Members were required to update their information as soon as they became aware of any changes and there was a standing agenda item at each meeting where declarations of interest were called for and recorded in the meeting minutes. Should a member have identified as having a significant real or perceived conflict of interest, a requirement was that the member would be requested to leave the room or not participate in discussions on matters where a conflict was identified.

8 Glossary

Average number of decayed, and filled primary teeth (mean dmft score)
Sum of individual dmft values divided by the population of children aged 5 to 10.

Average number of decayed, and filled permanent teeth (mean DMFT score)
Sum of individual DMFT values divided by the population of children aged 6 to 14 years.

Bone fractures
Complete or incomplete breaks in bone.

Caries free
Absence of dental caries (see dental caries).

Community Fluorosis Index
An index that measures both the prevalence and the severity of dental fluorosis

Dean's Index
An index developed by Dean (1942) to classify dental fluorosis into five broad categories, which was based on the degree of enamel alteration on the two most severely affected teeth.

Dental caries
The process in which tooth structure is destroyed by acid produced by bacteria in the mouth. See dental decay.

Dental caries experience (Dental decay experience)
The cumulative effect of the caries process through a person's lifetime, manifesting as teeth that are decayed, missing or filled.

Dental decay
Cavity resulting from dental caries.

Dental Fluorosis
Discolouration or pitting of the dental enamel caused by exposure to excessive amounts of fluoride during enamel formation.

dmft/dmfs
An index of dental caries experience measured by counting the number of primary decayed (d), missing (m), and filled (f) teeth (t) or surfaces (s).

DMFT/DMFS
An index of dental caries experience measured by counting the number of permanent decayed (D), missing (M), and filled (F) teeth (T) or surfaces (S).

DDE
Developmental defects of enamel (due to fluorosis and other causes)

Enamel
Hard white mineralised tissue covering the crown of a tooth.

Epidemiology
The study of the distribution and causes of health and disease in populations.

Extraction
Removal of a natural tooth.

Fluoride
A naturally occurring trace mineral that helps to prevent tooth decay.

Fluorosis risk index
An index developed for accurate identification of associations between age-specific exposures to fluoride sources and the development of enamel fluorosis.

Health-based guidance values
Guidance on the safe consumption of substances that take into account current safety data, uncertainty in these data and the likely duration of consumption.

Index of relative socioeconomic advantage and disadvantage (IRSAD)
One of four indices measuring area-level disadvantage derived by the Australian Bureau of Statistics. The IRSAD is derived from attributes such as low income, low educational attainment, high unemployment and jobs in relatively unskilled occupations.

Mean maximum temperature
The average daily maximum air temperature, for each month and as an annual statistic, calculated over all the years of record.

NNS
National Nutrition Survey

Primary teeth
Baby teeth (deciduous teeth).

Permanent teeth
Adult teeth (secondary teeth).

Prevalence
The proportion of people with a defined disease within a defined population.

Skeletal fluorosis
A condition where long-term exposure to fluoride causes changes in bone structure leading to weakened bone.

Thylstrup and Fejerskov Index
An index based on biological aspects of dental fluorosis that classifies individuals into 10 categories.

Tooth surface index of fluorosis
An index that considers aesthetic aspects of tooth surface and classifies individuals into eight categories.

Trend
The general direction in which change over time is observed.

9 List of abbreviations

ABBREVIATION	TITLE
AI	Adequate Intake
ANCNPAS	Australian National Children's Nutrition and Physical Survey
ARCPOH	Australian Research Centre for Population Oral Health
ATDS	Australian Total Diet Study
BMD	Benchmark Dose
BMDL	Lower 95^{th} confidence limit on the BMD
CATMOD	Categorical Model
CTE	Central Tendency Exposure
DDE	The Development Defects of Enamel
DMFT	Decayed/Missing/Filled Teeth-Permanent Teeth
dmft	Decayed/Missing/Filled Teeth-Primary Teeth
DOHA	Department of Health and Ageing
DOSS	Dentistry and Oral Sciences
DRI	Dietary Reference Intake
DRV	Dietary Reference Values
DUFE	Daily Urinary Excretion of Fluoride
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
EEWG	Expert Working Group
FUFE	Fractional Urinary Fluoride Excretion
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
IOM	Institute of Medicine
LOAEL	Lowest Observed Adverse Effect Level
MCLG	Maximum Containment Level Goal
MOH	Ministry of Health

ABBREVIATION	TITLE
NFCS	Nationwide Food Consumption Survey
NHMRC	The National Health and Medical Research Council
NNS 1995	National Nutrition Survey
NOAEL	No Observed Adverse Effect Level
NRC	National Research Council
NRV	Nutrient Reference Value
NUTTAB	Nutrient Tables
NUTTAB10	Nutrient Tables 2010
NZTDS	New Zealand Total Diet Survey
OW	Office of Water
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred reporting of Systematic Reviews and Meta Analyses
RDA	Recommended Dietary Allowance
RDI	Recommended Dietary Intake
RfD	Reference Dose
RME	Reasonable Maximum Exposure
RSC	Relative Source Contribution
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	Scientific Committee on Health and Environmental Risk
SD1	Supporting Document 1
SD2	Supporting Document 2
SD3	Supporting Document 3
SD4	Supporting Document 4
SMCL	Secondary Maximum Containment Level
TDFI	Total Dietary Fluoride Intake
TSF	Total Soluble Fluoride
UF	Uncertainty Factor

ABBREVIATION	TITLE
UL	Upper Level of Intake
EWG	Working Group

Supporting Document 1

LOR	Limit of Reporting

Supporting Document 2

CFI	Community Fluorosis
CSFII	Continuing survey of Food Intakes by Individuals
dfs	Decayed Filled Surfaces
TSIF	Tooth Surface Index of Fluorosis

Supporting Document 3

EAR	Estimated Average Requirement
FNB	Food and Nutrition Board
MCL	Maximum Containment Level
NHSCRD	National Health Service Centre for Reviews and Dissemination
NNT	Number Needed to Treat
SCCP	Scientific Committee on Consumer Products

Supporting Document 4

FRI	Fluorosis Risk Index
FUFE	Fractional Urinary Fluoride Excretion
IMF	Infant Milk Formula
NHANES	National Health and Nutrition Survey
QLD	Queensland
RTF	Ready To Feed
SA	South Australia
SDS	School Dental Service

10 Reference List

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14 Appendix 1. Risk of bias assessment, summary of findings – GRADE assessment

14.1 Risk of bias assessment

Table A1: Risk of bias assessment, Dean (1942, 1944) – dental caries

Criteria[1]	**Assessment**
Study design	Cross-sectional (high risk)
Selection bias	*1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?* Limited information is provided on inclusion and exclusion criteria, but participants must have been exposed to a consistent community water supply throughout life, and be 12-14 years of age. Convenience sample of almost all white children attending public schools in the selected towns were examined; there was an even representation of boys and girls. No reason given for not including African-American children nor of reasons why some eligible children may not have participated. High risk *2. Does the strategy for recruiting participants into the study differ across groups?* Based on limited information, it appears that the same strategy was used across different towns. Low risk. *3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?* Not applicable; no comparison group.
Performance and Detection bias	*4. Does the study fail to account for important variations in the execution of the study from the proposed protocol?* A protocol was established, albeit with limited information provided, and this protocol was followed throughout. Low risk. *Was the outcome assessor not blinded to the intervention or exposure status of participants?* Blinding of assessors not discussed. It is likely that assessors would have had some knowledge of the fluoride levels in the community water supply. Participants were allocated to one of two assessors based on pre-assigned numbers. High risk *5. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding?* Assessors have used a consistent approach to outcome measurement across all groups studied. A consistent method of analysing water fluoride content was also used. Author describes the outcome assessment method that was used in all communities studied. The assessment method had a degree of subjectivity as it required a visual assessment of the severity of caries. Low risk. *6. Was the length of follow-up different across study groups?* Not applicable.

Criteria[1]	Assessment
	7. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (e.g., through sensitivity analysis or other adjustment method)? Not applicable.
Reporting bias	*8. Are any important primary outcomes missing from the results?* No. All stated outcomes are reported. Low risk. *9. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?* Not applicable.
Confounding	*10. Any attempt to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores).* Not applicable *11. Were important confounding variables not taken into account in the design and/or analysis?* Two of the key confounders identified by the authors (age of child, lifetime use of a consistent community water source) were taken into account in the study selection criteria. However the study did not investigate the amount of water participants consumed or examine other dietary differences. Further, at the time the study was conducted, there was no confounding by non-dietary sources of fluoride, such as toothpastes. Study also examined other possible contributors to dental caries (sunlight exposure, water hardness).
Overall assessment	*12. Are results believable taking study limitations into consideration?* Cross-sectional study designs are generally regarded as being at high risk of bias by the nature of their design. Overall, this study has a high risk of selection, performance and detection bias, judged by current standards, which may reflect the time at which this study was conducted and reported. However the consistent application of the outcome assessment tools and reporting of important primary outcomes were assessed as being low risk. Further, the study controlled for two of the three key confounders at that time and investigated the effects of other factors potentially affecting caries.

[1] Based on the assessment tool in Vishwanathan et al. (2013)

Table A2: Risk of bias assessment, Dean (1942) – dental fluorosis

Criteria[1]	Assessment
Study design	Cross-sectional (high risk)
Selection bias	*13. Do the inclusion/exclusion criteria vary across the comparison groups of the study?* Limited information is provided on inclusion and exclusion criteria, but it is likely that participants must have been exposed to a consistent community water supply throughout life, and be 12-14 years of age. No information provided on how participants were selected within included communities. Unclear risk *14. Does the strategy for recruiting participants into the study differ across groups?* No information provided; not possible to determine. Unclear risk *15. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?* Not applicable; no comparison group.
Performance and Detection bias	*16. Does the study fail to account for important variations in the execution of the study from the proposed protocol?* Report does not state whether or not a protocol was established. Unclear risk *17. Was the outcome assessor not blinded to the intervention or exposure status of participants?* Blinding of assessors not discussed. It is unclear whether or not assessors would have had some knowledge of the fluoride levels in the community water supply. Unclear risk *18. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding?* Assessors have used a consistent approach to outcome measurement across all groups studied. A consistent method of analysing water fluoride content was also used. Author describes the outcome assessment method that was used in all communities studied. The assessment method had a degree of subjectivity as it required a visual assessment of the severity of fluorosis. Low risk. *19. Was the length of follow-up different across study groups?* Not applicable. *20. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (e.g., through sensitivity analysis or other adjustment method)?* Not applicable.
Reporting bias	*21. Are any important primary outcomes missing from the results?* No. All stated outcomes are reported. Low risk.

Criteria[1]	Assessment
	22. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results? Not applicable.
Confounding	*23. Any attempt to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores).* Not applicable *24. Were important confounding variables not taken into account in the design and/or analysis?* Two of the key confounders identified by the authors (age of child, lifetime use of a consistent community water source) were taken into account in the selection criteria. However the study did not investigate the amount of water participants consumed or other dietary differences. Further, at the time the study was conducted, there was no confounding by non-dietary sources of fluoride, such as toothpastes.
Overall assessment	*25. Are results believable taking study limitations into consideration?* Cross-sectional study designs are generally regarded as being at high risk of bias by the nature of their design. This study has an unclear risk of selection, performance and detection bias because of the lack of important information, which may reflect the time at which this study was conducted and reported. However the consistent application of the outcome assessment tools and reporting of important primary outcomes were assessed as being low risk. Further, the study controlled for two of the three key confounders at that time.

[1] Based on the assessment tool in Vishwanathan et al. (2013)

14.2 Summary of findings – GRADE assessment

Author: EWG for Fluoride
Date: July 2015
Question: What is the prevalence and severity of dental caries among children (<14 y of age) consuming drinking water with natural fluoride levels above or below 0.4 mg F/L[1]?
Setting: General population

Bibliography: Dean HT 1942*. The investigation of physiological effects by the epidemiological method. In: Fluorine and dental health. Moulton FR, ed. Washington, DC: American Association for the Advancement of Science; (publication No. 19) pp. 23-31.

(note this information is also summarised in Dean 1944, 1946).

		Quality Assessment					No of participants and extent of dental caries at different drinking water (DW) fluoride concentrations (mean DMFT score - severity)			Effect		Quality	Importance
No. of stud-ies	**Study design**	**Risk of bias**	**Inconsis-tency**	**Indirect-ness**	**Imprec-ision**	**Other consider ations**	**DW fluoride conc ≤0.4 mg F/L**	**DW fluoride conc >0.4 - ≤1.0 mg F/L**	**DW fluoride conc >1.0 mg F/L**	**Relative[2] (95%CI)**	**Absolute (95%CI)**		
1	Cross-sectio-nal	High	Not applicable. Single study, more recent studies support outcomes[3]	Not serious[3] (direct measures)	Not serious (narrow confid-ence intervals)	Dose respon-se gradient	n=3867 DMFT PER person (SE): 7.40 (0.32)	n=1140 DMFT PER person (SE): 4.16 (0.21)	n=2250 DMFT PER person (SE): 2.75 (0.12)	Rate Ratio:[2] *≤0.4 mg F/L:* referent *>0.4 - ≤1.0 mg F/L:* 0.54 (0.29-0.98)	324 fewer teeth with dental caries per 1000 children when F >0.4 to ≤1.0 mg/L (from 214 to 433 fewer teeth), compared to F≤0.4 mg/L	MODERA TE[4]	CRITICAL

										Rate Ratio:[2] *≤0.4 mg F/L:* referent *>1.0 mg F/L:* 0.36 (0.22-0.60)	464 fewer teeth with dental caries per 1000 children when F >1.0 mg/L (from 378 to 550 fewer teeth), compared to F≤0.4 mg/L	MODERATE[4]	CRITICAL

[1] Cut off point of 0.4 mg F/L selected for calculations of relative prevalence based on the concentration of fluoride in the water supply below which the effect on dental caries is negligible, children in this group are the referent group. The upper level of 1.0 mg F/L was selected as the concentration of fluoride in the water supply for near maximal caries prevention. Note the upper range of target levels for Australian and New Zealand water fluoridation programs is approximately 1 mg F/L (target range 0.7-1.1 mg F/L).

[2] Relative risk presented in two ways:

- as a Relative Prevalence ratio as the Dean study reported the prevalence of dental caries assessed by direct measurement (proportion of children observedwith one or more teeth with dental caries as measured by DMFT);
- as a Relative Rate ratio as the Dean study also reported the mean DMFT score for the sample of children in each of the study locations (number of teeth with dental caries as measured by mean DMFT score/person).

SE: Standard Error of mean

[3] 'Not Serious' assigned as there were direct measurements of dental caries (DMFT score) and the level of fluoride in water supply which provided consistent results and had good precision.

[4] In the GRADE assessment the Dean observational study was determined to be of moderate quality because it included a large number of children, observations of a large number of communities with a wide range of drinking water fluoride concentrations; a clear dose response relationship between fluoride in water and prevalence and extent of dental caries and the absence of potential confounding factors from the use of fluoridated water supplies and toothpaste, supplements and dental treatments containing fluoride.

Author(s): EWG for Fluoride
Date: July 2015
Question: What is the prevalence of severe fluorosis among children (<14 y of age) consuming drinking water with natural fluoride levels above or below 2.2 mg F/L[1]?
Setting: General population
Bibliography: Dean HT 1942. The investigation of physiological effects by the epidemiology method. In: "Fluorine and dental health" F. R. Moulton (ed.), Publ. Amer. Assoc Advanc. Sci.; 19: 23–31

		Quality Assessment					**No of participants with severe fluorosis out of total at different drinking water (DW) fluoride concentrations (Proportion with severe fluorosis)**		**Effect[2]**		**Quality**	**Importance**
No of Studies	**Study design**	**Risk of bias**	**Inconsis-tency**	**Indirectness**	**Imprecision**	**Other consider ations**	**DW fluoride conc ≤2.2 mg/L**	**DW fluoride conc >2.2 mg/L**	**Relativ e (95%CI)**	**Absolute (95%CI)**		
1	Cross-sectional	High. Cross-Section-nal Study.	Not Applicable Single study	Not Serious[3] (direct measures)	Not serious (narrow confidence intervals)	Dose response gradient	1/4635 (0.02%)	164/1024 (13.8%)	PR 640 (90 – 4566)	1280 more cases of severe dental fluorosis per 100,000 when F >2.2 mg F/L (from 177 more to 9130 more per 100,000) compared to F≤2.2 mg F/L	MODERAT E[4]	CRITICAL

[1] Cut off point of 2.2 mg F/L selected for calculations of relative risk as the minimum fluoride concentration at which some cases of severe fluorosis were observed (using Dean Index 4 to measure severe fluorosis). Note Australian and New Zealand water guidelines set a maximum fluoride level in the water supply of 1.5 mg F/L.

[2] Relative risk presented as a Prevalence ratio (PR). The PR was calculated for fluorosis rather than a risk ratio (RR) as the Dean study reported direct measurement of fluorosis at levels of fluoride (using Dean's index of fluorosis).

[3] 'Not Serious' assigned as there were direct measurements of fluorosis (Dean's index of fluorosis) and the level of fluoride in water supply which provided consistent results and had good precision.

[4] In the GRADE assessment the Dean observational study was determined to be of moderate quality because it included a large number of children, observations of a large number of communities with a wide range of drinking water fluoride concentrations; a clear dose response relationship between fluoride in water and prevalence of dental fluorosis and the absence of potential confounding factors from the use of fluoridated water supplies and toothpaste, supplements and dental treatments containing fluoride.

15 Attachments

Supporting Document 1: Fluoride intake estimates

Supporting Document 2: Dose-response relationship between fluoride and oral health

Supporting Document 3: Summary of previous reports

Supporting Document 4: Literature review