Australian and New Zealand Nutrient Reference Values for Fluoride

A report prepared for the Australian Government

Department of Health

By

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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 95th 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 95th 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 75th percentile (0.05 mg/kg bw/day or more) and 90th percentile (0.07 mg/kg bw/day or more) held across all age groups. Some children were ingesting significantly more fluoride than others depending on 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.