Australian and New Zealand Nutrient Reference Values for Fluoride

A report prepared for the Australian Government Department of Health

By

Expert Working Group for Fluoride

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Executive Summary

The Nutrient Reference Values (NRVs) are a set of recommended nutrient intakes used to assess dietary requirements of individuals and population groups. The current NRVs for Australia and New Zealand were published in 2006 (NHMRC & MOH 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 (DoH), 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 (Nous Group 2013). The purpose of the present review is to test this framework on three nutrients, one being fluoride.

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 & 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 demineralization. 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 demineralization-remineralization 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 dental caries (an Adequate Intake) without exceeding intakes that are associated with moderate or severe dental fluorosis (an Upper Level of Intake). However, there is evidence that 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. The EWG noted the term 'Tolerable Upper Level of Intake' was an appropriate way to describe the UL for fluoride that has been used 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 reports including the landmark US Institute of Medicine 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 methodology 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, 1946) 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).

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, 1946) 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.

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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).

The EWG identified the critical fluoride concentrations in the water supply from Dean's data for the near maximal prevention of dental caries (the AI) and for prevention of moderate or severe dental fluorosis (the UL). 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 95^{th} percentile of intake.

The distribution of fluoride intakes for a range of child ages and their associated body weights at the critical fluoride concentration of 1.9 mg/L water was determined and the 95^{th} percentile of fluoride intakes used to establish an Upper Level of Intake of fluoride. The Upper Level of Intake of 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 Upper Level of Intake of 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 Upper Intake Level 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 interpret fluoride intakes at the critical fluoride concentration did not provide a robust basis to derive an Upper Level of Intake for fluoride.

The average fluoride intake was calculated for a range of children's ages and their associated body weights at a fluoride concentration of 1.0 mg F/L in drinking water. The current Adequate Intake 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 was not established for infants less than 6 months of age, as fluids for the majority of these infants were assumed to be breast milk.

The Upper Level of Intake of 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 0.10 to 0.14 mg F/kg bw/day across different age groups considered, which is considerably lower than the established Upper Level of Intake of 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 Upper Level of Intake of fluoride of 0.2 mg F/kg bw/day for children aged 4-8 years. The most recent US reference body weight data were used for infants and children aged 1-3 years as no suitable Australian and New Zealand data were available for these age groups (NRC 2005, Appendix B).

Upper Level of Intake	Age	Mean bw (kg)	UL
Infants	0–6 months	6	1.2 mg/day
	7–12 months	9	1.8 mg/day
Children	1–3 years	12	2.4 mg/day
	4–8 years	22	4.4 mg/day

The Adequate Intake of 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.

Adequate Intake	Age	Mean bw (kg)	AI
Infants	0–6 months	6	Not applicable
	7–12 months	9	0.45 mg/day
Children	1–3 years	12	0.6 mg/day
	4–8 years	22	1.1 mg/day

The EWG considers there is a Moderate degree of certainty in the estimates of the AI and UL, using the GRADE system. Strengths of the evidence include the large number of children included in the Dean observational studies, the wide range of drinking water fluoride concentrations reported, the clear dose response relationships found between the water fluoride concentrations and dental caries or fluorosis 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 increasing the rating based on the strength of the evidence from the usual Low for evidence from observational studies to Moderate. Although data for food and fluid consumption and body weights were not directly available from the Dean studies and had to be drawn from other sources, the three sources of information used for this purpose provided consistent results and had good precision.

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.

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).

Nutrient reference values were established for fluoride by NHMRC/MoH in 2006 following a review, which drew on an earlier review by the US Institute of Medicine in 1997. Nutrient reference values 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 Adequate Intakes (AI) and Upper Levels of Intake (UL) were established for fluoride intake for different age groups.

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 systematic 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.

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 systematic literature review did not find any more recent data, observational or experimental, that could replace it.

Based on these 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/litre and 1.9 mg fluoride/L respectively. From these values, together with nationally representative data on water and food consumption and body weight data for Australian and New Zealand populations, the Upper Level of Intake of fluoride for infants and children up to 8 years old was estimated to be 0.2 mg fluoride/kg body weight/day. The Adequate Intake was reaffirmed to be 0.05 mg F/kg body weight/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 body weight 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 the strength of the evidence from the usual Low, for evidence from observational studies, to Moderate. Although data for food and fluid consumption and body weights 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 values for the UL and AI 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.

1. Introduction

1.1 Funding source

This review has been funded by the Australian Department of Health and the New Zealand Ministry of Health.

1.2 Use of Nutrient Reference Values

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

The current NRVs for Australia and New Zealand were published in 2006 after a comprehensive review process of the Recommended Dietary Intakes (the only type of nutrient reference value that had been produced at the time), commissioned by the 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.

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 Nous Group and a technical team led by Baker IDI, to develop a Methodological Framework to guide future NRV reviews.

A Steering Group is overseeing the review process and is responsible for all strategic, funding and technical decisions of the review. It consists of representatives from both funding agencies, Health and the NZ MoH, with the NHMRC as an observer. The Steering Group is also responsible for the ongoing monitoring of triggers for a new review, and ensuring nutrient reviews are conducted in a timely manner.

Reviews are being conducted on a rolling basis to ensure NRVs remain relevant and appropriate. The process complies with the *2011 NHMRC Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines.*

The DOH appointed an Advisory Committee as an expert reference and advisory group which 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 from Australia and New Zealand.

The scoping study also identified the rationale and triggers for reviewing specific nutrients including changes or developments to NRVs in comparable OECD countries, emergence of new evidence, impact on public health priorities and/or concerns regarding the strength of the underlying methodology or evidence. Fluoride was identified as a priority nutrient for review and this has been funded by Health and NZ MoH.

The Health (with the advice from NZ MoH and the Advisory Committee), established a group of experts to conduct this fluoride review. The Expert Working Group was primarily responsible for examining scientific evidence and establishing nutrient values.

Membership of the groups involved in the development of the NRV guidelines can be found in Section 5.

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, Nous Group 2013).

NRV terms

EAR **Estimated Average Requirement**

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

RDI **Recommended Dietary Intake**

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

AI **Adequate Intake**

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

EER **Estimated Energy Requirement**

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

UL **Upper Level of Intake**

The highest level of nutrient intake level likely to pose no adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk effect increases.

AMDR **Acceptable Macronutrient Distribution Range**

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

SDT **Suggested Dietary Target**

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

1.3 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 are summarised in Table 1.

Table 1.1: Overview of NRVs for fluoride (NHMRC 2006)

Age group	AI* mg/day	UL# mg/day	Comments
Infants 0–6 months	0.01	0.7	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 non-pregnant 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 non-pregnant women

*AIs for older infants and children based on AI of 0.05 mg.kg bw/day and standard body weights 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).

1.4 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, 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 calls for a re-evaluation of the data which underpins the current UL. As part of this review an evaluation of the AI was also included for completeness. As this report was a pilot for a 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.

1.5 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 & 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 demineralization. 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 demineralization-remineralization 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 moderate or severe dental fluorosis (a UL).

2. Scope and Purpose

The purpose of this review was to discuss and derive a UL and an AI for fluoride intake for infants and young children, by conducting a systematic review of relevant literature released since the 2006 NHMRC review and by considering recent international reviews in this context.

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 body weight 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 in that fluoride is not an essential nutrient, 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. Time and resources available for the task restricted the scope of the work to be undertaken and included in this report by the EWG; it was not possible to assess AIs or ULs for older children or adults.

The Evidence Review in section 3 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 4.

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.

3. Evidence Review

3.1 Fluoride intake estimates in infants and young children

3.1.1 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, 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 2009a, NHMRC 2006). All infants fed solely with infant formula made with non-fluoridated 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 2009a).

Cressey et al. in 2010 updated the estimates for fluoride intake in New Zealand 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 et al. 2010). 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 (Cressey et al. 2010). 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 water (deionised water) had intakes well below the UL, a sizable proportion 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 in 1996 (0.24 mg/kg), a decade earlier (Clifford et al. 2009, Silva et al. 1996). Using these new data, revised fluoride intakes for infants were estimated by FSANZ for this review following recommended fluid intakes. When infant formula was reconstituted with water with no fluoride, the UL was not exceeded. However when some formulae were reconstituted with fluoridated water, the UL 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.

3.1.2 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 non-fluoridated 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 socio-economic 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 non-fluoridated 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/d) (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 Upper Level of Intake for fluoride.

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 75^{th} 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 socio-demographic 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 Tolerable Upper Level of Intake of 0.1 mg/kg bw/d for their age group (from toothpaste alone).

In a subsequent publication by Zohoori et al. (Zohoori et al.2014), fluoride intake was estimated for infants 1–12 months old living in fluoridated and non-fluoridated areas of the UK via a 3 day food diary coupled with analysis of the fluoride content of foods and drinks consumed. 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.

3.2 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.

3.2.1 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 demineralization 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 demineralization 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 industrialized 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 well-being (Petersen et al. 2005).

The measurement of dental caries has largely remained unchanged since the 1930s. Whilst 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 (DMF) 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 3.1 below. The data presented in Table 3.1 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 3.1: 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	dmft: 2.75 (2.16-3.34) dmft: (4.31 (3.79-4.84) DMFT: 0.82 (0.65-0.99) DMFT: 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 & 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 at 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 at 2012

Year	dmft/DMFT	%Caries free	Region	Age (years)	Fluoridation (mg/L water)	Study
2003	dmft 0.63 (0.37–0.88)	75	NSW	6	F area	Evans et al. 2009
	dmft 0.95 (0.57–1.32)	61		8		
	DMFT 0.33 (0.13–0.54)	79		11		
2009	dmft : 0.8 (0.3–1.2)	79.7 (71.7–87.7)	NZ, National	2–4	NS	NZ MoH 2010
	dmft: 1.9 (1.5–2.3)	51.0 (53.2–58.8)		5-11	NS	
	DMFT: 0.5 (0.3–0.6)	75.0 (71.4–83.5)		5-11	NS	
	dmft+DMFT 2.4 (2.0–2.8)	na		5–17	Non-F areas	
	dmft+DMFT 1.5 (1.1–1.9)	na		5-17	F areas	

Notes: F area = fluoridated area 0.8–0.85 mg F/L, NF area = non-fluoridated area <0.2–0.3 mg F/L.

NS = not specified.

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)[2]. 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

[2] 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.

and Vermillian (1957), Eklund and Striffler (1980), Heller et al. (1997) and two systematic reviews - the York Review (McDonagh et al. in 2000 and Rugg-Gunn and Do (2012)[3]. 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 from these reports is also summarised in Supporting Document 3.

3.2.2 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 focussed on dental fluorosis, not dental caries. Dental fluorosis is a developmental condition or defect of the enamel layer of teeth. It is characterized 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 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 non-fluorotic. 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 whilst examining a person, and/or the application of these sorts 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 1946).

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

[3] The EWG note a more recent systematic review was published in 2015 but could not be included in the report due to timing of its publication (Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, Alam R, Tugwell P, Welch V, Glenny AM 2015.Water fluoridation for the prevention of dental caries., Cochrane Database Syst Rev. 2015 Jun 18;6:CD010856. doi: 10.1002/14651858.CD010856.pub2).

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, 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 & Spencer 2007) (see Table 3.2).

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. 2014) 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, its measurement and reports of the prevalence of fluorosis in Australian and New Zealand populations and other countries is given in Supporting Document 2.

Table 3.2: Summary of data for the prevalence of any dental fluorosis (Prevalence TF1+ or Deans's Index 1+) in Australia and New Zealand

	Non-Fluoridated water area		Fluoridated water area		
Year	**Town/city**	**Prevalence (%)**	**Town/city**	**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 & Do 2007 Age: 7–15 years
2003			Blue Mountains, NSW	39.0+	Bal et al. 2004
2004/2005	Mt Gambier, Bordertown, Kingscote	15.0	Adelaide	29.5	Do & Spencer 2007
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 Ministry of Health 2010 Age: 8–30 years

+ Using Dean's Index

* Whole population-based study samples

Further details on the research on the links between dental fluorosis and fluoride levels in water supplies is summarised in Supporting Document 2 and is identified in the review of reports in Supporting Document 3.

3.2.3 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.

Osteoporosis, osteosarcoma, pineal gland physiology, IQ 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 (Cohn 1992, Douglass and Joshipura 2006, Kim et al. 2011, Levy et 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 1997, 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, either naturally or as a result of dental treatment. 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). Therefore delayed eruption was not considered suitable as a biomarker.

3.3 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 (DRI) 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.

3.3.1 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 3.3 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 body weights 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) (as 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 3.5.

Table 3.3: Summary of previous reports

Report	Overview	Methodology	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 (UF) 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/kg bw/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 fractures, cancers or other adverse effects. Evidence for caries preventive effect of fluoride should be considered along with increasing prevalence of fluorosis.	A clear search strategy extended to non-English articles. Extensive and independent review process transparent to public. Scoring system used for validity assessment of studies was not sensitive enough to detect how well studies were carried out.

Report	Overview	Methodology	Findings/estimates	Comments
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 end-points 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 concentrations below 2 mg/L (SMCL).	A specific search strategy was not available.
US EPA -Fluoride: Exposure and Relative Source Contribution (RSC) Analysis - (EPA 2010a)	Office of Water (OW) was assigned the task of quantifying exposure and relative source contribution 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.

Report	Overview	Methodology	Findings/estimates	Comments
US EPA -Fluoride: Dose–response analysis for non-cancer 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 50th percentile (median) or mean of the log-normal 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 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	Search strategy information is not available in report – a	No consistent evidence to show that biomarkers can be	A broad range of material has

Report	Overview	Methodology	Findings/estimates	Comments
	to provide a scientific opinion on Dietary Reference Values (DRV) for fluoride.	narrative review.	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.	been reviewed. Narrative nature of review. Basis of AI and UL values not reviewed. Adopted IOM AI and UL values.

3.3.2 Systematic review of new literature

3.3.2.1 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 Upper Level (UL) of fluoride intake among children up to 8 years of age?
2. What is the recommended Adequate Intake (AI) of fluoride among children up to 8 years of age?

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 3.2.3.

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

3.3.2.2 Literature Search

A comprehensive literature search was undertaken to address these two questions in December 2013–February 2014. The databases that were searched included the Cochrane Library, Pubmed, EMBASE, Ovid Medline, Dentistry and Oral Sciences Source (DOSS), Web of Knowledge, Toxline and the ANZ Reference centre. The search was updated in December 2014/January 2015 to identify any major new studies relevant to this report. References of key reports that were identified in the review of reports (Section 3, Supporting Document 4) were also searched for any relevant papers. The PICO model as shown in Box 3.1 was used to develop the search strategy for the two questions.

Box 3.1: 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 3.2 and 3.3. Variations of the search terms were used in different databases as appropriate to their structure (for example, Medical Subject Headings (MeSH) 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 3.2: 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 3.3: 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

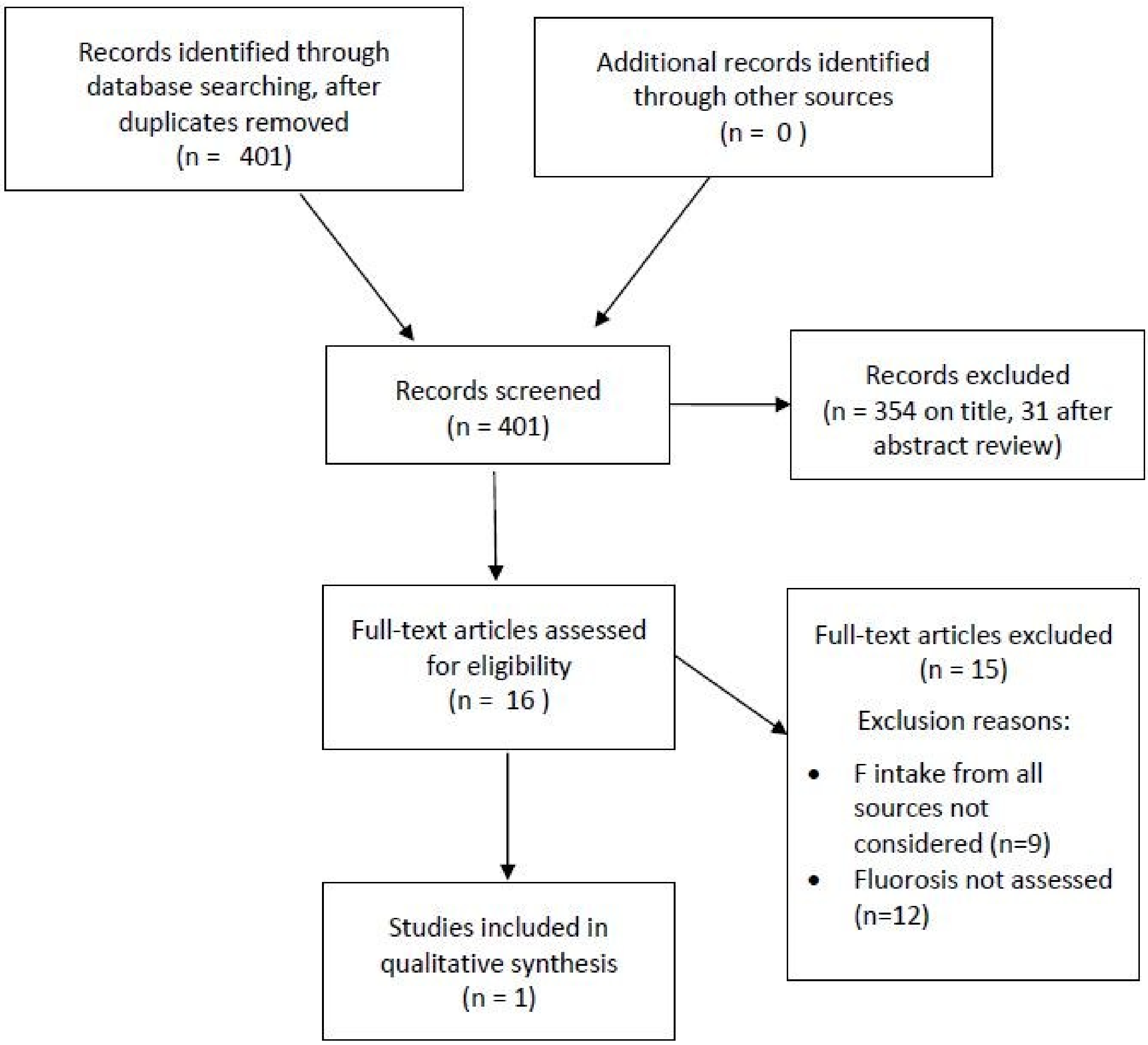
3.3.3 Systematic Literature Review Results

3.3.3.1 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. These 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 information to include in the report though they did not meet all inclusion criteria. Figure 3.1 sets out the systematic literature search results in PRISMA format.

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 3.1: PRISMA diagram of literature search findings, fluoride intake and fluorosis



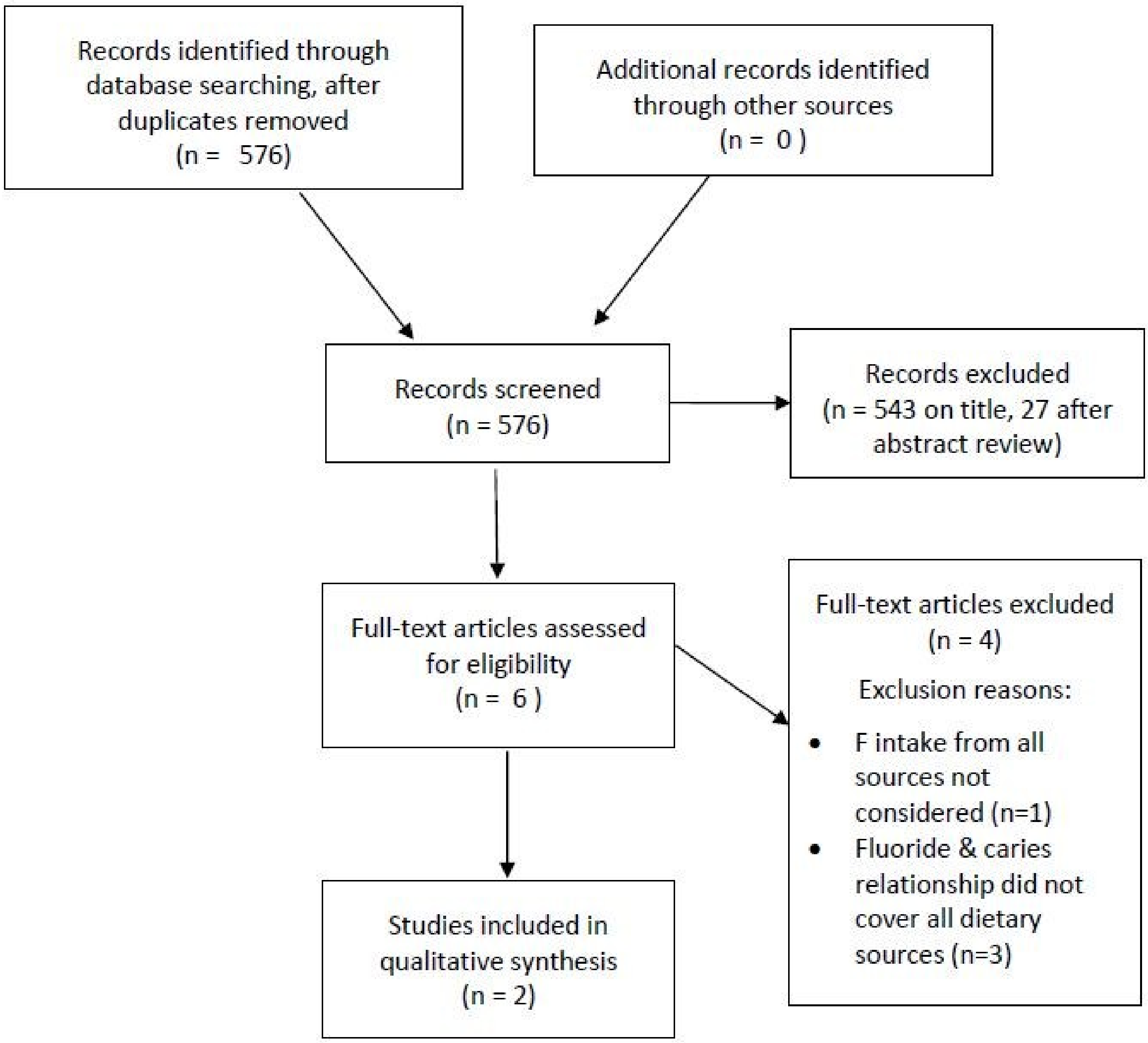
3.3.3.2 Fluoride and Dental Caries

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 and exclusion criteria (Warren et al. 2009, Kirkeskov et al. 2010). Figure 3.2 sets out the systematic literature search results in PRISMA format.

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 0.125-1.25 mg F/L, and a 50% reduction at highest level of fluoride of 1 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 3.2: PRISMA diagram of literature search findings, fluoride intake and dental caries



3.3.3.3 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 (DRI) for fluoride along with calcium, phosphorus, magnesium and vitamin D from the IOM reports (IOM 1997), pointed out that defining adequate intakes 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 over-simplified 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.

3.4 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 pilot review, only literature published since the time of the NRV review in 2005 (NHMRC 2006) was searched and reviewed. 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 focussed on older children and adults. Similarly, the review focused largely on evidence emerging from developed countries with similar socio-economic and dietary patterns to those found in Australia and New Zealand, potentially missing evidence arising from studies in developing countries. 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 systematic way, literature relating to fluoride and health outcomes other than dental caries and dental fluorosis, as outlined in section 3.2.3.

3.5 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 fluorisis 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 body weight 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 body weight 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 body weight of infants and young children.

3.5.1 Dose response assessment to establish a UL

3.5.1.1 Selection of an end-point

Over time the selection of the end-point in terms of dental fluorosis has shifted from aesthetically objectionable fluorosis to severe fluorosis. This reflects the changed community perception of what is aesthetically objectionable. Recent research has shown that very mild and mild fluorosis (Dean's labels) is not an aesthetic concern. Further, anterior teeth with very mild and mild fluorosis 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 (Chankanka et al. 2009). As a result, mild or moderate dental fluorosis is no longer regarded as a harm or 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 a harm or an adverse effect. The notion of harm is justified on the basis of potentially 'weakened' tooth enamel which may be more prone to dental caries and/or the expectation that anterior teeth with such enamel defects will be perceived 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 3.2.2 and Supporting Document 2).

3.5.1.2 Specification of the threshold prevalence

When aesthetically objectionable (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 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.

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

The reports reviewed in Section 3.3.1 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. 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, whilst 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).

3.5.1.4 Analysis of critical fluoride concentrations

The determination of a No observed adverse effect level (NOAEL) and Lower 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 3.4), 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% bound for 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.

Table 3.4: Percent distribution of fluorosis in populations studied by Dean (1942), sorted by concentration of fluoride in community-specific drinking water supplies

Town , State	No	Age (yrs)	F (mg/L)	Dean's Index					
				0	0.5	1	2	3	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).

3.5.1.5 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 (138 to 404 individuals; Table 5.1). 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.

3.5.2 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 3.5) 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 1943.

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 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 3.6).

Table 3.5: Summary of estimated daily fluoride intakes with 1 mg F/L in water with dry substances of food (McClure 1943)

Age (yrs)	Body weight (kg)	Tapwater consumption[ǂ] mL/day	Drinking water mg F/day	Food[ɫ] mg F/day	Total F intakes mg F/day	Total daily F intakes mg F/kg bw
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.

ɫ Contains between 0.1 and 1 mg F/kg

Table 3.6: Summary of estimated daily fluoride intakes with 1.9 mg F/L in water with dry substances of food (adapted from McClure 1943)

Age (yrs)	Body weight (kg)	Tapwater consumption[ǂ] mL/day	Drinking water mg F/day	Food[ɫ] mg F/day	Total F intakes mg F/day	Total daily F intakes mg F/kg bw
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.

ɫ 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 body weights and water intakes for children during the time when the Dean data were collected (Dean 1942). Consequently the US EPA considered that the results of the first comprehensive US Nationwide Food Consumption Survey (NFCS) from 1977–1978, which gave body weight 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 3.7 (0.06–0.20 mg F/kg bw) and are in good agreement with the estimates using the dietary model proposed by McClure (Table 3.6), especially in relation to the upper range of intakes for 1–6 year old children.

Table 3.7: Summary of estimated daily fluoride intakes with 1.9 mg F/L in water (adapted from EPA 2010b)

Age yrs	Mean body weight kg	Tapwater consumption[‡] mL/day	Drinking water mg F/day	Food mg F/day	Total F intakes mg F/day	Total daily F intakes mg F/kg bw
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

‡ 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 to calculate likely fluoride intakes with fluoridated drinking water at 1.9 mg F/L (Table 3.8) there was also very good agreement with the upper range of intake estimates obtained by the US EPA (Table 3.7) and the McClure model diet (Table 3.6) at equivalent fluoride concentrations. Further details are given on the fluoride intake estimates in Supporting Document 1.

Table 3.8: Summary of estimated daily fluoride intakes with 1.9 mg F/L in water (Australian data - FSANZ)

Age yrs	**Body weight kg**	**Tapwater consumption[‡] mL/day**	**Drinking water mg F/day**	**Food[‡] mg F/day**	**Total F intakes mg F/day**	**Total daily F intakes mg F/kg bw**
2–3	16	559–1250	1.30–2.87	0.3–0.03	1.6–3.0	0.10–0.19
4–8	24	642–1520	1.68–3.48	0.22–0.02	1.9–3.5	0.08–0.15

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

3.5.3 Upper Level of Intake (UL)

While the Dean et al. 1942 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 an Upper Level of Intake 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 Nationwide Food Consumption Survey 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. 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. 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. An Upper Level of Intake 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 Nationwide Food Consumption Survey, 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 Galesburg, IL community where the drinking water fluoride concentration was 1.9 mg/L (Table 5). 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.

3.5.4 Adequate Intake (AI)

While fluoride has been classified by some as essential to human health, others have classified it as important to human health, the NHRMC defined fluoride as a 'normal constituent of the human body, involved in the mineralisation of both teeth and bone' (NHMRC 2006). The difference between these classifications is whether the criterion of involvement in metabolic pathways needs to be satisfied. If fluoride is not considered an essential nutrient in the human diet, the establishment of a Recommended Dietary Intake (RDI) is not appropriate. Hence a key nutrient reference value will be an AI for children, including infants. The AI is based on estimated 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 1.0 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 3.9. 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 3.9: Summary of Daily Tap Water Consumption in US during 1977–78 (Ershow and Cantor 1989)

Age (years)	Mean body weight (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 exclusively breast 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. It was not considered necessary to establish an AI for infants less than 6 months of age.

3.5.5 Current fluoride intake in Australia and New Zealand

In order to examine current fluoride exposures 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 exposures for each age group (Table 3.10). 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 in the 2007 ANCNPAS 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, MoH 2005). The fluoride exposure estimates for Australian population groups aged 2 years and above were derived using food consumption data from the 1995 Australian National Nutrition Survey (Table 3.10).

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, whereas it rose to 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 daily fluoride dietary intake estimates for Australian children aged 4–8 years (0.88–1.83 mg F/day).

For infants (3 months solely formula-fed; 9 month olds in Australia; 6–12 month olds in New Zealand), model diets were used to estimate dietary intakes of fluoride (Table 3.10, Table 5 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 fully formula fed 6-12 month old infant, where formula was assumed to be prepared with water fluoridated at 1.0 mg F/L (0.71 mg F/day) (Cressey at al. 2010).

3.5.5.1 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 emphasizes 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 emphasizes 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 body weight =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 1 g 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 3.10: Summary of estimated total daily fluoride intakes assuming 1.0 mg F/L drinking water and toothpaste use (Australian Data – Adapted from Tables 5, 6 in Supporting Document 1)

Age (years)	Body weight kg	Tapwater consumption‡ mL/day	Drinking water mg F/day	Food Fluoride intakes + other sources* mg F/day	Total mg F/day	Total F intakes mg/kg bw/day
0.25	6.5	–	–	–	0.80**	0.12
0.75	9	–	–	–	1.23**	0.14
2–3	16	559–1250	0.68–1.51	0.80–0.66	1.48–2.17	0.09–0.14
4–8	24	642–1520	0.88–1.83	0.76–0.65	1.64–2.48	0.07–0.10

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

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

**Only mean intake values are shown. See Table 5 in Supporting Document 1 for intake calculations.

Table 11 shows that the upper range of fluoride intake estimates were from 0.10 to 0.14 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 3.2.2). 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).

4 Guideline recommendations

4.1 Draft NRVs

4.1.2 Upper Level of Intake (UL)

The estimated UL for fluoride, based on the endpoint 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 methodology to derive them based on ideal bodyweights at median BMI 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 body weights 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.

Upper Level of Intake	Age	Mean bw	UL
Infants	0–6 months	6	1.2 mg/day
	7–12 months	9	1.8 mg/day
Children	1–3 yrs	12	2.4 mg/day
	4–8 yrs	22	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.

4.1.3 Adequate Intake (AI)

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 result in near maximal caries prevention is around 0.05 mg/kg bw/day. For 9–month old formula fed infants in Australia and New Zealand the intake may be up to 1.5 mg F/kg bw/day and 0.9 mg F/kg bw/day respectively. 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 the New Zealand estimate for 6–12 month old infants it is assumed that there is no energy, and hence fluoride, contribution from complementary foods, that is the infant is solely formula fed. In general the average daily dietary fluoride intakes by children with fluoridated drinking water at 1 mg F/L increases across older ages but declines when expressed as a proportion of body weight. The following recommendations for the AI can be made, based on the revised IOM body weights for infants and children 1-3 years, in the absence of updated values for the Australian (ABS 2014) and New Zealand populations, and new bodyweights for Australian New Zealand children aged 4-8 years, rounded up to the nearest whole number. An AI for infants under 6 months of age was not considered to be appropriate because breastfed infants will not be consuming fluoridated tap water.

Adequate Intake	Age	Mean bw	AI
Infants	0–6 months	6	Not applicable
	7–12 months	9	0.45 mg/day
Children	1–3 years	12	0.6 mg/day
	4–8 years	22	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.

4.2 Validity of Recommendations

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 body weights 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 (see Appendix 1 for GRADE assessment of Dean's data).

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 95th 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 makes a strong recommendation that these values be adopted as revised NRVs for fluoride intakes for infants and young children up to 8 years of age, in Australia and New Zealand.

4.3 Further research

Information on 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 body weight data for these age groups could be assessed and, if appropriate, the data reviewed prior to future nutrient reviews. Agreed reference body weights for Australian and New Zealand populations should be included in the final 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. It would be desirable to update the fluoride content databases for the more recent national nutrition surveys prior to starting this work so that the most recent food consumption data for the Australian and New Zealand populations could be used in the review (2002 NZ National Children's Nutrition Survey, 2008/09 NZ Adult Nutrition Survey , 2011-13 Australian Health Survey for ages 2 years and over).

5 Membership of groups and committees involved in the development process

Membership of the Nutrient Reference Values Steering Group

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

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6 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).

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.

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.

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 ten 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.

7 List of abbreviations

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
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

AI	Adequate Intake
IOM	Institute of Medicine
LOAEL	Lower Observed Adverse Effect Level
MCLG	Maximum Containment Level
MOH	Ministry of Health
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
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

AI	Adequate Intake
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
UL	Upper Level of Intake (for fluoride, UL may be defined as Tolerable Upper Level of Intake in international literature)
EWG	Working Group

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

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

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9 List of tables

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12 Appendix 1. Summary of findings – GRADE assessment

Author: Expert Working Group 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]?

Bibliography: Dean HT 1946. Epidemiological studies in the United States. In Moulton FR, ed. Dental caries and fluorine. Lancaster: Science Press, American Association for the Advancement of Science (note this publication brings together information from Dean et al. 1941, Dean et al. 1942)

		Quality Assessment					No of participants with dental caries out of total at different drinking water (DW) fluoride concentrations (Proportion with dental caries - prevalence)			Effect		Quality	Importance
No of Studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirect-ness**	**Imprecision**	**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-sectional	Not serious	Single study, more recent studies support outcomes[3]	Not serious[3] (direct measures)	Not serious (narrow confidence intervals)	Dose response gradient	3769/3867 (97.5%)	1007/1140 (88.3%)	1703/2250 (75.7%)	Relative prevalence: *≤0.4 mg F/L:* referent *>0.4 - ≤1.0 mg F/L:* 0.91 (0.89-0.92)	90 fewer cases of children with dental caries per 1000 when F >0.4 to ≤1.0 mg/L (from 80 to 110 fewer cases), compared to F≤0.4 mg/L	MODERATE[4]	CRITICAL

										Relative prevalence:[2] *≤0.4 mg F/L:* referent *>1.0 mg F/L:* 0.77 (0.76-0.80)	230 fewer cases of children with dental caries per 1000 when F >1.0 mg/L (from 200 to 240 fewer cases), compared to F≤0.4 mg/L	MODERATE[4]	CRITICAL

		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 Studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirect-ness**	**Imprecision**	**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-sectional	Not serious	Single study, more recent studies support outcomes[3]	Not serious[3] (direct measures)	Not serious (narrow confidence intervals)	Dose response 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	MODERATE[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): Expert Working Group 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**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DW fluoride conc ≤2.2 mg/L**	**DW fluoride conc >2.2 mg/L**	**Relative (95%CI)**	**Absolute (95%CI)**		
1	Cross-sectional	Not serious	Not Serious (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	MODERATE[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.

13 Attachments

Supporting Document 1: Fluoride intake estimates

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

Supporting Document 3: Summary of reports

Supporting Document 4: Systematic literature review