Australian Government

National Health and Medical Research Council

A SYSTEMATIC REVIEW OF THE EFFICACY AND SAFETY OF FLUORIDATION

PART A: REVIEW METHODOLOGY AND RESULTS

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1 EXECUTIVE SUMMARY

The current systematic review considers the recent evidence relating to the efficacy and safety of fluoride interventions, with emphasis upon those able to be delivered as a widespread public health initiative. Therefore, the systematic review's research questions relate to the caries-reducing benefits and associated potential health risks of providing fluoride systemically (via addition to water, milk and salt) and the use of topical fluoride agents (such as toothpaste, gel, varnish and mouthrinse). Whilst the review summarises the recent evidence, it does not constitute health policy or clinical practice recommendations.

A search of the literature was undertaken in the MEDLINE and EMBASE databases using EMBASE.com. In addition, the Cochrane Systematic Review and Clinical Trial Databases were searched to help identify additional systematic reviews and original studies. Due to the availability of recent systematic reviews, searches were limited to publications from 1996 onwards, with the intention that the current review would update the most relevant existing systematic review. Searches were also limited to English-language publications. The search was conducted in December 2006. In total, 5418 non-duplicate citations were identified. After reviewing the potentially eligible, 77 citations were included in the review.

Based on type of intervention (ie, individual or population) and the outcomes assessed (efficacy or safety), the hierarchy of study designs considered most relevant for answering each of the clinical questions was defined. As the aim of the current review was to build upon the most relevant and recent existing systematic review for each research question, the lowest level of evidence accepted was also determined by the criteria that had been applied in the existing systematic review.

The findings of the systematic review are present in the context of the research questions:

Research question: *Is intentional water fluoridation more efficacious than no water fluoridation in the prevention of dental caries?*

The existing body of evidence strongly suggests that water fluoridation is beneficial at reducing dental caries. After adjustment for potential confounding variables, McDonagh et al (2000a) showed in their systematic review that the introduction of water fluoridation into an area significantly increased the proportion of caries-free children, and decreased mean dmft/DMFT scores compared with areas which were non-fluoridated over the same time period. The findings of McDonagh et al (2000a) also suggest that cessation of fluoridation resulting in a narrowing of the difference in caries prevalence between the fluoridated and non-fluoridated populations. Only one additional relevant original study was identified in the current review and this did not change the conclusion of the existing systematic review.

Research question: *Is intentional milk fluoridation more efficacious than no milk fluoridation in the prevention of dental caries?*

The results of the systematic review suggest that milk fluoridation is beneficial in the prevention or reduction of caries, although there is less good quality evidence than is the case for water fluoridation. The results of the two included original studies represent low levels of evidence; however, the results are consistent with milk fluoridation being associated with caries prevention, and cessation of milk fluoridation associated with worsening dental health.

Research question: *Is intentional salt fluoridation more efficacious than no salt fluoridation in the prevention of dental caries?*

No studies were identified which met the criteria for inclusion in this review. The results of the three before-and-after cross-sectional studies suggest that salt fluoridation reduces caries in populations of children aged from 6-15. However, it should be noted that these studies were considered to be of poor methodological quality, primarily due to the lack of assessment of, and adjustment for, potential confounding factors.

Research question: *Is the use of topical fluoride supplementation more efficacious than no topical fluoride supplementation in the prevention of dental caries?*

There is consistent Level I evidence from existing systematic reviews and a review of additional original studies that topical fluoride agents reduce caries in children, when compared to no topical fluoride supplementation. When compared to placebo/no treatment the magnitude of the effect achieved with varnish is greater than the other topical agents. However, when compared directly to each other, there is no significant difference between agents.

Research question: *Is a combination of topical fluoride supplementation products more efficacious than a single topical fluoride supplementation product in the prevention of dental caries?*

There is Level I evidence that some combinations of topical agents may be more effective at preventing/reducing caries than single agents.

Research question: *Does intentional water fluoridation result in dental fluorosis over and above no intentional water fluoridation?*

There is consistent Level III/IV evidence from existing systematic reviews that water fluoridation results in the development of dental fluorosis. However, the majority of dental fluorosis is mild and is not considered to be of 'aesthetic concern'. The number needed to harm (NNH) with water fluoridation at an optimal level compared with no fluoridation to get one additional person with 'any fluorosis' is approximately 6. The corresponding NNH to get one additional person with 'fluorosis of aesthetic concern' is approximately 22. Meta-analysis of additional original studies provides results consistent with those seen in the existing systematic reviews.

Research question: *Does intentional milk fluoridation result in dental fluorosis over and above no intentional milk fluoridation?*

One study provided Level IV evidence that milk fluoridation is not associated with significant levels of fluorosis. A statistically significant increase in fluorosis was seen in a number of age groups following the introduction of milk fluoridation; however, the majority of this fluorosis was mild and would not be considered to be of aesthetic concern.

Research question: *Does intentional salt fluoridation result in dental fluorosis over and above no intentional salt fluoridation?*

One level IV study provided evidence of a significantly increased risk of 'any fluorosis' associated with salt fluoridation. Two additional supportive studies which did not strictly meet the inclusion criteria were in agreement with the included study. There was no data relating to the risk of 'fluorosis of aesthetic concern'.

Research question: *Does topical fluoride supplementation result in dental fluorosis over and above no topical fluoride supplementation?*

Two level IV studies provide evidence regarding the impact of the use of topical fluorides on dental fluorosis. One study showed that fluoridated toothpaste may be associated with 'any fluorosis'. However, when 'fluorosis of aesthetic concern' was examined, no statistically significant difference between the higher fluoride dose group and the control group was found, and the prevalence of fluorosis in the higher dose toothpaste group was low (< 2%). One poor quality study in which fluorosis was measured after a campaign was implemented to reduce the amount of topical fluoride use in children suggested that a decrease in fluorosis was seen.

Research question: *Does a combination of topical fluoride supplementation products result in dental fluorosis over and above a single topical fluoride supplementation product?*

There is currently no evidence comparing combinations of topical agents with a single topical agent.

Research question: *Does intentional water fluoridation result in fracture over and above no intentional water fluoridation?*

The authors of the three existing systematic review concur that water fluoridation at levels aimed at preventing dental caries has little effect on fracture risk - either protective or deleterious. The results of the subsequent original studies support this conclusion, although suggest that optimal fluoridation levels of 1 ppm may indeed result in a lower risk of fracture when compared to excessively high levels (well beyond those experienced in Australia). One study also indicated that optimal fluoridation levels may also lower overall fracture risk when compared to no fluoridation (the latter was not the case when hip fractures were considered in isolation).

Research question: *Does intentional milk fluoridation result in osteoporosis or fracture over and above no intentional milk fluoridation?*

There is currently no evidence available to determine the impact of milk fluoridation upon fracture risk.

Research question: *Does intentional salt fluoridation result in osteoporosis or fracture over and above no intentional salt fluoridation?*

There is currently no evidence available to determine the impact of salt fluoridation upon fracture risk.

Research question: *Does topical fluoride supplementation result in osteoporosis or fracture over and above no topical fluoride supplementation?*

There is currently no evidence available to determine the impact of topical fluoride supplementation upon fracture risk.

Does a combination of topical fluoride supplementation products result in osteoporosis or fracture over and above a single topical fluoride supplementation product?

There is currently no evidence available to determine the impact of combination topical fluoride supplementation upon fracture risk.

Research question: *Does intentional water fluoridation increase the risk of cancer over and above no intentional water fluoridation?*

The existing systematic review by McDonagh et al (2000a) concluded that there is no clear association between water fluoridation and overall cancer incidence or mortality (for 'all cause' cancer, and specifically for bone cancer and osteosarcoma). The authors state that the evidence relating fluoridation to cancer incidence or mortality is mixed, with small variations on either side of the effect.

The current literature review identified four additional studies that investigated the relationship between water fluoridation and cancer incidence or mortality, including three Level IV ecological studies and one Level II-3 matched case-control study (Bassin et al, 2006). The latter study compares the fluoride exposure of histologically-confirmed osteosarcoma cases with that of matched controls - a sub-set of patients from a larger case-control study initiated by the Harvard School of Dental Medicine that is yet to report its findings. After adjusting for significant differences at baseline between the cases and controls, the results of Bassin et al (2006) suggest an increased risk of osteosarcoma amongst young males (but not females) with water fluoridation. However, the attention of the reader is drawn to a Letter to the Editor by co-investigators of Bassin in which the letter authors point out that they have not been able to replicate these findings in the broader Harvard study, that included prospective cases from the same 11 hospitals. Furthermore, the bone samples that were taken in the broader study corroborate a *lack* of association between the fluoride content in drinking water and osteosarcoma in the new cases. The final publication of the full study is not yet available, and the authors of the Letter caution readers not to over-interpret the results of Bassin and colleagues in the interim.

Research question: *Does intentional milk fluoridation increase the risk of cancer over and above no intentional milk fluoridation?*

There is currently no evidence available to determine the impact of milk fluoridation upon cancer risk.

Research question: *Does intentional salt fluoridation increase the risk of cancer over and above no intentional salt fluoridation?*

There is currently no evidence available to determine the impact of salt fluoridation upon cancer risk.

Research question: *Does topical fluoride supplementation increase the risk of cancer over and above no topical fluoride supplementation?*

There is currently no evidence available to determine the impact of topical fluoride supplementation upon cancer risk.

Research question: *Does a combination of topical fluoride supplementation products increase the risk of cancer over and above a single topical fluoride supplementation product?*

There is currently no evidence available to determine the impact of combination topical fluoride supplementation upon cancer risk.

Research question: *Is intentional water fluoridation associated with other adverse effects over and above no intentional water fluoridation?*

The authors of previous systematic reviews concluded that the studies examining other possible negative effects of water fluoridation provide insufficient evidence to reach a conclusion.

Research question: *Is intentional milk fluoridation associated with other adverse effects over and above no intentional milk fluoridation?*

There is currently no evidence available to determine the impact of milk fluoridation upon other harms.

Research question: *Is intentional salt fluoridation associated with other adverse effects over and above no intentional salt fluoridation?*

There is currently no evidence available to determine the impact of salt fluoridation upon other harms.

Research question: *Is topical fluoride supplementation associated with other adverse effects over and above no topical fluoride supplementation?*

There is currently no evidence available to determine the impact of topical fluorides upon other harms.

Research question: *Is a combination of topical fluoride supplementation products associated with other adverse effects over and above a single topical fluoride supplementation product?*

There is currently no evidence available to determine the impact of combination topical fluorides upon other harms.

2 INTRODUCTION

In 1979 a submission was made to the Committee of Inquiry into the Fluoridation of Victorian Water Supplies. The review provided further justification for the endorsement of fluoridation of public water supplies as a safe and effective method of control of dental caries. This finding was confirmed in a NHMRC 1985 *review of the safety and effectiveness of water fluoridation* (National Health and Medical Research Council, 1985).

The 1991 report *The effectiveness of water fluoridation* (National Health and Medical Research Council, 1991), commissioned by the NHMRC, outlined the following conclusions:

– Water fluoridation to 1ppm is deemed to provide an optimal balance between reduction of caries and occurrence of fluorosis;

– There is no evidence of adverse health effects of water fluoridation at 1ppm;

– Increase in caries is evident when water is defluoridated; and

– Water fluoridation at 1ppm provides a 20-40% reduction in caries.

In 1998 the NHMRC commissioned the *Review of Water Fluoridation and Fluoride Intake from Discretionary Fluoride Supplements* (National Health and Medical Research Council, 1999), which confirmed the conclusions reached in the 1991 report. The 1999 review also concluded that water fluoridation is the most effective and socially equitable means of achieving community wide exposure to the caries preventative effect of fluoride. The review however, was abandoned due to a lack of resources and consequently was never published.

The current review was commissioned in December 2006 to evaluate the scientific literature relating to the health effects of fluoride and fluoridation. This report provides a detailed analysis of the scientific literature pertaining to the health effects of fluoride and fluoridation from 1996 to December 2006.

This report is primarily concerned with the caries-reducing benefits and associated health risks of providing fluoride systemically (via addition to water, milk and salt) and the use of topical fluoride agents (such as toothpaste, gel, varnish and mouthrinse). These sources are the focus of the current review as they represent the main methods by which a widespread public health intervention for the prevention of dental caries would occur in Australia, or represent methods that groups or individuals may chose to supplement their fluoride intake (eg, amongst communities that do not receive an adequately fluoridated water supply). Whilst the review presents a summary of the relevant evidence, the potential effectiveness of any public health intervention must be considered in context of practicalities associated with implementing the intervention, issues surrounding compliance, and issues related to equity of access.

The reader is also referred to recent comprehensive reports regarding water fluoridation published by the World Health Organisation (WHO, 2006) and the National Research Council of the National Academies (NAS, 2006). The NAS report refers to the adverse health effects from fluoride at 2-4 mg/L, the reader is alerted to the fact that fluoridation of Australia's drinking water occurs in the range of 0.6 to 1.1 mg/L.

3 BACKGROUND

Fluorine (F) is an element of the halogen family, which also includes chlorine, bromine and iodine. It forms inorganic and organic compounds called fluorides. Living organisms are mainly exposed to inorganic fluorides through food and water. The most relevant inorganic fluorides are hydrogen fluoride (HF), calcium fluoride (CaF2), sodium fluoride (NaF), sulfur hexafluoride (SF6) and silicofluorides. Fluorides represent approximately 0.06-0.09% of the earth's crust.

This report is primarily concerned with the caries-reducing benefits and associated health risks of providing fluoride systemically (via addition to water, milk and salt) and the use of topical fluoride agents (such as toothpaste, gel, varnish and mouthrinse). These sources are the focus of the current review as they represent the main methods by which a widespread public health intervention for the prevention of dental caries would occur in Australia, or represent methods that groups or individuals may chose to supplement their fluoride intake (eg, amongst communities that do not receive an adequately fluoridated water supply).

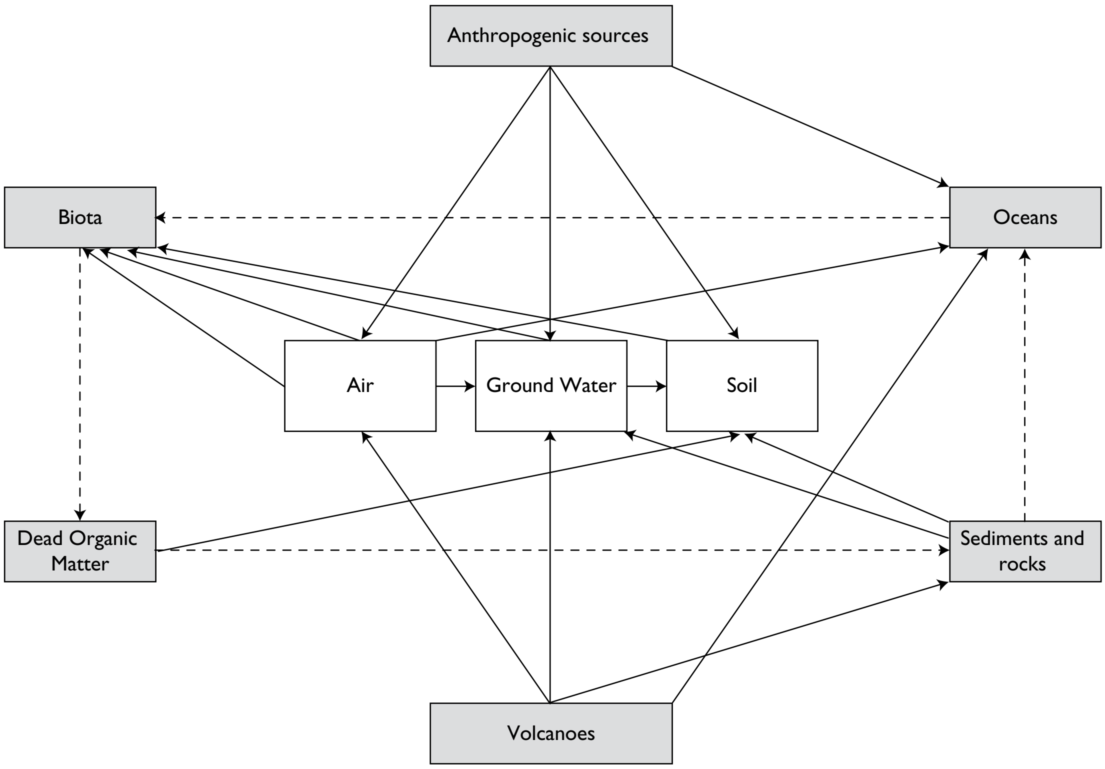
However, there are additional sources of fluoride in the environment which can occur naturally, or as a result of industrial processes. This chapter will provide a brief summary of the environmental sources of fluoride and the supplementation of fluoride. The background information included here has been principally garnered from the World Health Organization (WHO, 2006), and American National Academies of Science (NAS, 2006) reports on fluoride in drinking-water and the International Programme of Chemical Safety (IPCS, 2002) report on fluoride. Whilst environmental exposure is a relevant inadvertent source of fluoride, the extent of exposure to the individual is, under normal Australian circumstances, trivial relative to the extent of exposure from intentional supplementation. This does not obviate the need for careful assessment of the fluoride exposure from industry on a case by case basis.

3.1 ENVIRONMENTAL SOURCES OF FLUORIDE

Fluorides are released into the environment through a combination of natural and anthropogenic processes. Natural processes include the weathering of fluoride containing minerals and emissions from volcanoes. Additionally, a number of industrial processes such as coal combustion, steel production, and other manufacturing processes (aluminium, copper and nickel production, phosphate ore processing, phosphate fertilizer production, glass, brick and ceramic manufacturing) further contribute to fluoride levels.

These processes result in the dispersion, accumulation, and ubiquitous prevalence of fluoride at various concentrations in all surface and groundwater reserves, mostly as fluoride ions or combined with aluminum; in the air, as gases or particulates; in soils, mainly combined with calcium or aluminum; and in living organisms. The cycle of fluoride through the environment in summarised in **Figure 1**.

Figure 1 Environmental and anthropogenic sources of fluoride and their interaction with the environment



Adapted from the ICPS report on fluoride

3.1.1 FLUORIDE LEVELS IN NATURALLY-OCCURRING WATER

Fluoride levels in surface waters vary widely according to geographical location and proximity to emission sources but are generally low, ranging from 0.01 to 1.5 mg/L. Concentrations in seawater commonly range from 1.2 to 1.5 mg/L. Freshwater concentrations are usually lower than seawater ranging from 0.01 to 0.3 mg/L.

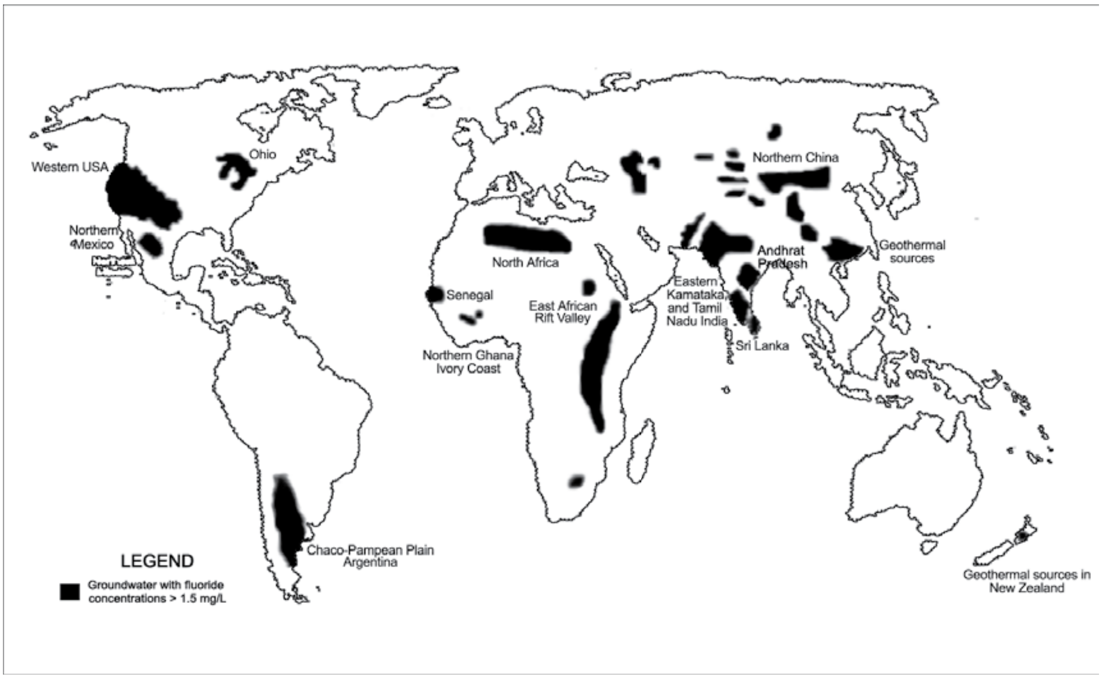
Factors known to influence water fluoride levels include the presence of natural rock rich in fluoride (such as granites and gneisses and sediment of marine origin). Additionally, elevated inorganic fluoride levels are often seen in regions where there is geothermal or volcanic activity. Low levels of calcium in water supplies may also lead to higher levels of fluoride solubility.

Geographical areas associated with high groundwater fluoride concentrations include the East African Rift system (running from Jordan in northern Africa to Kenya and Tanzania in east Africa), large tracts of the Middle East (Iran, Iraq, and Syria) and Indian sub-continent (India, Pakistan, Sri-Lanka), parts of Asia (China), and parts of the USA (**Figure 2**).

Fluoride concentrations greater than 8 mg/L are not uncommon in many of these areas and have been measured as high as 2800 mg/L at Lake Nakuru in Kenya

In Australia, naturally-occurring fluoride levels are generally very low (<0.1 mg/L), with the exception of some remote well water supplies in South Australia.

Figure 2 Geographical areas with high natural fluoride levels



3.1.2 FLUORIDE LEVELS IN AIR

Airborne fluoride enters the atmosphere in gaseous and particulate forms from a variety of natural and anthropogenic sources including volcanic eruptions and combustion of fluoride containing coal. Airborne concentrations are highest in areas close to emission sources and range from 2–3 μg/m^3 in urban and industrialized zones to 0.05-1.90 μg/m^3 in non-industrial areas. Prevailing weather conditions, the type and strength of emission sources and chemical reactivity of the particulate matter may influence the distribution and deposition of airborne fluoride. High concentrations of airborne fluoride (16-46 μg/m^3) are noted in some communities that burn high-fluoride coal for cooking and curing food.

3.1.3 FLUORIDE LEVELS IN SOIL

Fluoride is a component of most types of soil, with total fluoride concentrations ranging from 20 to 1000 μg/g in areas without natural phosphate or fluoride deposits and up to several thousand micrograms per gram in mineral soils with deposits of fluoride. The clay and organic carbon content as well as the pH of soil are primarily responsible for the retention of fluoride in soils. In general, fluoride bound to soil is relatively resistant to leaching and it is the soluble content that is most important to terrestrial animals and plants.

According to the IPCS (2002) report the relative contribution of various anthropogenic sources to total emissions of fluoride to air, water and soil in industrialized countries such as Canada are estimated at 48% for phosphate fertilizer production, 20% for chemical production, 19% for aluminium production, 8% for steel and oil production and 5% for coal burning.

3.1.4 FLUORIDE LEVELS IN FOOD

The levels of fluoride in most fruits, vegetables, meats are very low (0.1 – 5 mg/kg) and are unlikely to contribute significantly to daily fluoride exposure. Exceptions to this general rule include tea, and trona, a vegetable tenderizer used in parts of Tanzania.

Tea contains relatively high levels of fluoride with the highest concentrations found in mature and fallen tea leaves. Concentrations of fluoride in black and green teas, made from the buds and younger tea leaves, range from ~170-400 mg/kg dry weight. Brick tea, made from the mature tea leaf and other parts of the tea plant may have fluoride concentrations 2-4 times as much as black and green leaf tea. Tea infusions made from green, black or brick tea typically have fluoride concentrations 100 fold lower than the dry weight product. Therefore, tea drinks made with brick tea contain fluoride at 2-4 times the concentration of black and green tea infusions. Consumption of brick teas is associated with significant fluoride ingestion and fluorosis in some countries.

Trona, is a sedimentary salt commonly added in cooking to tenderise certain vegetables and beans in regions of Tanzania. Concentrations of fluoride in trona are high and may range from 36-6800 mg/L. Severe fluorosis is endemic in children aged 12 to 17 in villages which regularly consume trona.

Silva and Reynolds (1996) measured the fluoride content of milk-based formulae commonly used in Australia. The fluoride content of milk-based powders ranged from 0.23 to 3.71 g/kg and soy-based powders ranged from 1.08 to 2.86 g/kg. When reconstituted according to manufacturers instructions, with water not containing fluoride, the fluoride content of the liquid formulae ranged from 0.031 to 0.532 ppm (average 0.240 ppm). Assuming average body weights and formula consumption, in all cases this equated to a fluoride exposure of below the suggested threshold for fluorosis avoidance of 0.1 mg F/kg body mass ('optimal' being 0.05–0.07 mg F/kg body mass/day, Riordan 1993). However, if reconstituted with water fluoridated at 1.0 ppm, all brands of formula would have provided a daily fluoride intake above this suggested threshold - with the majority of the fluoride coming from the water rather than the formula. Subsequent to the Silva and Reynolds study, the Australia New Zealand Food Standards Code, 2004 (Standard 2.9.1) recommends that infant formula should contain a low concentration of fluoride in infant formula, and that infant formula containing more than 17 μg F/100 kJ of powder must include a warning about dental fluorosis on the label. This allows for reconstitution with fluoridated water. Measurements were made of 49 samples of formula available at supermarkets, finding that the fluoride concentrations have fallen considerably since the Silva and Reynolds study to a mean of 0.37 (SD 0.19) mg/kg (unpublished data, personal communication with author). These data may somewhat overestimate the actual fluoride exposure to the infant, as a result of reduced bioavailability of fluoride in milk-based products.

Another consideration with respect to the association between infant formula consumption and fluorosis is the timing of the exposure. It is understood that the critical period for fluorosis of the anterior permanent teeth is after the first twelve months of life (Osuji et al, 1988; Evans & Stamm, 1991), by which time the majority of Australian children have ceased exclusive formula consumption.

3.2 INTENTIONAL FLUORIDE SUPPLEMENTATION

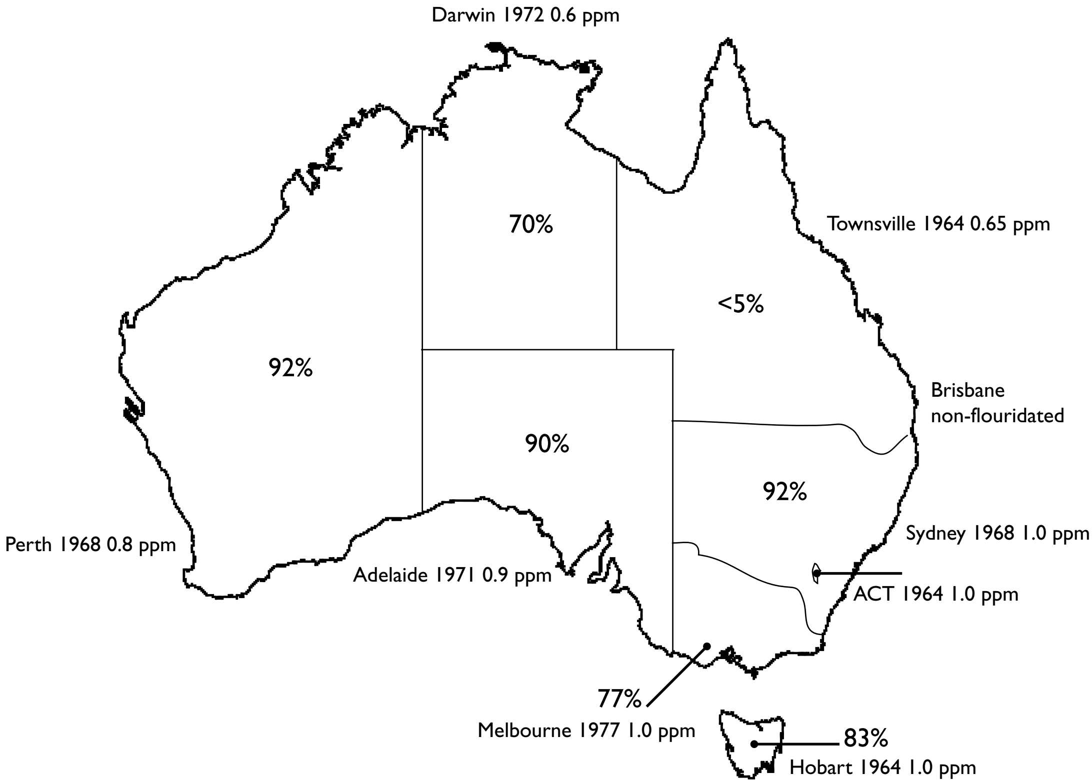
3.2.1 WATER FLUORIDATION

Although research into the beneficial effects of fluoride began in the early 1900's the first community fluoridation program did not begin until 1945 in Grand Rapids Michigan, USA. Three other studies followed in Newburgh, New York (USA) in May 1945, Brantford, Ontario (Canada) in June 1945, and Evanston, Illinois (USA) in February 1947. The results from these studies were used to establish the effectiveness and safety of fluoridation of public water supplies.

In Australia, the first inclusion of fluoride into a municipal water supply occurred in Beaconsfield, near Launceston, Tasmania in 1953. Subsequently all Australian capital cities, including Canberra but excluding Brisbane, have implemented water fluoridation (**Figure 3**).

The aim of water fluoridation is the adjustment of the natural fluoride concentration in fluoride-deficient water to that recommended for optimal dental health (ie, representing a trade-off between maximal prevention of caries and minimal levels of fluorosis). In Australia, nominal target fluoride levels vary according to climate and local water needs but range from 0.6 parts per million (ppm) to 1.0 ppm. Fluoride supplementation levels are lower in hot and humid areas, eg, Darwin, and higher in temperate zones, eg, Hobart. Approximately 76% of Australians have access to fluoridated water supplies. The highest coverage rate of fluoridation is in the Australian Capital Territory (100%) and the lowest is in Queensland at less than 5%.

Figure 3 Dates of introduction of water fluoridation to Australian capital cities and percentage of the population who have access to fluoridated water



Source: Water fluoridation information for health professionals, State of Queensland, Queensland Health 2005.

Percentages confirmed from personal communication with State/Territory offices in September 2007.

The compounds most commonly used for water fluoridation of public water supplies are sodium hexafluorosilicate (Na2SiF6), fluorosilicic acid (H2SiF6) and sodium fluoride (NaF).

3.2.2 OTHER FLUORIDE SUPPLEMENTATION

A range of topical agents and supplements designed to reduce dental decay contain fluoride, including toothpaste; dental varnishes, gels, rinses, tablets and drops. Fluoride concentrations in these products vary according to frequency of use and application.

Fluoride containing toothpastes typically contain 0.1% or 1000 ppm fluoride and are recommended for use by all age groups by the Australian Dental Association (ADA). For children under the age of six the ADA recommends only a ‘pea’ size amount of paste should be placed on the brush.

Fluoride solutions and gels for topical treatment generally contain much higher concentrations of fluoride than toothpaste (up to 24000 ppm). These products are not intended to be used regularly.

Fluoride supplements available as drops, chewable tablets and chewing gum tablets have not been explicitly included within the current review. However, these individual-level interventions may be used in areas where it is not feasible or not acceptable to fluoridate drinking water. The effectiveness of fluoride supplementation by these methods may be influenced by poor compliance, a factor which is less of an issue in interventions implemented at the population level, such as water fluoridation.

4 LITERATURE REVIEW METHODOLOGY

4.1 RESEARCH QUESTIONS

The current systematic review seeks to address the following research questions related to the proposed benefits and harms of fluoridation on the basis of the available published evidence:

A. Benefits

*Is intentional **water fluoridation** more efficacious than no water fluoridation in the prevention of dental caries?*

*Is intentional **milk fluoridation** more efficacious than no milk fluoridation in the prevention of dental caries?*

*Is intentional **salt fluoridation** more efficacious than no salt fluoridation in the prevention of dental caries?*

*Is the use of **topical fluoride supplementation** more efficacious than no topical fluoride supplementation in the prevention of dental caries?*

*Is a **combination of topical fluoride supplementation** products more efficacious than a single topical fluoride supplementation product in the prevention of dental caries?*

B. Harms

Dental fluorosis

*Does intentional **water fluoridation** result in dental fluorosis over and above no intentional water fluoridation?*

*Does intentional **milk fluoridation** result in dental fluorosis over and above no intentional milk fluoridation?*

*Does intentional **salt fluoridation** result in dental fluorosis over and above no intentional salt fluoridation?*

*Does **topical fluoride supplementation** result in dental fluorosis over and above no topical fluoride supplementation?*

*Does a **combination of topical fluoride supplementation** products result in dental fluorosis over and above a single topical fluoride supplementation product?*

Fracture

*Does intentional **water fluoridation** result in fracture over and above no intentional water fluoridation?*

*Does intentional **milk fluoridation** result in fracture over and above no intentional milk fluoridation?*

*Does intentional **salt fluoridation** result in fracture over and above no intentional salt fluoridation?*

Does ***topical fluoride supplementation*** *result in fracture over and above no topical fluoride supplementation?*

Does a ***combination of topical fluoride supplementation*** *products result in fracture over and above a single topical fluoride supplementation product?*

Cancer

Does intentional ***water fluoridation*** *increase the risk of cancer over and above no intentional water fluoridation?*

Does intentional ***milk fluoridation*** *increase the risk of cancer over and above no intentional milk fluoridation?*

Does intentional ***salt fluoridation*** *increase the risk of cancer over and above no intentional salt fluoridation?*

Does ***topical fluoride supplementation*** *increase the risk of cancer over and above no topical fluoride supplementation?*

Does a ***combination of topical fluoride supplementation*** *products increase the risk of cancer over and above a single topical fluoride supplementation product?*

Other adverse effects

Is intentional ***water fluoridation*** *associated with other adverse effects over and above no intentional water fluoridation?*

Is intentional ***milk fluoridation*** *associated with other adverse effects over and above no intentional milk fluoridation?*

Is intentional ***salt fluoridation*** *associated with other adverse effects over and above no intentional salt fluoridation?*

Is ***topical fluoride supplementation*** *associated with other adverse effects over and above no topical fluoride supplementation?*

Is a ***combination of topical fluoride supplementation*** *products associated with other adverse effects over and above a single topical fluoride supplementation product?*

4.2 LITERATURE SEARCH

A search of the literature was undertaken in the MEDLINE and EMBASE databases using EMBASE.com. In addition, the Cochrane Systematic Review and Clinical Trial Databases were searched to help identify additional systematic reviews and original studies. Due to the availability of recent systematic reviews, searches were limited to publications from 1996 onwards. Searches were also limited to English-language publications. The search was conducted in December 2006. The search strategy is shown in **Table 1**.

Table 1 Search strategy

Search no.	Database	Date searched	Search terms	Citation
1	MEDLINE EMBASE	1996-2007	1. fluorid*: ab,ti OR fluorin*:ab,ti OR flurid*:ab,ti OR florin*:ab,ti AND [1996-2007]/py	13,177
			2. fluorid*: ab,ti OR fluorin*:ab,ti OR flurid*:ab,ti OR florin*:ab,ti AND [1996-2007]/py AND [english]/lim AND [humans]/lim	5,034
2	Cochrane Library	1996-2007	fluoride OR fluorine OR fluoridation OR fluoridated	2635
TOTAL	Non-duplicate citations			5418

In total, 5418 non-duplicate citations were identified. Three reviewers assessed the eligibility of abstracts (approximately one third each). After applying the inclusion/exclusion criteria, 408 citations were considered potentially eligible for inclusion in the review (see **Table 2**).

Table 2 Reasons for exclusion

Reason for exclusion	Description	Title/ abstracts
Total citations		5418
Imaging study	Citation describes a study assessing radioactive fluorine for imaging	978
Not a clinical study	Citation does not describe the results of a systematic review, randomised controlled trial or observational study Narrative reviews, case reports, letters, in vitro, ex vivo and animal studies were excluded	2439
Wrong intervention	Citation did not examine the effect of fluoride ingested via water, milk or topical agents Industrial sources of fluoride (eg, from aluminium smelting) and consumption of brick tea and trono are excluded	826
Wrong comparator	Citation does not compare fluoride intake with no fluoride intake or different levels of fluoride intake	88
Wrong indication/population	Citation does not include the general population Specific populations including those treated for osteoporosis and those undergoing orthodontic work are excluded	59
Wrong outcomes	Citation does not include assessment of one of the included outcomes. Included outcomes are caries prevention (measured by DMFT/dmft, DMFS/dmfs) or any safety outcome	614
Not in English	Due to time constraints, only English-language articles were eligible for inclusion in the review	5
Abstract only	Published in abstract form only	1
Citations remaining		408

After the review of the full papers of potentially eligible articles, 77 citations were included in the review. More detail on the inclusion of studies is available in each section, while a full list of included and excluded citations and the reasons for exclusion, are available in Volume II.

4.3 LITERATURE SYNTHESIS

The aim of this review was to synthesise the highest level of evidence to answer each clinical question. The highest level of evidence for the assessment of an intervention (in this case fluoride) is a systematic review of randomised controlled trials, which is the study type least subject to various biases. However, in some cases it is not possible or feasible to conduct a randomised (or non-randomised) controlled trial. This may be due to a number of factors including: (i) the nature of the intervention; (ii) the types of outcomes being assessed; and (iii) ethical or financial constraints.

With regards to the nature of the intervention, the use of fluoride for the prevention of dental caries can be implemented at the individual or population level. Topical fluorides such as toothpaste, mouthrinse, gel and varnish are implemented at the individual level. On the other hand, fluoride can also be implemented at the population level, such as is the case with water, milk or salt fluoridation. The most appropriate study type for assessing an intervention at the individual level is a RCT, and the highest level of evidence is a systematic review of RCTs. Alternatively, when an intervention is applied at the population level, individuals cannot be randomised to a treatment or control group, and different study types are required to assess the efficacy of the intervention. The most appropriate study type in this case would be a prospective, comparative cohort study. The highest level of evidence would be a systematic review of prospective, comparative cohort studies.

Different study types are also more relevant depending on the outcome being assessed. Generally, RCTs are the study type of choice for assessing the efficacy of an intervention. However, safety/harms associated with an intervention may best be assessed using an observational study such as a cohort, case-control, cross-sectional or ecological study. This is particularly the case for rare outcomes or outcomes which develop long after an exposure or after prolonged exposure (eg, cancer, osteoporosis and cardiovascular disease).

Based on the different types of fluoride interventions available (ie, individually-applied and population-based) and the different types of outcomes to be assessed (ie, efficacy as measured by a reduction in caries, and potential harms such as fluorosis, decreased bone density/fracture, cancer and other adverse effects), two different types of evidence hierarchies were required: one for intervention studies, and one for aetiology/harm studies. The interim levels of evidence currently being trialled by the NHMRC for intervention and aetiological studies are summarised in Table 3.

Table 3 Hierarchy of evidence

Level	Intervention[a]	Aetiology/harms[b]
I[c]	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A prospective cohort study
III-1	A pseudorandomised controlled trial (ie, alternate allocation of some other method)	All or none[f]
III-2	A comparative study with concurrent controls Non-randomised experimental trial[d] Cohort study Case-control study Interrupted time series with a control group	A retrospective cohort study
III-3	A comparative study without concurrent controls Historical control study Two or more single arm studies[e]	A case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	A cross sectional study

a Definitions of these studies are provided on pages 7-8 of *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000).

b If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie, cannot allocate groups to a potential harmful exposure; eg, nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

c A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

d This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie, utilise A vs B and B vs C, to determine A vs C).

e Comparing single-arm studies (ie, case series from two studies).

f All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of a specific virus; and clear proof of the causal link has come from the disappearance of smallpox after large-scale vaccination.

Based on types of intervention (ie, individual or population) and the outcomes assessed (efficacy or safety) the hierarchy of study types considered most relevant for answering each of the clinical questions defined in **Section 4.1** is presented in **Table 4**. It should be noted that the levels of evidence accepted for fluoride intervention at the population level was based on those chosen for the McDonagh et al (2000a) review of water fluoridation. For each clinical question, the body of evidence using the highest available level of evidence would be assessed. Where a higher level of evidence was available, lower levels would not be assessed. For example, in the case of the assessment of harms associated with the use of topical agents, if RCTs were available then assessment would be limited to RCTs. The types of studies included to answer each clinical question will be discussed in the results section.

Table 4 Hierarchy of evidence accepted for each clinical question

	Intervention		Aetiology/harms		
	Prevention of dental caries	Dental fluorosis	Fracture	Cancer	Other adverse effects
Population level intervention					
Water fluoridation	Cohort study (Level III-2)		Prospective cohort study (Level II)		
	Case-control study (Level III-2)		Retrospective cohort study (Level III-2)		
Milk fluoridation	Comparative cross-sectional study I[ab] (Level IV)		Case-control study (Level III-3)		
Salt fluoridation			Comparative cross-sectional study I[a] (Level IV)		
			Comparative cross-sectional study II[b] (Level IV)		
Individual level intervention					
Topical	RCT (Level II)		RCT (Level II-Intervention)		
			Retrospective cohort study (Level III-2)		
			Case-control study (Level III-3)		
			Comparative cross-sectional study I[a] (Level IV)		
			Comparative cross-sectional study II[b] (Level IV)		

a Evaluated at multiple timepoints (for caries assessment), with baseline assessment associated closely with the implementation/cessation of intervention and the final assessment at a time sufficient for the intervention to have had an effect on the outcome under investigation.

b Evaluated at a single timepoint (for fluorosis, and other harms assessment) with sufficient time for intervention to have had effect on the outcome under investigation.

4.4 DATA EXTRACTION

Data were extracted for all included systematic reviews and individual studies using standardised data extraction forms. This included information about the study design, NHMRC level of evidence, population, intervention, comparator, outcome definitions, and results. Information relating to potential biases and study quality were also extracted. All data extraction forms are included in **Appendix A**.

4.5 DATA PRESENTATION AND SYNTHESIS

Each section contains a summary of the characteristics and results of each of the included studies. The NHMRC level of evidence and a quality rating is provided for each study. The reader is referred to Appendix B for a more detailed discussion of the study characteristics and quality. Where appropriate, study results will be pooled using standard meta-analysis techniques.

4.6 METHODOLOGICAL ISSUES

4.6.1 TYPES OF STUDIES INCLUDED FOR EACH QUESTION

This systematic review is to be based on the best levels of evidence to answer each research question. The most appropriate level of evidence to answer questions regarding the efficacy/effectiveness of an intervention is a randomised controlled trial (RCT), or a systematic review of RCTs. Other comparative study types (ie, cohort, case-control and cross-sectional studies) can also provide useful information on the efficacy/effectiveness of an intervention; however, to minimise the effect of confounding in these studies, it is best that the intervention under investigation have been instigated at, or around, the time of the beginning of the study, and that the effect of the intervention be assessed over a relevant timeframe. For this reason, where possible the effect of fluoride on dental caries will be assessed using only comparative longitudinal studies, in which fluoridation was either introduced or withdrawn in one treatment group within a short time of the beginning of the study.

In the case of measuring the harms associated with fluoride use, a wider range of studies will be included. Many potential harms of fluoride occur over a longer time-frame and as such, it is not feasible or ethical to assess these outcomes using RCTs. Therefore, other comparative study types, including cross-sectional and ecological studies, will be included in this review.

In conducting fluoride exposure studies, social attitudes can pose problems with regard to efficacy. These include a lack of knowledge of sugar intake, uptake and adherance to dental hygiene regimes. The problem of adherence is particularly relevant in communities with low social economic status. This leads to uncertainty regarding individual exposure. These, and other, factors can account for small differences in studies.

It should be noted that these study inclusion criteria are consistent with those used in a large and comprehensive systematic review of the efficacy and safety of water fluoridation conducted by the University of York in 2000 (McDonagh et al, 2000).

Australian researchers have been active in the field of fluoride research, particularly with respect to water fluoridation. However, many of the relevant Australian epidemiological studies have not been included in the current systematic review, as they do not meet the inclusion and exclusion criteria specified by the precedent existing systematic review. The reader with a special interest in Australian fluoride research is referred to recent research amongst Australian army recruits conducted by Hopcraft, Morgan and their colleagues (eg., Hopcraft & Morgan, 2003; Hopcraft & Morgan, 2005) and various investigations amongst Australian school children conducted by Armfield, Do, Spencer, Slade and Riordan, amongst others (eg., Spencer et al, 1996; Slade et al, 1996; Riordan, 1991; Singh et al, 2003; Armfield 2005; Do & Spencer, in press).

These studies primarily relate to the impact of water fluoridation upon dental caries and dental fluorosis. As considerable high quality epidemiological evidence is available to inform the impact of water fluoridation upon these health outcomes, the current review's inclusion and exclusion criteria were kept consistent with those of the York review upon which the current review builds. For the dental caries outcome, this required that epidemiological evidence included data for two or more levels of water fluoridation, at two points in time (ie., before and after data in two populations) in order to observe the impact of fluoridation whilst minimising confounding due to other population or environmental factors that may have been changing concurrently. For dental fluorosis, the study had to report data from two different populations with two different levels of fluoridation, one of which could be considered optimal fluoridation. The majority of the Australian epidemiological studies were not included in the current review as they did not fulfil these criteria (eg, cross-sectional comparisons). Others are not included because they were published outside the date span of the updated literature search performed for the current review (1996-2006). However, such research is of interest, particularly the comparison of dental caries amongst those Australian communities that do receive fluoridated water and those that don't. For example, the seminal work of Slade, Spencer, Davies and Stewart (1996) that compared the dental caries rates amongst children in fluoridated Townsville and unfluoridated Brisbane, illustrating that the children of Townsville had 32 to 55% fewer tooth surfaces affected with caries, when compared to the children of Brisbane.

All of the above-mentioned researchers took part in a consensus workshop in October 2005 that produced Australian guidelines regarding the use of fluoride (*The Use of Fluorides in Australia: Guidelines, 2006*), and therefore the reader is referred to this document as a consensus summary of their views, based upon Australian and international research.

4.6.2 DEFINITIONS OF OUTCOMES

The primary goal of the use of fluoride is to prevent/reduce dental caries. Dental caries results when demineralisation of the tooth enamel occurs, the effect of which can range from aesthetic concerns and tooth pain, to abscess or serious infection. The most common adverse effect associated with the use of fluoride is fluorosis, a mottling of teeth which occurs when excess fluoride is ingested during tooth development. Fluorosis is generally mild and manifests as whitish striations, although a more severe form can occur which involves pitting and discolouration of the enamel. The outcome measures commonly used to assess dental caries and fluorosis are outlined below. In addition, outcome measures used to assess other known or potential adverse effects of fluoridation are described.

4.6.2.1 Measures of dental caries

The most common outcomes used in studies measuring the effect of fluoridation on caries are: (i) the percentage of caries-free children, which measures the prevalence of caries in the population; and (ii) dmft/DMFT and dmfs/DMFS, which measure the prevalence of caries in an individual. The measures are defined as follows:

- **dmft** measures the number of decayed, missing or filled teeth in the primary (deciduous/baby) dentition. This outcome is sometimes designated as *deft*, with 'e' indicating 'extracted tooth'. If a tooth has both caries and a filling it is classified as 'decayed'. The maximum score is 20.
- **DMFT** measures the number of decayed, missing or filled teeth in the permanent (adult) dentition. If a tooth has both caries and a filling it is classified as 'decayed'. The maximum score is 28, or 32 if the wisdom teeth are included.
- **dmfs** measures the number of decayed, missing or filled surfaces in the primary (deciduous/ baby) dentition. This outcome is sometimes designated as *defs*, with 'e' indicating 'extracted tooth'. If a surface has both caries and a filling it is classified as 'decayed'. The maximum score for 20 primary teeth is 88.

- **DMFS** measures the number of decayed, missing or filled surfaces in the permanent (adult) dentition. If a surface has both caries and a filling it is classified as 'decayed'. As molars are considered to have five surfaces, and front teeth have four surfaces, the maximum DMFS score for 28 teeth is 128.
- Percentage of caries-free children is based on the percentage of children with dmft/DMFT=0 or dmfs/DMFS=0.

In addition, some studies measure the efficacy of fluoridation vs no fluoridation using the prevention fraction (PF). The PF is defined as follows: (mean increment in controls minus mean increment in the treated group) divided by the mean increment in controls.

4.6.2.2 Measures of fluorosis

The three most commonly used measures of dental fluorosis are Dean's Index, the Thylstrup and Fejerskov (TF) Index and the Tooth Surface Index of Fluorosis (TSIF) index. The criteria for scoring these indices are shown in Table 5, Table 6 and Table 7. It should be noted that Dean's Index and the TF Index are 'wet' indices, indicating that the teeth are assessed when wet. The TSIF is a 'dry' index, indicating that the teeth must be dried prior to assessment. Furthermore, the TSIF can be scored in natural light, while scoring of fluorosis using Dean's Index and the TF Index requires the use of artificial light.

Table 5 Dean's fluorosis index

Score	Description	Criteria
0	Normal	The enamel represents the usual translucent semivitriform type of structure. The surface is smooth, glossy and usually of a pale creamy white colour.
1	Questionable	The enamel discloses slight aberrations from the translucency of normal enamel, ranging from a few white flecks to occasional white spots. This classification is utilized in those instances where a definite diagnosis of the mildest form of fluorosis is not warranted and a classification of "normal" is not justified.
2	Very mild	Small opaque, paper white areas scattered irregularly over the tooth but not involving as much as 25% of the tooth surface. Frequently included in this classification are teeth showing no more than about 1-2 mm of white opacity at the tip of the summit of the cusps of the bicuspids or second molars.
3	Mild	The white opaque areas in the enamel of the teeth are more extensive but do not involve as much as 50% of the tooth.
4	Moderate	All enamel surfaces of the teeth are affected, and the surfaces subject to attrition show wear. Brown stain is frequently a disfiguring feature.
5	Severe	Includes teeth formerly classified as "moderately severe and severe." All enamel surfaces are affected and hypoplasia is so marked that the general form of the tooth may be affected. The major diagnostic sign of this classification is discrete or confluent pitting. Brown stains are widespread and teeth often present a corroded-like appearance.

Table 6 Thylstrup and Fejerskov (TF) Index

Score	Criteria
0	Normal translucency of enamel remains after prolonged air drying.
1	Narrow white lines corresponding to the perikymata.
2	Smooth surfaces: more pronounced lines of opacity that follow the perikymata. Occasionally confluence of adjacent lines. Occlusional surfaces: scattered areas of opacity < 2 mm in diameter and pronounced opacity of cuspal ridges.
3	Smooth surfaces: merging and irregular cloudy areas or opacity. Accentuated drawing of areas of perikymata often visible between opacities. Occlusional surfaces: confluent areas of marked opacity. Worn areas appear almost normal but usually circumscribed by a rim of opaque enamel.
4	Smooth surfaces: the entire surface exhibits marked opacity of appears chalky white. Parts of surface exposed to attrition appear less affected. Occlusional surfaces: entire surface exhibits marked opacity. Attrition is often pronounced shortly after eruption.
5	Smooth surfaces and occlusional surfaces: entire surface displays marked opacity with focal loss of outermost enamel (pits) < 2 mm in diameter.
6	Smooth surfaces: pits are regularly arranged in horizontal bands < 2 mm in vertical extension. Occlusional surfaces: confluent areas < 3 mm in diameter exhibit loss of enamel. Marked attrition.
7	Smooth surfaces: loss of outermost enamel in irregular areas involving < ½ of entire surface. Occlusional surfaces: changes in the morphology caused by merging pits and marked attrition.
8	Smooth and occlusional surfaces: loss of outermost enamel involving > ½ of surface.
9	Smooth and occlusional surfaces: loss of main part of enamel with change in anatomic appearance of surface. Cervical rim of almost unaffected enamel is often noted.

Table 7 Tooth Surface Index of Fluorosis (TSIF)

Score	Criteria
0	Enamel shows no evidence of fluorosis.
1	Enamel shows definite evidence of fluorosis, namely, areas with parchment-white colour that total less than one –third of the visible surface. This category includes fluorosis confined only to incisal edges of anterior teeth and cusp tips of posterior teeth ("snowcapping").
2	Parchment-white fluorosis totals at least one-third of the visible surface, but less than two-thirds.
3	Parchment-white fluorosis totals at least two-thirds of the visible surface.
4	Enamel shows staining in conjunction with any of the preceding levels of fluorosis. Staining is defined as an area of definite discolouration that may range from light to very dark brown.
5	Discrete pitting of the enamel exists, unaccompanied by evidence of staining of intact enamel. A pit is defined as a definite physical defect in the enamel surface with a rough floor that is surrounded by a wall of intact enamel. The pitted area is usually stained or differs in colour from the surrounding enamel.
6	Both discrete pitting and staining of the intact enamel exist.
7	Confluent pitting of the enamel surface exists. Large areas of enamel may be missing and the anatomy of the tooth may be altered. Dark-brown stain is usually present.

4.2.6.3 Other outcome measures

Other outcome measures are provided as reported by the systematic reviewers or authors of individual papers. The current review had a preference for patient-relevant outcomes, therefore sub-clinical outcomes were not reported.

5 SYSTEMATIC REVIEW RESULTS

The following section presents the results of the review for the following outcomes: prevention/ treatment of dental caries (**Section 5.1**), dental fluorosis (**Section 5.2**), fracture (**Section 5.3**), cancer (**Section 5.4**) and other harms (**Section 5.5**). For each outcome, results will be presented for each fluoridation type: water, milk, salt and topical.

5.1 PREVENTION/TREATMENT OF DENTAL CARIES

The following section presents the evidence regarding the efficacy of fluoride in reducing/ preventing caries. Each of the different methods of providing fluoride will be assessed separately. These include providing fluoride systemically (ie, via water, milk or salt fluoridation) or topically (ie, via toothpaste, varnish, gel or mouthrinse; individually or in combination). While the main comparison will be made between fluoride vs no fluoride, for some of the topical agents, data regarding different dose levels of fluoride are available and will be presented also.

The types of evidence considered appropriate to answer the clinical question of whether fluoride is efficacious at preventing dental caries varied depending on the nature of the intervention. For topical agents, which are implemented at the individual level, RCTs were considered to be the most appropriate. However, water fluoridation, milk fluoridation and salt fluoridation occur at the population level, and as such lower levels of evidence were allowable, including cohort studies, case-control studies and cross-sectional studies which met specific pre-defined criteria, as noted below.

5.1.1 WATER FLUORIDATION

Summary

Research question: Is intentional water fluoridation more efficacious than no water fluoridation in the prevention of dental caries?

The existing body of evidence strongly suggests that water fluoridation is beneficial at reducing dental caries. After adjustment for potential confounding variables, McDonagh et al (2000a) showed in their systematic review that the introduction of water fluoridation into an area significantly increased the proportion of caries-free children, and decreased mean dmft/DMFT scores compared with areas which were non-fluoridated over the same time period. The findings of McDonagh et al (2000a) also suggest that cessation of fluoridation resulting in a narrowing of the difference in caries prevalence between the fluoridated and non-fluoridated populations. Only one additional relevant original study was identified in the current review and this did not change the conclusion of the existing systematic review.

5.1.1.1 Identification of relevant studies

Of the 109 potentially relevant citations identified, three represented systematic reviews. The review by McDonagh et al (2000a,b) was considered to be the most relevant and comprehensive, and as such was chosen to form the basis of this section. The search for literature conducted by McDonagh et al (2000a) included up to February 2000. Therefore, literature from 2000 – 2007 from the original literature search was to be reviewed in order to identify additional original studies of the efficacy of water fluoridation in reducing dental caries.

Only one original study was identified which met the same inclusion criteria as those defined by McDonagh and associates. Specifically, this study was: (i) a prospective study comparing at least two populations, one receiving fluoridated water and the other receiving non-fluoridated water; (ii) evaluating at least two time points; and (iii) a change in the level of fluoride in the water supply of at least one the study areas occurred within three years of the baseline survey. No relevant RCTs, cohort studies or case-control studies were identified by the literature search. The exclusion of citations for this section is summarised in **Table 8**.

Table 8 Exclusion of citations: prevention of caries using water fluoridation

Reason for exclusion	Number of citations
Potentially relevant citations	109
Not a clinical study	1
Original study published pre-2000	35
Publication included in McDonagh review	3
Duplicate data from McDonagh review	1
Wrong study type	65
Remaining relevant citations	4

5.1.1.2 Systematic reviews

Two systematic reviews examining the effect of water fluoridation on dental caries have been published since 1996: Truman et al (2002) and McDonagh et al (2000a). A summary of the main characteristics of these reviews is shown in **Table 9**. Both of these studies were considered to be of good methodological quality and provided Level III/IV evidence. Detailed quality assessment of these reviews is presented in **Appendix A.1.1**.

The Truman review (Truman et al, 2002) was conducted by the Task Force on Community Preventive Services in the US, with the aim being to develop recommendations on interventions to prevent oral disease (ie, dental caries, oral and pharyngeal cancers and sports-related craniofacial injuries). The component of the Truman review relevant to this review was the effect of water fluoridation on the prevention or control of dental caries. To be eligible for inclusion in the review, studies had to meet the following criteria: (i) be a report of a primary study; (ii) be published in English between 1966 and 2000; (iii) address the prevention or control of dental caries; (iv) compare a group of people exposed to the intervention (ie, water fluoridation) with a group of people who had not been exposed or who had been less exposed. Twenty one studies were included. The review concludes that there is "strong evidence that CWF [community water fluoridation] is effective in reducing the cumulative experience of dental caries within communities."

The review by McDonagh et al (2000a) was commissioned by the Chief Medical Officer of the Department of Health in the UK. The review covered a number of objectives with the following being the most relevant to this section of the review: "what are the effects of fluoridation of water drinking supplies on the incidence of caries?" Eligibility of studies for inclusion in the review for dental caries was based on the following criteria: (i) prospective studies comparing at least two populations, one receiving fluoridated water and the other receiving non-fluoridated water, with at least two time points evaluated: (ii) a change in the level of fluoride in the water supply of at least one the study areas, within three years of the baseline survey; and (iii) assessing any measure of dental decay. Twenty-six studies (reported in 73 publications) were included. The authors concluded that "the meta-analysis showed a statistically significant effect of water fluoridation in reducing dental caries as measured by both dmft/DMFT and the proportion of caries-free children." However, they also note that there was significant heterogeneity between studies, which was further examined using meta-regression.

It should be noted that 12 of the 21 studies included in the Truman review were amongst the 26 studies included in the McDonagh review. The lack of overlap between the two reviews is predominantly due to the fact that that the Truman review assessed both fluoridation vs no fluoridation and fluoridation vs fluoridation at a lower level, while the McDonagh review assessed only fluoridation vs no fluoridation. In addition, in the McDonagh review the search was not limited to English language studies, and studies published in a number of languages were translated.

The McDonagh review was also more stringent in requiring data from two time points which enabled the change over time to be reported. This minimises the possibility of any difference in dental caries being due to other underlying differences between the populations.

Table 9 Systematic reviews of the effect of water fluoridation on caries prevention

Citation NHMRC Level of Evidence Quality Rating	Number and type of included studies	Intervention	Comparator	Outcomes
Truman et al (2002) Level III/IV Good	8 cross-sectional surveys 1 non-randomised trial 8 prospective cohorts 1 time series	Water fluoridation	No water fluoridation or fluoridation at a lower level	Change in dental caries prevalence
McDonagh et al (2000a) Level III/IV Good	23 before-and-after studies 2 prospective cohort studies 1 retrospective cohort study	Water fluoridation	No water fluoridation	dmft/DMFT, percentage of caries-free children

The McDonagh et al (2000a) review has been chosen to form the evidence base for the effect of water fluoridation on dental caries in this current review as it provides more detailed and comprehensive results than those shown in the Truman et al (2002) review. It should be noted that all studies included in the McDonagh review were considered to be B level evidence (moderate quality and a moderate risk of bias).

The results of the McDonagh review are divided into two groups: (i) including studies in which fluoridation was initiated during the study time-frame, and (ii) including studies in which fluoridation was terminated during the study time-frame. The predefined outcomes assessed in the McDonagh review included the proportion of caries-free children and the mean difference in dmft/DMFT scores. As such, the percentage of caries-free children and the difference in dmft/DMFT will be the main outcomes used in this current review. For each study, data regarding the change from baseline to study end was measured for each outcome in each group (ie, fluoridated or non-fluoridated) and then the change from baseline was compared between groups (ie, fluoridated vs non-fluoridated). It should be noted that the results of a number of different outcomes are briefly noted in the McDonagh review, and these will be presented in this review also. These outcomes include change in DMFS score, average number of all approximal and approximal dentinal lesions, deft score, number of erupted permanent teeth per child and percentage with false teeth.

The results of the analysis of change in the percentage of caries-free children following fluoridation of water is shown in **Table 10**. The majority of study analyses (20/30) of different ages and teeth types showed a significant increase in the percentage of caries-free children following the introduction of water fluoridation, while 7/31 analyses showed a non-significant increase. The remaining 3/31 analyses showed a small, non-statistically significant decrease in the percentage of caries-free children following water fluoridation.

Pooling of the data shown below resulted in a mean difference of 15.4 % (95% CI 10.8, 20.1), $p<0.001$. However, heterogeneity was high with the between study variance being 163.0. Univariate meta-regression analysis showed four variables to be significant (baseline percentage of caries free subjects, tooth type, setting and study duration). In addition, validity score was also included in the multivariate analysis. After adjustment for these variables in a multivariate meta-regression model, the resulting mean difference was similar, being 14.3% (95% CI 6.7, 21.9), p<0.001. The results suggest that the introduction of water fluoridation is strongly associated with an increase in the percentage of caries-free children.

Table 10 Initiation of water fluoridation: change in proportion of caries-free children between non-fluoridation and fluoridation (McDonagh et al, 2000)

Citation	Age	Teeth type	Mean difference (%) (95% CI)
Kunzel (1997)	5	Primary	9.4 (0.9, 17.9)
	8	Permanent	41.1 (36.0, 46.2)
	8	Primary	19.4 (15.9, 22.9)
	12	Permanent	25.2 (21.1, 29.3)
	15	Permanent	9.5 (6.3, 12.7)
Beal (1981)	5	Primary	16.0 (3.2, 28.8)
	8	Permanent	19.0 (4.8, 33.2)
	8	Primary	6.0 (-3.4, 15.4)
	12	Permanent	-5.0 (-15.0, 5.0)
DHSS (1969)			
England	5	Primary	17.0 (2.1, 31.9)
	8	Not stated	18.0 (0.7, 35.3)
	12	Not stated	8.0 (-1.2, 17.2)
	14	Permanent	5.0 (-4.4, 14.4)
Wales	5	Primary	14.0 (3.5, 24.5)
	12	Not stated	9.0 (1.2, 16.8)
	14	Permanent	3.0 (-2.9, 8.9)
Scotland	5	Primary	14.6 (4.79, 24.4)
Adriasola (1959)	5	Primary	5.1 (-1.9, 12.1)
	8	Not stated	5.0 (0.1, 9.9)
	12	Not stated	-4.9 (-8.3, -1.5)
Guo (1984)	5	Primary	-2.0 (-6.4, 2.4)
	8	Permanent	64.1 (55.4, 72.8)
	8	Primary	0.4 (-4.8, 5.6)
	12	Permanent	28.5 (20.5, 36.5)
	15	Permanent	34.4 (19.7, 49.1)
Beal (1971)	5	Not stated	4 (-8.0, 16.0)
Ast (1951)	5	Primary	22.1 (10.9, 33.3)
Brown (1965)	12-14	Permanent	15.8 (11.8, 19.8)
	9-11	Permanent	36.1 (30.5, 41.7)
Gray (1999)	5	Primary	26.0 (19.4, 32.6)
Unadjusted pooled result	Between study variance 163.0		15.4 (10.8, 20.1)
Adjusted pooled resulta	Between study variance 53.1		14.3 (6.7, 21.0)

[a] After multivariate meta-regression analysis, adjusting for variables shown in the univariate analyses to be statistically significant. These include baseline percentage of caries-free children, setting and study validity score.

The unadjusted risk differences and numbers needed to treat to prevent one additional person developing dental caries were calculated by teeth type and age categories and are presented in **Table 11** and range from 3-11. It should be noted that there was significant heterogeneity for all analyses ($p<0.001$); however, based on the results of the multivariate meta-regression shown in **Table 10** above, it is unlikely that adjusting for potentially confounding variables would have a major impact on the results.

Table 11 Initiation of water fluoridation: risk difference and NNT to prevent one additional person developing dental caries (McDonagh et al, 2000)

Age	Teeth type	Number of studies	Risk difference (95% CI)	Q-statistic	NNT (95% CI)
All	All	31	15.5 (10.7, 20.2)	1421.0	6 (5, 9)
	Primary	15	11.4 (6.5, 16.3)	354.4	9 (6, 15)
	Permanent	16	19.1 (11.4, 26.7)	751.3	5 (4, 9)
5	Primary	11	13.2 (6.8 (20.0)	137.5	8 (5, 15)
8	Primary	4	7.2 (-3.6, 18.0)	211.3	14 (6, ∞)
	Permanent	4	35.6 (22.4, 48.8)	39.1	3 (2, 5)
12	Permanent	6	13.1 (0.8, 25.5)	215	8 (4, 125)
14-15	Permanent	4	8.8 (0.7, 16.9)	36.8	11 (6, 143)

The results of the analysis of change in dmft/DMFT following fluoridation of water are shown in Table 12. Once again, the majority of study analyses which provided a measure of variance (14/15) showed a greater improvement in caries following the introduction of water fluoridation, while 1/15 analyses showed a non-significant increase.

Pooling of the data shown below resulted in a mean difference in dmft/DMFT score of 2.3 (1.8, 2.8), $p<0.001$. However, heterogeneity was high with the between study variance being 1.068. Univariate meta-regression analysis showed four variables to be significant (baseline dmft/DMFT, setting, validity score and age). After adjustment for these variables in a multivariate meta-regression model, the resulting mean difference was consistent, being 2.61 (2.31, 2.91), p value not reported. The results suggest that introduction of water fluoridation is strongly associated with an improvement in dmft/DMFT scores. However, it should be noted that the analyses did not take into account the use of other sources of fluoride, including topical agents.

Table 12 Initiation of water fluoridation: change in change in dmft/DMFT scores between non-fluoridation and fluoridation (McDonagh et al, 2000)

Citation	Age	Teeth type	Mean difference (95% CI)
Kunzel (1997)	5	Primary	0.6 (0.2, 1.0)
	8	Primary	2.1 (1.8, 2.4)
	8	Permanent	1.3 (1.2, 1.4)
	12	Permanent	2.9 (2.6, 3.2)
	15	Permanent	3.7 (3.3, 4.1)
Beal (1981)	5	Primary	1.7 (0.6, 2.8)
	8	Permanent	0.5 (0.1, 0.9)
	8	Primary	1.2 (0.4, 2.0)
	12	Permanent	0.6 (-0.2, 1.4)
DHSS (1969)			
England	5	Primary	1.6
	8	Permanent	0.8
	12	Permanent	1.0
	14	Permanent	1.5
Wales	5	Primary	2.1
	12	Permanent	2.5
	14	Permanent	2.3
Loh (1996)	7-9	Permanent	3.1
	7-9	Permanent	2.1
Guo (1984)	5	Primary	3.6 (2.6, 4.6)
	8	Permanent	1.6 (1.4, 1.8)
	8	Primary	4.4 (3.9, 4.9)
	12	Permanent	2.6 (2.2, 3.0)
	15	Permanent	3.8 (2.7, 4.9)
Alvarez-Ubilia (1959)	5	Primary	2.2
Arnold (1956)	8	Permanent	1.2
	12	Permanent	1.2
	15	Permanent	3.1
Blayney (1960)	8	Permanent	1.8
	12	Permanent	3.4
Brown (1965)	12-14	Permanent	4.1 (3.4, 4.8)
	9-11	Permanent	2.1 (1.7, 2.5)
Unadjusted pooled result[a]	Between study variance 1.068		2.3 (1.8, 2.8)
Adjusted pooled result[a,b]	Between study variance 0.111		2.61 (2.31, 2.91)

[a] Only studies which included data on variance have been included in meta-regression analysis.

[b] After multivariate meta-regression analysis, adjusting for variables shown in the univariate analyses to be statistically significant. These include baseline dmft/DMFT, age, study duration and setting.

A number of additional caries outcomes were examined, but not meta-analysed. These are shown in **Table 13**. Once again the majority of the results show a caries benefit in favour of the fluoridated areas, with the exception of the number of erupted permanent teeth in eight year olds in the study by Ast (1951).

Table 13 Initiation of water fluoridation: other caries outcomes (McDonagh et al, 2000)

Citation	Age	Outcome	Mean difference (95% CI)
Hardwick (1982)	12	Increment in DMFS score	2.5 (1.0, 3.0)
	12	Increment in DMFT score	1.1 (0.4, 1.8)
Backer-Dirks (1961)	11-15	Average number of approximal lesions	2.7
	11-15	Average number of approximal dental lesions	1.4
Beal (1971)	5	deft score	2.5 (1.3, 3.7)
Arnold (1956)	5	deft score	1.6
	8		0.9
Ast (1951)	12	Number of erupted permanent teeth per child	0.1
	8		-0.3
	12	DMFT rate per 100 erupted permanent teeth	10.5
	8		7.1
Pot (1974)	5-55	Percentage with false teeth	11.2 (3.8, 18.6)

The McDonagh et al (2000a) review also assessed the mean difference in caries outcome measures in studies where water fluoridation was discontinued. These results are summarised in **Table 14**. A negative result indicates that that the difference in caries between newly-unfluoridated areas and previously unfluoridated areas narrowed. The results are generally consistent, with the cessation of water fluoridation resulting in a narrowing of difference in caries in 14/22 analyses. Of the seven analyses which showed a negative result and provided standard error data, only one showed a statistically significant result.

Table 14 Cessation of water fluoridation: change in caries outcome measures (McDonagh et al, 2000a)

Citation	Age	Teeth type	Mean difference (95% CI)
Proportion of caries-free children			
Kunzel (1997)	8	Permanent	8.6
	12	Permanent	-5.3
	15	Permanent	-2.5
DHSS (1969)	5	Primary	-2.7
Wragg (1992)	5	Primary	-21.6 (-37.1, -16.3)
Mean difference in dmft/DMFT			
Kunzel (1997)	8	Permanent	0.3
	12	Permanent	-0.4
	15	Permanent	0.1
Kalsbeek (1993)	15	Permanent	-7.4 (-8.5, -6.3)
DHSS (1969)	5	Primary	-16

Citation	Age	Teeth type	Mean difference (95% CI)
Attwood (1988)	10	Permanent	-0.6 (-1.3, 0.1)
Hobbs (1994)	5	Primary	-1.2
Wragg (1992)	5	Primary	-1.5 (-2.2, -0.7)
DMFS score			
Seppa (1998)	6	Not stated	-0.1
	9	Not stated	0.2 (-0.5, 0.9)
	12	Not stated	-1.1 (-2.3, 0.1)
	15	Permanent	-0.9 (-4.2, 2.4)
Kalsbeek (1993)	15	Permanent	-18.8 (-21.3, -16.3)
Mean difference in D1D2MFS scores[a]			
Maupomé (2000)	8	Permanent	0.59 (0.41, 0.77)
	14	Permanent	1.39 (0.23, 2.55)
D1D2MFS incidence			
Maupomé (2000)	11	Permanent	0.13 (-0.07, 0.34)
	17	Permanent	0.47 (-0.02, 0.96)

Note: Studies are ordered by validity score from highest to lowest.

[a] D1D2MFS is a modified DMFS score where D1=an incipient lesion and D2=a cavitated lesion.

5.1.1.3 ADDITIONAL ORIGINAL STUDIES

The results of the analyses presented by McDonagh et al (2000a) strongly suggest that water fluoridation has a beneficial effect by reducing dental caries. Only one additional original study (Level IV evidence) met the criteria for inclusion in this review. The study, by Seppä et al (2000), was a controlled before-and-after study in which caries trends were compared in two cities: one which was non-fluoridated (Jyväskylä) and one in which fluoridation had just ceased (Kuopio). A previously published study (Seppä et al, 1998; included in the McDonagh review) provides data at 1992 and 1995. The 2000 paper provides data at an additional time-point; 1998. The outcome measure used was dmfs/DMFS with both mean values and percentage of children with dmfs/DMFS=0 (ie, caries-free) reported. It should be noted that the methodological quality of this study was assessed and was considered to be poor due to the lack of information regarding sampling procedures, the lack of information regarding potential confounding variables and the lack of blinding of outcome assessment. Detailed assessment of this study is included in **Appendix A.1.1**.

Data regarding the percentage of caries-free children at the first and last time-points (ie, 1992 and 1998) are presented in **Table 15**. There was a substantial increase in the percentage of caries-free children from 1992 to 1998 in Kuopio, six years after the cessation of fluoridation of the water supply in 3, 6 and 9 year olds. In 12 and 15 year olds, the percentage of caries-free children decreased during this time frame. In the never-fluoridated control town, Jyväskylä, there was a small increase in the percentage of caries-free children between 1992 and 1998 for 3 and 6 year-olds, a small decrease for 9 year olds, and substantial increases for 12 and 15 year olds. The percentage of caries-free children was significantly increased in Kuopio compared with Jyväskylä for 3, 6 and 9 year olds and significantly decreased in Kuopio compared with Jyväskylä for 12 and 15 year olds.

Table 15 Cessation of water fluoridation: change in proportion of caries-free children (Seppä et al, 2000)

Age	Kuopio			Jyväskylä			Mean percent difference (95% CI) p value[a]
	1992	1998	Mean percent change from baseline ± SE[a]	1992	1998	Mean percent change from baseline ± SE[a]	
3	63/74 (85)	144/147 (98)	12.8 ± 4.3	59/64 (92)	134/143 (94)	1.5 ± 3.9	11.3 (-0.1, 22.7) 0.05
6	30/68 (44)	105/156 (67)	23.2 ± 7.1	45/66 (68)	102/148 (69)	0.7 ± 6.9	22.5 (3.1, 41.8) 0.02
9	17/80 (21)	58/165 (35)	15.9 ± 6.0	31/69 (45)	59/147 (40)	-4.8 ± 7.2	20.7 (2.3, 39.1) 0.03
12	29/66 (44)	55/161 (34)	-9.8 ± 7.2	22/77 (29)	74/154 (48)	19.5 ± 6.5	-29.3 (-48.3, -10.3) 0.003
15	17/64 (27)	39/156 (25)	-1.6 ± 6.5	6/60 (10)	63/153 (41)	31.2 ± 5.6	-32.7 (-49.5, -16.0) <0.001

Post-hoc analyses conducted for the purpose of this review.

The results of the analysis of DMFS are summarised in **Table 16**. There was no significant increase in mean DMFS scores in Kuopio following cessation of water fluoridation. This result differs from the results of earlier studies, in which cessation of fluoridation led to an increase in caries. The authors suggest it may be the result of a concurrent policy change in Finland which aimed to specifically target preventive measures to children and adolescents based on individual needs.

Table 16 Cessation of water fluoridation: mean DMFS valuesa (Seppä et al, 2000)

Age	Kuopio		Jyväskylä	
	1992 Mean ± SE	1998 Mean ± SE	1992 Mean ± SE	1998 Mean ± SE
6	0.1 ± nr	0.1 ± nr	0.1 ± nr	0.1 ± nr
9	0.8 ± 0.1	0.4 ± 0.1	0.7 ± 0.1	0.8 ± 0.2
12	1.9 ± 0.7	2.0 ± 0.4	3.0 ± 0.9	1.5 ± 0.2
15	4.0 ± 1.2	3.2 ± 0.6	5.6 ± 1.1	2.8 ± 0.6

[a] Values estimated from graph.

5.12 MILK FLUORIDATION

Summary

Research question: *Is intentional milk fluoridation more efficacious than no milk fluoridation in the prevention of dental caries?*

The results of the systematic review suggest that milk fluoridation is beneficial in the prevention or reduction of caries, although there is less good quality evidence than is the case for water fluoridation. The results of the two included original studies represent low levels of evidence; however, the results are consistent with milk fluoridation being associated with caries prevention, and cessation of milk fluoridation associated with worsening dental health.

5.1.2.1 Identification of relevant studies

The literature search identified one systematic review which assessed the benefit of fluoridated milk in preventing dental caries (Yeung et al, 2005). The literature search conducted for the Yeung review encompassed the period up to May 2005 and only RCTs were eligible for inclusion. The search conducted for this current review identified no additional RCTs. In addition there were no relevant cohort studies or case-control studies identified. Two studies met the criteria for the lowest level of evidence allowable for this question. Both studies were cross-sectional in design, assessed two different populations (one exposed to fluoride and one not exposed to fluoride), and were measured at multiple time-points. The exclusion of citations for this section is summarised in Table 17.

Table 17 Exclusion of citations: prevention of caries using milk fluoridation

Reason for exclusion	Number of citations
Potentially relevant citations	7
Original study published pre-2005	4
Remaining relevant citations	3

5.1.2.2 Systematic reviews

The literature search identified one systematic review which assessed the benefit of fluoridated milk in preventing dental caries. This Cochrane review, by Yeung et al (2005), was considered to be of good methodological quality. Studies were included if they were randomised or quasi-randomised, had follow-up of at least 3 years, compared fluoridated milk with non-fluoridated milk, and assessed various caries measures. A summary of the characteristics of this study are shown in Table 18. A detailed assessment of this review is included in Appendix A.1.2.

Table 18 Systematic reviews of the effect of water fluoridation on caries prevention

Citation NHMRC Level of Evidence Study Quality	Number and type of included studies	Intervention	Comparator	Outcomes
Yeung et al (2005) Level I Good	2 RCTs	Fluoridated milk	Non-fluoridated milk	dmft/DMFT, dmfs/DMFS, pain, antibiotics, general anaesthesia, adverse effects

As the only systematic review on milk fluoridation, the Yeung review will be used as the basis for this section. The results of the review are summarised in **Table 19**. It should be noted that two out of three analyses included only one study, and data were not pooled for the one analysis containing two studies due to the differences in fluoride concentration. As such, results for individual studies are presented.

While the results of the studies suggest that milk fluoridation is beneficial in the prevention or reduction of caries, the authors note that there is a lack of studies with good quality evidence to sufficiently examine this issue.

Table 19 Milk fluoridation: change in change in dmft/DMFT scores between non-fluoridation and fluoridation (Yeung et al, 2005)

Outcome	Follow-up (years)	No. of participants	Statistical method	Effect size (95% CI)
DMFT				
Stephen 1984	3	143	WMD (REM)	-0.36 (-0.72, 0.00)
Maslak 2004	3	166	WMD (REM)	-0.13 (-0.24, -0.02)
Stephen 1984	5	106	WMD (REM)	-0.97 (-1.94, 0.00)
dmft				
Maslak 2004	3	166	WMD (REM)	-1.14 (-1.86, -0.42)

Abbreviations: dm(e)fs, decayed/missing (extraction indicated)/filled ; DMFS, decayed/missing/filled surfaces in permanent teeth; DMFT, decayed/missing/filled permanent teeth; PF, prevention fraction; REM, random effects method; RR, relative risk.
a Nearest to 3 years.

5.1.2.3 Additional original studies

The search for additional original studies which have assessed milk fluoridation resulted in the identification of two additional studies (Riley et al, 2005; Mariño et al, 2004). Both studies were cross-sectional in design and compared populations exposed/not exposed to milk fluoridation which were examined at multiple time-points. Detailed assessments of these studies are provided in **Appendix A.1.2**.

It should be noted that an earlier abstract relating to the study by Riley was excluded from the Yeung review (Riley 2004). In addition, an earlier publication of the Mariño study was excluded from the Yeung review. Both were excluded because they were not RCTs.

Mariño et al, 2004 presented the results of a cross-sectional study assessing the effect of ending a milk fluoridation programme (Level IV, poor quality). The impact of the implementation of the milk fluoridation programme was examined by Mariño et al (2001; Level IV, poor quality). This study was excluded from the Yeung review as it was not a randomised clinical trial. As these studies provide controlled data on the impact of the introduction and cessation of milk fluoridation on dental caries, as it meets the inclusion criteria defined for the section of water fluoridation used by McDonagh et al (2000; ie, effect on caries is assessed at two time-points related to the introduction and cessation of the programme) this study is included in this review. It should be noted that these studies were considered to be of poor methodological quality due to the lack of assessment of demographic and other potential differences between the two communities, and subsequent adjustment for these in the analysis, as well as the fact that baseline values for the introduction of the milk fluoridation programme were conducted at different timepoints in the two communities (1995 in the test community and 1997 in the control community).

The study by Mariño et al (2001) examined the effect of milk fluoridation on caries prevalence and the percentage of caries-free children in two regions of Chile: one in which milk fluoridation was implemented in 1994 (Codegua) and one in which milk fluoridation was not implemented (La Punta). Baseline fluoride exposure in both communities was low with water fluoride levels of between 0.06 and 0.09 ppm. The main exposure to fluoride was from toothbrushing with fluoridated toothpaste which was conducted twice a day in all day care centres and may or may not have been used at home. The results of this study (presented in **Table 20**), show that caries prevalence decreased and the percentage of caries-free children increased in Codegua in 1999 following the introduction of milk fluoridation in 1995. There was no significant change in caries prevalence or the percentage of caries-free children in the control town, La Punta. Endpoint caries prevalence was significantly greater and percentage of caries-free children was significantly lower in La Punta compared with Codegua in 1999.

The study by Mariño et al (2004) assessed caries prevalence and the percentage of caries-free children in Codegua in 2002, following cessation of the milk fluoridation programme in 1999, compared with La Punta which had never received milk fluoridation. The results of this study are summarised in **Table 20** also. The results showed that caries prevalence significantly increased in Codegua in the 3 years following cessation of milk fluoridation in 3, 4 and 5 year-olds. There was no significant difference in caries prevalence over this time in 6 year-olds. The percentage of caries-free children decreased. In the control group who had never received milk fluoridation, there was no significant change in caries prevalence or percentage of caries-free children for an age group between 1999 and 2000. There was no significant difference in caries prevalence or percentage of caries-free children between Codegua and La Punta in 2002. These results strongly suggest that milk fluoridation played a significant role in caries prevention.

Table 20 Change in caries following introduction and cessation of milk fluoridation programme (Mariño et al, 2001; 2004)

			Codegua Fluoridated 1995 Ceased fluoridation 1999		La Punta Never fluoridated		La Punta vs Codegua
Age	Year	Outcome	Endpoint	Difference (P value)	Endpoint	Difference (P value)	Endpoint P value
3	1994/1997[a]	Mean dmfs	3.11 ± 5.07	-	2.25 ± 3.05	-	-
3	1999	Mean dmfs	1.52 ± 2.48	–51% (ns)	3.85 ± 5.67	71% (ns)	<0.01
3	2002	Mean dmfs	5.20 ± 10.54	242% (<0.05)	3.28 ± 6.16	-15% (ns)	ns
3	1994/1997[a]	Percent caries-free	40.7	-	42.5	-	-
3	1999	Percent caries-free	63.3	56% (<0.05)	37.3	14% (ns)	<0.01
3	2002	Percent caries-free	42.0[a]	-34% (<0.05)	52.0[b]	39% (ns)	ns
4	1994/1997[a]	Mean dmfs	5.40 ± 8.10	-	2.78 ± 3.58	-	-
4	1999	Mean dmfs	3.18 ± 7.27	–41% (<0.05)	4.22 ± 5.00	52% (ns)	<0.01
4	2002	Mean dmfs	5.73 ± 9.12	80% (<0.05)	6.91 ± 9.34	64% (ns)	ns
4	1994/1997[a]	Percent caries-free	33.3	-	38.9	-	-
4	1999	Percent caries-free	53.1	59% (<0.05)	31.7	23% (ns)	<0.05
4	2002	Percent caries-free	35.4	-33% (<0.05)	34.5	9% (ns)	ns

			Codegua Fluoridated 1995 Ceased fluoridation 1999		La Punta Never fluoridated		La Punta vs Codegua
Age	Year	Outcome	Endpoint	Difference (P value)	Endpoint	Difference (P value)	Endpoint P value
5	1994/1997[a]	Mean dmfs	13.75 ± 16.12	-	7.44 ± 8.36	-	-
5	1999	Mean dmfs	3.03 ± 4.83	–78% (<0.01)	5.61 ± 7.05	-25% (ns)	<0.05
5	2002	Mean dmfs	5.85 ± 6.85	93% (<0.05)	8.43 ± 10.38	50% (ns)	ns
5	1994/1997[a]	Percent caries-free	21.8	-	23.1	-	-
5	1999	Percent caries-free	50.0	129% (<0.01)	33.9	-32% (ns)	ns
5	2002	Percent caries-free	32.7	-35% (<0.05)	29.4	-13% (ns)	ns
6	1994/1997[a]	Mean dmfs	19.21 ± 12.94	-	8.67 ± 8.57	-	-
6	1999	Mean dmfs	5.63 ± 6.23	71% (<0.01)	8.79 ± 8.89	1% (ns)	<0.05
6	2002	Mean dmfs	7.94 ± 7.91[b]	41% (ns)	12.33 ± 12.64	40% (ns)	ns
6	1994/1997[a]	Percent caries-free	3.8	-	16.4	-	-
6	1999	Percent caries-free	27.4	629% (<0.01)	16.1	2% (ns)	ns
6	2002	Percent caries-free	19.6	-28% (ns)	11.9	-26% (ns)	ns
3-6	1994/1997[a]	Mean dmfs	11.78 ± 13.69	-	5.85[a]	-	-
3-6	1999	Mean dmfs	3.35 ± 5.68	72% (<0.01)	5.65 ± 7.08	nr	<0.01
3-6	2002	Mean dmfs	6.19 ± 8.70[a]	85% (<0.01)	7.74 ± 10.36	37% (ns)	ns
3-6	1994/1997[a]	Percent caries-free	22.0	-	28.0	-	-
3-6	1999	Percent caries-free	48.4	120% (<0.01)	29.6	-5% (ns)	<0.01
3-6	2002	Percent caries-free	32.5	-33% (< 0.01)	31.9	8% (ns)	ns

Note: Difference calculations for Codegua (2002) and La Punta (1997 and 2002) were performed post hoc for this review.
[a] Estimated using weighted mean dmfs for ages 3, 4 5 and 6.

The study by Riley et al (2005) examines the dental health of children in two school communities: (i) which included schools that had been receiving fluoridated milk (Wirral) and (ii) which included schools with no fluoridation programme (Sefton). Inclusion criteria for both groups were that a full population dental health survey of 5 year-old children had been carried out in 1997/1998. Inclusion criteria for schools in the test group included at least six years of milk fluoridation and at least 50% uptake of milk fluoridation within the school. Schools were then matched on this age cohort as well as a number of key deprivation indicators. Exclusion criteria for the comparison group were the presence of milk, water or tablet fluoridation schemes. Sefton was chosen as the comparison group as it most closely matched Wirral. Individual schools were then matched with one test school matched to two comparison schools, resulting in 14 test schools and 28 comparison schools.

A summary of the dental health of first permanent molars in the test group and comparison group is shown in Table 21. A number of the measures appeared quite different between the test and comparison groups, with the mean DMFT, DT and DFS being lower in the test group compared with the comparison group, and the percentage of children with any DMFT, DT or DFS being lower in the test group compared with the comparison group.

Table 21 Milk fluoridation: dental health of the first permanent molars (Riley et al, 2005)

Outcome	Test group (Wirral)	Comparison group (Sefton)
	Mean (95% CI)	Mean (95% CI)
DMFT	1.01 (0.91, 1.10)	1.46 (1.40, 1.53)
DT	0.59 (0.51, 0.66)	1.02 (0.96, 1.08)
MT	0.12 (0.08, 0.16)	0.14 (0.11, 0.16)
FT	0.30 (0.24, 0.35)	0.31 (0.28, 0.34)
DFS	1.20 (1.06, 1.34)	1.89 (1.78, 2.00)
Sealed teeth	0.5 (0.42, 0.58)	0.5 (0.45, 0.55)
	Percent (95% CI)	Percent (95% CI)
Children with fissure sealants	23 (20, 26)	24 (22, 26)
Children with DMFT > 0	48 (44, 52)	61 (59, 63)
Children with DT > 0	35 (32, 39)	51 (49, 53)
Children with DFS > 0	46 (42, 50)	59 (58, 62)

Multiple linear regression and logistic regression models were fitted to continuous outcomes (mean DMFT, DMT or DFS) and dichotomous outcomes (absence vs presence of DMFT, DT, DFS) respectively. The results are summarised in **Table 22**. The results show that there is less dental disease in children attending schools with a fluoridated milk program compared with schools without a fluoridated milk programme.

Table 22 Milk fluoridation: comparisons of dental health (Riley et al, 2005)

Dependant variable	Mean difference[a] (95% CI) (comparison – test)	Robust SE[b]	p value
DMFT	0.49 (0.27, 0.72)	0.11	<0.001
DT	0.43 (0.26, 0.61)	0.09	<0.001
DFS	0.74 (0.48, 1.00)	0.13	<0.001
	Odds ratio[a] (95% CI) (comparison/test)	Robust SE[b]	p value
DMFT	1.71 (1.32, 2.23)	0.23	<0.001
DT	1.99 (1.52, 2.60)	0.27	<0.001
DFS	1.73 (1.36, 2.20)	0.21	<0.001

[a] Adjusted for age, gender and IMD 2000 (Index of Multiple Deprivation).
[b] Taking into account clustering.

Based on the results of their study the authors conclude that while the study has demonstrated a difference in caries between children attending schools with a fluoridated milk programme with children in schools which do not, definitive evidence of effectiveness is required from randomised controlled trials.

While both studies provide only low levels of evidence for assessing the effectiveness of an intervention, both studies show consistent results which suggest that milk fluoridation may be an effective method for preventing dental caries.

5.1.3 SALT FLUORIDATION

Summary

Research question: ***Is intentional salt fluoridation more efficacious than no salt fluoridation in the prevention of dental caries?***

No studies were identified which met the criteria for inclusion in this review.

The results of the three before-and-after cross-sectional studies suggest that salt fluoridation reduces caries in populations of children aged from 6-15. However, it should be noted that these studies were considered to be of poor methodological quality, primarily due to the lack of assessment of, and adjustment for, potential confounding factors.

5.1.3.1 Identification of relevant studies

No systematic reviews of the effect of salt fluoridation of prevention of dental caries were identified by the literature search. In addition, no RCTs, cohort studies, case-control studies or cross-sectional studies meeting the criteria defined by McDonagh et al (2000a) were identified. The exclusion of citations for this section is summarised in **Table 23**.

Table 23 Exclusion of citations: prevention of caries using salt fluoridation

Reason for exclusion	Number of citations
Potentially relevant citations	6
Wrong study type	6
Remaining relevant citations	0

It should be noted that of the six studies excluded, three were before-and-after cross-sectional studies. While they do not strictly meet the inclusion criteria for this review, as they do not compare a fluoridated and non-fluoridated group, they do provide some useful evidence, and so will be briefly discussed here. They are not formally included in the review.

5.1.3.2 Systematic reviews

No systematic reviews of the effectiveness of salt fluoridation were identified by the literature search.

5.1.3.3 Additional original studies

Three single time-point cross-sectional studies were identified which assessed the effectiveness of salt fluoridation at reducing dental caries. All studies measured dental caries were measured before and after the introduction of salt fluoridation. The studies were conducted in Mexico (Irigoyen and Sánchez-Hinojosa, 2000), Jamaica (Estupiñán-Day et al, 2001) and Costa Rica (Solórzano et al, 2005). It should be noted that all three studies failed to provide information about demographic and other differences between the baseline and endpoint populations, and failed to adjust results for any differences, and other potentially contributing factors.

The study by Solórzano et al (2005) was conducted in children aged 6-8, 12 and 15. The baseline measurement was taken in 1984, 3 years prior to salt fluoridation, and the follow-up measurement was conducted in 1999. The study by Estupiñán-Day et al (2001) was also conducted in children aged 6-8, 12 and 15. Baseline measurement was conducted in 1984, 3 years prior to introduction of salt fluoridation, and follow-up measurement was made in 1995. Finally, the study by Irigoyen and Sánchez-Hinojosa (2000) was conducted in 12-year old children in 1988 (the year salt-fluoridation was introduced) and followed-up in 1997.

The results of the salt fluoridation studies are summarised in **Table 24**. The most recent study, by Solórzano et al (2005), did not present the results of the initial 1984 survey; therefore, formal before and after comparisons can not be made. However, the authors report that there was a 73% reduction in DMFT between 1984 and 1999. The study by Estupiñán-Day et al (2001) provided both before and after values for DMFT. Although a formal comparison was not made in their study, this had been carried out for this review, with caries being significantly reduced from 1984 to 1997. Finally, the study by Irigoyen and Sánchez-Hinojosa (2000) provided a formal comparison of the difference in the percentage of caries-free children over time, showing a significant reduction between 1988 and 1997. Post-hoc comparisons of the DMFT data also showed a significant improvement in dental caries during this time period. It is important to note that all of these analyses were crude, with no adjustment made for potentially confounding variables.

Table 24 Salt fluoridation: results of original studies

Citation	Outcome	Pre-salt fluoridation Mean DMFS/T score	Post-salt fluoridation Mean DMFS/T score	Difference Pre minus post
Solórzano et al (2005)	dmft (age 6-8)	nr	3.32 (3.08, 3.45)	-
	DMFT (age 6-8)	nr	0.49 (0.39, 0.59)	-
	DMFT (age 12)	9.13	2.46 (2.25, 2.69)	Reduction 73%
	DMFT (age 15)	nr	4.37 (3.92, 4.82)	-
Estupiñán-Day et al (2001)	DMFT (age 6)	1.71 ± 1.4	0.22 ± 0.6	WMD 1.49 (1.32, 1.66)[a]
	DMFT (age 12)	6.72 ± 3.6	1.08 ± 3.0	WMD 5.64 (5.24, 6.04)[a]
	DMFT (age 15)	9.60 ± 4.3	3.02 ± 3.0	WMD 6.58 (6.06, 7.10)[a]
Irigoyen and Sánchez-Hinojosa (2000)	Percentage of caries-free children	10.3%	27.7%	OR 3.26 (2.7, 3.9)
	DMFT	4.39 ± 2.9	2.47 ± 2.4	WMD 1.92 (1.74, 2.10)[b]
	DMFS	6.93 ± 4.9	3.84 ± 4.3	WMD 3.09 (2.77, 3.41)[b]

[a] Post-hoc calculation using Meta-View 1.0.

[b] Post-hoc calculation using Meta-View 1.0. DMFT comparison 95% CI similar to that reported in the publication (1.73, 2.11).

5.1.4 TOPICAL FLUORIDES

Topical fluorides aim to deliver high concentrations of fluoride directly to the surface of the tooth, and are not intended to be ingested. Topical fluorides include toothpastes and mouthrinses, which are self-applied, and varnishes and gels, which are generally professionally applied.

The following section will assess the evidence for each of these modalities, both alone and in combination.

Summary

Research question: *Is the use of <u>topical fluoride supplementation</u> more efficacious than no topical fluoride supplementation in the prevention of dental caries?*

Research question: *Is a <u>combination of topical fluoride supplementation</u> products more efficacious than a single topical fluoride supplementation product in the prevention of dental caries?*

There is consistent Level I evidence from existing systematic reviews and a review of additional original studies that topical fluoride agents reduce caries in children, when compared to no topical fluoride supplementation. When compared to placebo/no treatment the magnitude of the effect achieved with varnish is greater than the other topical agents. However, when compared directly to each other, there is no significant difference between agents. There is also Level I evidence that some combinations of topical agents may be more effective at preventing/reducing caries than single agents.

5.1.4.1 Identification of relevant studies

The literature search identified 128 potentially relevant citations. Of these, 15 represented systematic reviews. The most comprehensive of these was the review by Marinho et al (2003d) which presents a combination of four previously conducted Cochrane reviews. As the most comprehensive of the systematic reviews, this was chosen to form the basis of this section. A literature search for original studies published from 2000 onwards was conducted and found 32 potentially relevant RCTs. Due to the large number of RCTs identified, a decision was made to limit inclusion of RCTs in this review to those containing greater than 500 subjects. This resulted in inclusion of 16 RCTs, with 16 smaller RCTs excluded. The exclusion of citations for this section is summarised in **Table 25**.

Table 25 Exclusion of citations: prevention of caries using topical fluorides

Reason for exclusion	Number of citations
Potentially relevant citations	128
Not a clinical study	3
Wrong intervention	1
Wrong/no comparator	2
Wrong outcomes	2
Original study published pre-2000	38
Wrong study type	26
Duplicate data	9
Study size (< 500 subjects)	16
Remaining relevant citations	31

5.1.4.2 Systematic reviews

The literature search identified fifteen relevant systematic reviews/meta-analyses which assessed the effect of topical fluoride agents on caries prevention/treatment. Of these, eleven were formally included in the review. A summary of the identified studies is shown in **Table 26**. The majority of included reviews were considered to be of good methodological quality. Three reviews were considered to be of fair methodological quality (Steiner et al, 2004; Ammari et al, 2003; van Rijkom et al, 1998). The reasons for these studies being considered of fair methodological quality were (i) the criteria for including studies in the review were not stated; (ii) no formal assessment of study quality was undertaken; or (iii) the search strategy used to identify relevant studies was not considered to be comprehensive. Detailed assessments of these reviews are provided in **Appendix A.1.3**. Two of the included reviews examined different caries-preventive measures, not limited to fluoride (Axelsson et al, 2004; Bader et al, 2001). As these reviews provided only the original results of the included studies, and did not attempt to pool any data, they will be considered separately below.

It should be noted that the review by Marinho et al (2003d) is a combined analysis of four individual reviews which assessed (i) fluoride toothpaste (Marinho et al, 2003b), (ii) gel (Marinho et al, 2003a), (iii) mouthrinse (Marinho et al, 2003c) and (iv) varnish (Marinho et al, 2002). The individual reviews are not included in this review of caries prevention.

Table 26 Systematic reviews of the effect of topical fluoride agents on caries prevention

Citation NHMRC Level of Evidence Study Quality	Number and type of included studies	Intervention	Comparator	Outcomes
Fluoride vs placebo/no therapy				
Petersson et al (2004) Level I Good	24 RCTs and CCTs of > 2 years duration[a]	Professionally-applied fluoride varnish	Placebo/no treatment	dmft/DMFT, dmfs/DMFS
Twetman et al (2004) Level I Good	25 RCTs/CCTs[a]	Fluoride mouthrinse	Placebo	DMFS/DMFT
Marinho et al (2003d) Level I Good	144 RCTs and quasi-RCTs	Any topical fluoride agent	Placebo/no treatment	dmft/DMFT, dmfs/DMFS, caries-free children, withdrawals
Twetman et al (2003) Level I Good	54 RCTs and CCTs of > 2 years duration[a]	Fluoride toothpaste	Placebo/no treatment	dmft/DMFT, dmfs/DMFS
van Rijkom et al (1998) Level I Fair	19 RCTs	Fluoride gel	Placebo/ no treatment	Caries incidence at surface level

Citation NHMRC Level of Evidence Study Quality	Number and type of included studies	Intervention	Comparator	Outcomes
Fluoride vs fluoride/other				
Marinho et al (2004a) Level I Good	12 RCTs and quasi-RCTs	Combination of topical fluoride agents	Single topical fluoride agents	dmft/DMFT, dmfs/DMFS, caries-free children, withdrawals
Marinho et al (2004b) Level I Good	17 RCTs or quasi-RCTs	Any topical fluoride applied for at least one year	Any topical fluoride applied for at least one year	dmft/DMFT, dmfs/DMFS, caries-free children, withdrawals
Petersson et al (2004) Level I Good	24 RCTs and CCTs of > 2 years duration[a]	Professionally-applied fluoride varnish	Other fluoride agents	dmft/DMFT, dmfs/DMFS
Steiner et al (2004) Level I Fair	4 RCTs	Toothpaste 1000 ppm F	Toothpaste 250 ppm F	DMFS
Twetman et al (2004) Level I Good	25 RCTs/CCTs[a]	Fluoride mouthrinse	Any	DMFS/DMFT
Ammari et al (2003) Level I Fair	7 RCTs	Toothpaste with < 600 ppm F	Toothpaste with ≥ 1000 ppm F	dmft/DMFT, dmfs/DMFS
Twetman et al (2003) Level I Good	54 RCTs and CCTs of > 2 years duration[a]	Fluoride toothpaste	Toothpaste with different fluoride concentrations	dmft/DMFT, dmfs/DMFS

Abbreviations: CCT, controlled clinical trials; defs, decayed, identified for extraction, filled primary surfaces; deft, decayed, identified for extraction, filled primary teeth; dmfs, decayed/missing (extraction indicated)/filled in primary teeth; DMFS, decayed/missing/filled surfaces in permanent teeth; DMFT, decayed/missing/filled permanent teeth; FEM, fixed effects method; PF, prevention fraction; REM, random effects method; RCTs, randomised controlled trials.

[a] Total number of included studies in review, regardless of comparator.

A summary of the results of the included meta-analyses are presented in Table 27. The results are consistent across studies with topical agents having a significantly beneficial effect at reducing caries compared with placebo/no therapy. There appears to be little difference between agents, although some evidence suggests that fluoride varnish may be more effective than the other topical agents. Combinations of agents may be slightly more effective than use of single agents.

Table 27 Summary of the results of systematic reviews of the effect of topical fluoride agents on caries prevention

Citation	Comparison	Type of dentition	Outcome	Prevention fraction (95% CI)	Summary
Fluoride vs placebo/no treatment					
Petersson et al (2004)	Varnish vs placebo/no treatment	Permanent	DMFS/T	0.30 (0.0, 0.69)	Fluoride found to be more effective than no fluoride. Evidence for use of fluoride in permanent dentition considered to be Level 3 (limited evidence). Authors note that evidence regarding fluoride toothpaste in primary dentition and adults was inconclusive (Level 4).
Marinho et al (2003d)[a]	Any agent vs placebo/no treatment	Permanent	DMFS	0.26 (0.23, 0.29)	Topical agents as a group, and when considered separately, were significantly more effect than placebo/no treatment in caries reduction. There was substantial heterogeneity in many of the analyses but the direction of the effect was consistent. After adjustment for variables shown to be significantly associated with the fluoride effect, the results remained similar.
	Toothpaste vs placebo	Permanent	DMFS	0.24 (0.21, 0.28)	
	Gel vs placebo	Permanent	DMFS	0.21 (0.14, 0.28)	
	Varnish vs placebo	Permanent	DMFS	0.40 (0.09, 0.72)	
	Mouthrinse vs placebo	Permanent	DMFS	0.26 (0.22, 0.29)	
	Gel vs no treatment	Permanent	DMFS	0.38 (0.23, 0.53)	
	Varnish vs no treatment	Permanent	DMFS	0.52 (0.35, 0.69)	
	Mouthrinse vs no treatment	Permanent	DMFS	0.26 (0.23, 0.29)	
	Gel vs placebo	Primary	defs	0.26 (-0.11, 0.63)	See below for further discussion of the results of this study.
Twetman et al (2004)	Mouthrinse vs placebo/no treatment (no background fluoride exposure)	Permanent	DMFS	0.29 (0.14, 0.53)	Results suggest that fluoride mouthrinses may have an anti-caries effect in children with limited exposure to background fluoride, while benefit in children with existing fluoride exposure is unclear. Other populations need further testing.
	Mouthrinse vs placebo/no treatment (no background fluoride exposure)	Permanent	DMFS	0.06	
Twetman et al (2003)	Toothpaste vs placebo/no treatment	Permanent	DMFS/T	0.25	Fluoride found to be more effective than no fluoride. Evidence for use of fluoride in permanent dentition considered to be Level 1 (strong evidence). Authors note that evidence regarding fluoride toothpaste in primary dentition was inconclusive (Level 4).
van Rijkom et al (1998)	Gel vs placebo/no treatment	Primary/ permanent	DMFS	0.20 (0.18, 0.25)	Fluoride found to be more effective than no fluoride. No significant effect on PF for variables 'baseline caries prevalence', 'general fluoride regimen', 'application method' and 'application frequency'.

Citation	Comparison	Type of dentition	Outcome	Prevention fraction (95% CI)	Summary
Fluoride vs fluoride/other					
Marinho et al (2004a)	Varnish vs gel	Permanent	DMFS	0.14 (-0.12, 0.40)	There were no significant differences between any of the comparisons. Varnish was non-significantly more effective than mouthrinse and gel however the result was not robust to sensitivity analysis.
	Varnish vs mouthrinse	Permanent	DMFS	0.10 (-0.12, 0.32)	
	Toothpaste vs gel	Permanent	DMFS	0.00 (-0.21, 0.21)	
	Toothpaste vs mouthrinse	Permanent	DMFS	0.00 (-0.18, 0.19)	
	Gel vs mouthrinse	Permanent	DMFS	-0.14 (-0.40, 0.12)	
	Toothpaste vs other fluoride	Permanent	DMFS	0.01 (-0.13, 0.14)	
Marinho et al (2004b)	Any combination vs single agent	Permanent	DMFS	0.10 (0.02, 0.17)	When analysed together, combinations of topical fluoride agents were significantly more effective than single topical fluoride agents although not all combinations were tested. All combinations were more effective than single agents; however, only 2/7 were statistically significant.
	Toothpaste/mouthrinse vs toothpaste	Permanent	DMFS	0.07 (0.00, 0.13)	
	Toothpaste/gel vs toothpaste	Permanent	DMFS	0.14 (-0.09, 0.38)	
	Toothpaste/varnish vs toothpaste	Permanent	DMFS	0.10 (0.02, 0.17)	
	Mouthrinse/gel vs mouthrinse	Permanent	DMFS	0.02 (-0.20, 0.24)	
	Gel/mouthrinse vs gel	Permanent	DMFS	0.23 (0.04, 0.43)	
	Mouthrinse/toothpaste vs mouthrinse	Permanent	DMFS	0.05 (-0.05, 0.15)	
	Gel/toothpaste vs gel	Permanent	DMFS	0.10 (-0.01, 0.21)	
Petersson et al (2004)	Varnish vs other fluoride	Permanent	DMFS/T	0.18 (0.0, 0.52)	Fluoride varnish was found to be more effective than other types of topical fluoride. Evidence for use of fluoride in permanent dentition considered to be Level 4 (inconclusive). Authors note that evidence regarding fluoride toothpaste in primary dentition and adults was inconclusive (Level 4).
Steiner et al (2004)	Toothpaste 1000 ppm F vs 250 ppm F	Primary/ permanent	DFS/DMFS	0.14 (0.07, 0.21) FEM 0.13 (0.01, 0.23) REM	Caries reduction was greater with the use of 1000 ppm F toothpaste compared with 250 ppm F toothpaste.
Ammari et al (2003)	Toothpaste ≥ 1000 ppm F vs 250 ppm F	Primary/ permanent	-	nr	1000 ppm fluoride found to be more effective than 250 ppm fluoride.
Twetman et al (2003)	Toothpaste 1500 ppm F vs 1000 ppm F	Permanent	DMFS/T	0.10	1500 ppm fluoride found to be more effective than 1000 ppm fluoride. Evidence for use of fluoride in permanent dentition considered to be Level I (strong evidence). Authors note that evidence regarding fluoride toothpaste in primary dentition was inconclusive (Level IV).

[a] This review is a combination of data from four reviews of each individual topical agent; ie, toothpaste, gel, varnish and mouthrinse (Marinho et al, 2003b,c,d,e; Marinho et al, 2002). While these separate reviews are not listed here, any relevant additional information contained within them will be included in the text.

The review by Axelsson et al (2004; fair methodological quality) aimed to examine the effectiveness of combined caries-prevention methods on the development of dental caries. The majority of the combinations examined included some form of topical fluoride. A total of 24 studies were included in the review, with 14 of these relating to the use of combinations in children and adolescents. Based on this body of evidence, which was graded as moderate, the authors conclude that "combinations of treatments involving fluoride have a preventive effect on caries in children and adolescents."

The review by Bader et al (2001; fair methodological quality) aimed to examine the effectiveness of professionally-applied caries preventive methods including fluoride, chlorhexidine, combinations of fluoride and chlorhexidine and a number of other agents. Seven studies were identified which examined fluoride. When compared with placebo/no therapy, the incremental percent reduction in caries score (ie, DMFS/DMFT) ranged from 7 to 30%. Of these, three comparisons were statistically significant: two involved fluoride varnish and one involved fluoride gel. The authors note the limitations of the studies included in their review and state that the strength of the evidence was judged 'fair' for fluoride.

The primary data for this section will be based on the Cochrane reviews by Marinho et al (2003d; 2004a; 2004b). The reviews compared (i) single fluoride agents with placebo/no therapy; (ii) single fluoride agents vs each other; and (iii) combinations of fluoride agents vs single agents.

Single-agent fluoride vs placebo/no therapy

The review by Marinho et al (2003d) compared the use of topical fluoride in the form of toothpaste, mouthrinse, gel or varnish with placebo or no treatment. As noted previously, this review is a combination of a number of other reviews which examined each of the agents individually (Marinho et al, 2003a,b,c; 2002).

The primary objective of the review by Marinho et al (2003d) was to "determine the effectiveness and safety of topical fluoride therapy in the form of toothpastes, mouthrinses, gels and varnishes in preventing dental caries in the child/adolescent population." Secondary objectives included investigation of whether certain predefined factors influenced the examined effect of topical agents on dental caries. Factors examined included: (i) level of caries severity; (ii) background exposure to fluoride; (iii) mode/setting of use; and (iv) type of topical agent used. The primary outcome assessed in the review was DMFS, while DMFT and dmfs were assessed also. Prevention fraction (PF) was chosen as the effect measure. This was calculated by subtracting the change in caries in the treated group from the change in caries in the control group, and dividing by the change of caries in the control group. Potential sources of heterogeneity were investigated using metaregression techniques.

The overall results of the analyses of the primary objective are presented in **Table 28**. These results suggest that topical fluorides are significantly effective at reducing dental caries. In addition, the lack of a significant difference in withdrawals between the intervention and control arms suggests that treatment with topical fluoride agents can be considered acceptable.

Table 28 Topical fluoride: caries prevention fractions and other outcomes for topical fluoride vs placebo/no therapy (Marinho et al, 2003d)

Outcome	No. of studies	No. of participants	Statistical method	Effect size (95% CI)
DMFS[a]	133	65179	PF (REM)	0.26 (0.23, 0.29)
DMFT[a]	79	41391	PF (REM)	0.26 (0.21, 0.30)
dm(e)fs[a]	5	1685	PF (REM)	0.33 (0.22, 0.44)
Developing one or more new caries	13	5297	RR (REM)	0.88 (0.82, 0.95)
Study withdrawals	10	2897	RR (REM)	1.20 (0.85, 1.70)

Abbreviations: dm(e)fs, decayed/missing (extraction indicated)/filled ; DMFS, decayed/missing/filled surfaces in permanent teeth; DMFT, decayed/missing/filled permanent teeth; PF, prevention fraction; REM, random effects method; RR, relative risk.
[a] Nearest to 3 years.

There was substantial heterogeneity in the majority of the analyses so metaregression was used to identify variables that may have an influence on the abovementioned results. Univariate analyses identified the following factors: fluoride type (ie, toothpaste, varnish, gel or mouthrinse); type of control group (placebo or no treatment); mean baseline caries; self-applied supervised vs unsupervised; intensity (frequency x concentration) and frequency of application. The manner in which these factors influence the results is as follows:

- There was a constant relative average increase in PF of 1% as the baseline risk of the study population increased.
- There was a 14% greater caries-inhibiting effect with fluoride varnish compared with gel, toothpaste and mouthrinse. There was no difference between gel, toothpaste and mouthrinse.
- There was a 10% decrease in PF with unsupervised home use of topical fluoride compared with supervised and operator-applied topical fluoride.
- PF was on average 14% greater in studies with no treatment as a control compared with placebo.

Due to the effect of topical fluoride type and control group type on the results, results were analysed in subgroups by type of topical agent (ie, toothpaste, varnish, gel and mouthrinse) and type of control (placebo and no treatment). The results of these analyses are shown in Table 29 and are consistent with the overall results presented above.

Table 29 Summary of results of the Marinho et al (2003d) Cochrane review

Outcome	Comparison	No. of included studies	Heterogeneity	Risk estimate (95% CI) P value
DMFS increment	Fluoride toothpaste vs placebo	70	P<0.001	PF 0.24 (0.21, 0.28) p<0.001
	Fluoride gel vs placebo	13	P=0.07	PF 0.21 (0.14, 0.28) p<0.001
	Fluoride varnish vs placebo	3	P<0.001	PF 0.40 (0.09, 0.72) p=0.01
	Fluoride mouthrinse vs placebo	30	P=0.009	PF 0.26 (0.22, 0.29) p<0.001
	Fluoride gel vs no treatment	9	P<0.001	PF 0.38 (0.23, 0.53) p<0.001

Outcome	Comparison	No. of included studies	Heterogeneity	Risk estimate (95% CI) P value
DMFS increment	Fluoride varnish vs no treatment	4	P=0.07	PF 0.52 (0.35, 0.69) P<0.001
	Fluoride mouthrinse vs no treatment	4	P=0.79	PF 0.33 (0.27, 0.40) p<0.001
	All agents vs placebo/no treatment	133	P<0.001	PF 0.26 (0.23, 0.29) p<0.001
DMFT prevention fraction	Fluoride toothpaste vs placebo	53	P<0.001	PF 0.23 (0.19, 0.28) p<0.001
	Fluoride gel vs placebo	4	P=0.35	PF 0.18 (0.09, 0.27) p<0.001
	Fluoride varnish vs placebo	2	P=0.001	PF 0.49 (0.02, 0.96)\ p=0.04
	Fluoride mouthrinse vs placebo	13	P=0.01	PF 0.24 (0.18, 0.30) p<0.001
	Fluoride gel vs no treatment	6	P<0.001	PF 0.43 (0.29, 0.57) p<0.001
	Fluoride varnish vs no treatment	1	NA	PF 0.60 (0.36, 0.84) p<0.001
	All agents vs placebo/no treatment	79	P<0.001	PF 0.29 (0.21, 0.30) p<0.001
defs prevention fraction	Fluoride gel vs placebo	2	P=0.11	PF 0.26 (-0.11, 0.63) p=0.2
	Fluoride varnish vs placebo	1	NA	PF 0.20 (0.02, 0.38) p=0.03
	Fluoride varnish vs no treatment	2	P=0.64	PF 0.41 (0.26, 0.55) p<0.001
	All agents vs placebo/no treatment	5	P=0.19	PF 0.33 (0.22, 0.44) p<0.001
Developing one or more new caries	All agents vs placebo/no treatment	13	P<0.001	RR 0.88 (0.82, 0.95) p=0.001
Study withdrawal	All agents vs placebo/no treatment	10	P<0.001	RR 1.20 (0.85, 1.70) P=0.3

Based on the results of their analyses, the authors conclude that "the benefits of topical fluorides have been firmly established on a sizeable body of evidence from randomized controlled trials."

Single-agent fluoride vs single-agent fluoride

The primary objective of the review by Marinho et al (2004b) was "to compare the effectiveness of one form of topical fluoride intervention with another when used for the prevention of dental caries in children." Specific objectives included comparison of the following: (i) any two forms of topical fluoride; (ii) professionally-applied topical fluoride varnishes with professionally-applied gels; (iii) fluoride mouthrinses with professionally applied varnishes or gels; and (iv) fluoride toothpastes with any other modality. As for the previously-described Marinho et al (2003c) review, DMFS was the primary outcome and prevention fraction was chosen as the effect measure.

The results of the review are summarised in **Table 30**. There were no statistically significant differences between different topical fluoride agents with regards to efficacy (ie, DMFS) or tolerability (ie, withdrawals).

Table 30 Topical fluoride: caries prevention fraction and other outcomes for single topical fluorides vs each other (Marinho et al, 2004b)

Comparison	Outcome	No. of studies	No. of participants	Statistical method	Effect size (95% CI)
Varnish vs gel	DMFS	1	254	PF (REM)	0.14 (-0.12, 0.40)
Varnish vs mouthrinse	DMFS	4	955	PF (REM)	0.10 (-0.12, 0.32)
Varnish vs mouthrinse	Withdrawals	2	626	RR (REM)	1.18 (0.85, 1.64)
Varnish vs toothpaste	Withdrawals	1	193	RR (REM)	1.28 (0.37, 4.41)
Gel vs mouthrinse	DMFS	1	257	PF (REM)	-0.14 (-0.40, 0.12)
Toothpaste vs gel	DMFS	3	1256	PF (REM)	0.00 (-0.21, 0.21)
Toothpaste vs mouthrinse	DMFS	6	2545	PF (REM)	0.00 (-0.18, 0.19)
Toothpaste vs other	DMFS	9	3801	PF (REM)	0.01 (-0.13, 0.14)
Toothpaste vs mouthrinse	Withdrawals	5	2752	RR (REM)	0.89 (0.78, 1.00)
Toothpaste vs other	Withdrawals	6	2945	RR (REM)	0.88 (0.78, 1.00)

Abbreviations: DMFS, decayed/missing/filled surfaces in permanent teeth; DMFT, decayed/missing/filled permanent teeth; PF, prevention fraction; REM, random effects method; RR, relative risk.

[a] Nearest to 3 years.

Based on the results of the review, the authors note the similar effectiveness of each of the topical agents and in particular that there is no clear evidence that professionally-applied fluoride varnish is more effective than other agents.

Combinations of fluoride agents vs single-agent fluoride

The primary objective of the review by Marinho et al (2004a) was to determine whether the addition of other modalities to fluoride toothpaste is beneficial. Secondary objectives included an evaluation of the addition of each modality to toothpaste separately and an evaluation of all other fluoride combinations. The chosen outcome (DMFS) and effect measure (PF) were the same as those used in the previously described Marinho Cochrane reviews (Marinho et al, 2003d; Marinho et al, 2004a).

The results of the Marinho et al (2004a) review are summarised in **Table 31**. The combination of varnish with toothpaste was significantly more effective than toothpaste alone (based on the result of one study), while the combination of mouthrinse and toothpaste with toothpaste alone showed a non-significant trend in favour of the combination (based on five studies). The only other combination to reach statistical significance was the combination of gel and mouthrinse vs gel alone (two studies). There was no difference in the number of withdrawals from the studies for combination vs single-agents.

Table 31 Topical fluoride: caries prevention fractions and other outcomes for combination topical fluorides vs single agents (Marinho et al, 2004a)

Comparison	Outcome	No. of studies	No. of participants	Statistical method	Effect size (95% CI)
Toothpaste/mouthrinse vs toothpaste alone	DMFS	5	2738	PF (REM)	0.07 (0.00, 0.13)
Toothpaste/gel vs toothpaste alone	DMFS	3	1217	PF (REM)	0.14 (-0.09, 0.38)
Toothpaste/varnish vs toothpaste alone	DMFS	1	71	PF (REM)	0.48 (0.12, 0.84)
Toothpaste/any other vs toothpaste alone	DMFS	9	4026	PF (REM)	0.10 (0.02, 0.17)
Toothpaste/mouthrinse vs toothpaste alone	Withdrawals	3	1704	RR (REM)	1.03 (0.84, 1.26)
Toothpaste/varnish vs toothpaste alone	Withdrawals	2	294	RR (REM)	1.29 (0.61, 2.71)
Toothpaste/any other vs toothpaste alone	Withdrawals	5	1998	RR (REM)	1.06 (0.93, 1.22)
Mouthrinse/gel vs mouthrinse	DMFS	1	252	PF (REM)	0.02 (-0.20, 0.24)
Gel/mouthrinse vs gel	DMFS	2	497	PF (REM)	0.23 (0.04, 0.23)
Mouthrinse/toothpaste vs mouthrinse	DMFS	4	1678	PF (REM)	0.05 (-0.05, 0.15)
Gel/toothpaste vs gel	DMFS	3	759	PF (REM)	0.10 (-001, 0.21)
Gel/mouthrinse vs gel	Withdrawals	1	344	RR (REM)	1.00 (0.72, 1.40)
Mouthrinse/toothpaste vs mouthrinse	Withdrawals	3	1697	RR (REM)	0.88 (0.67, 1.17)
Varnish/toothpaste vs varnish	Withdrawals	1	196	RR (REM)	0.75 (0.22, 2.59)

Abbreviations: dm(e)fs, decayed/missing (extraction indicated)/filled ; DMFS, decayed/missing/filled surfaces in permanent teeth; DMFT, decayed/missing/filled permanent teeth; PF, prevention fraction; REM, random effects method; RR, relative risk.
[a] Nearest to 3 years.

Based on the results of their review, the authors conclude that "topical fluorides…used in addition to fluoride toothpaste achieve a modest reduction in caries compared to toothpaste used alone." As for the other Marinho reviews, no conclusions regarding safety could be reached due to the lack of reporting of such outcomes in the included trials.

5.1.4.3 Additional original studies

The literature search identified 17 RCTs which provided data relevant to the analysis of the prevention of caries with topical fluorides. Studies ranged in duration from 21 months to 5 years and were conducted in a range of countries including Jordan, UK, China, Sweden, Netherlands, Puerto Rico, Guatemala, Hungary and the US. The majority of studies were placebo/no treatment-controlled and 10 studies were open-label, with the subject and/or investigator aware of the treatment allocation. The main characteristics of the included studies are shown in **Table 32**. Detailed assessments of these studies are provided in **Appendix A.1.3**.

Table 32 Caries prevention: topical fluoride (original studies)

Citation NHMRC Level of Evidence Study Quality	Study type/ location	Population	Intervention	Comparator	N	Outcomes presented
Al-Jundi et al (2006) Level II Poor	RCT Open-label 4 years Jordan	School children in the 1st and 6th grades	Oral hygiene instruction + tooth brushing demonstration + tooth brushing with fluoride toothpaste, 5 days, twice a year	Oral hygiene instruction only	856	deft/DMFT

Citation NHMRC Level of Evidence Study Quality	Study type/ location	Population	Intervention	Comparator	N	Outcomes presented
Jackson et al (2005) Level II Fair	Cluster-RCT Open-label 21 months UK	School children aged 5	Supervised tooth brushing with a fluoride toothpaste (1450 ppm)	No supervised tooth brushing	517	dmfs/DMFS Caries increment
Jiang et al (2005) Level II Fair	RCT Open-label 2 years China	School children aged 6-7	Acidulated phosphate fluoride foam (AFP) AFP gel	No AFP foam or gel	661	DMFS
Källestål (2005) Level II Poor	RCT Open-label 5 years Sweden	Children aged 12 attending 26 Swedish public health clinics	1. Tooth-brushing programme: yearly instruction on tooth brushing technique using fluoridated toothpaste 2. Fluoride lozenge programme: 0.25 mg x 3, daily up to 16 and thereafter 0.25 x 4, daily. 3. Fluoride varnish programme: fluoride varnish (Duraphat®) 3 times during 1 week, 6 monthly. 4. Individual programme: counselling and varnish every 3 months	Active treatments only (see intervention)	1134	DMFS
Truin and van't Hof (2005) Level II Good	RCT Double-blind 4 years Netherlands	Children aged 9.5-11.5 who were regular attendees at three paediatric dental clinics	% sodium fluoride gel (4500 ppm)	Placebo gel	594	DMFS Attributable risk Prevention fraction Incident cases

Citation NHMRC Level of Evidence Study Quality	Study type/ location	Population	Intervention	Comparator	N	Outcomes presented
Sköld et al (2005a) Level II Poor	RCT Open-label 3 years Sweden	School children aged 13	Fluoride mouthrinse (10 mL of a 0.2% neutral NaF solution) 1. First 3 schooldays each semester (6 rinses/school year - total 18) 2. First and last 3 schooldays per semester (12 rinses/ school year - total 36) 3. 3 days/month (27 rinses/ school year - total 81) 4. Once a fortnight (20 rinses/school year – total 60)	No fluoride mouthrinse at school	788	Caries prevalence (DFS) Prevention fraction
Sköld et al (2005b) Level II Poor	RCT Open-label 3 years Sweden	School children aged 13	Fluoride varnish 1. Twice a year at 6-month intervals (total – 6 times) 2. Three times a year in one week (total – 9 times) 3. 8 times per year during semesters with 1-month intervals (total – 24 times)	No varnish treatment at school	854	Caries prevalence (DFS) Prevention fraction
Stookey et al (2004) Level II Fair	RCT Double-blind 2 years Puerto Rico	School children aged 9-12	Fluoride toothpaste 1. 500 ppm sodium fluoride (low-NaF) 2. 2800 ppm sodium fluoride (high-NaF) 3. 0.454% stabilised stannous fluoride with sodium hexametaphosphate (1100 ppm; SnF_2-HMP)	Fluoride toothpaste 1100 ppm sodium fluoride	955	DMFS
van Rijkom et al (2004) Level II Fair	RCT Double-blind 4 years Netherlands	Children aged 4.5-6.5 who were regular attendees at three paediatric dental clinics	% sodium fluoride gel (4500 ppm)	Placebo gel	773	DMFS Attributable risk Prevention fraction Incident cases
Biesbrock et al (2003a) Level II Poor	RCT Double-blind 21 months Guatemala	School children ages 9-12	Fluoride toothpaste 1. 0.111% sodium fluoride (500 ppm) 2. 0.320% sodium fluoride (1450 ppm)	Placebo but switched to active treatment after 9 months	657	DMFS

Citation NHMRC Level of Evidence Study Quality	Study type/ location	Population	Intervention	Comparator	N	Outcomes presented
Biesbrock et al (2003b) Level II Poor	RCT Double-blind 21 months Guatemala	School children aged 9-12	Fluoride toothpaste 1. 0.243% sodium fluoride (1100 ppm) 2. 0.619% sodium fluoride (2800 ppm)	Placebo but switched to active treatment after 9 months	644	DMFS
Rong et al (2003) Level II Poor	RCT Open-label 2 years China	Kindergarten children aged 3	Monthly oral health education + twice daily tooth brushing with 1100 ppm fluoridated toothpaste on school days	No oral health education or twice daily supervised tooth brushing	514	dmfs
Davies et al (2002) Level II Fair	RCT Open-label (examiner-blind) 5 years UK	School children aged 1-5.5	Fluoride toothpaste 1. 440 ppm 2. 1450 ppm	No toothpaste	3731	dmfs
Madléna et al (2002) Level II Poor	Cluster-RCT Open-label 2 years Hungary	School children aged 14-16	1. Fluoride toothpaste + fluoride gel 2. Fluoride toothpaste + placebo gel	Usual oral care	586	DMFS/DMFT
You et al (2002) Level II Fair	RCT Open-label (examiner-blind) 2 years China	Preschool children attending 24 kindergarten classes	Fluoride toothpaste 1100 ppm	Placebo toothpaste	1334	dmfs

Citation NHMRC Level of Evidence Study Quality	Study type/ location	Population	Intervention	Comparator	N	Outcomes presented
Biesbrock et al (2001) Level II Fair	RCT Double-blind 3 years US	School children aged 6-15	Fluoride toothpaste 1. 0.243% sodium fluoride (1100 ppm) 2. 0.376% sodium fluoride (1700 ppm) 3. 0.486% sodium fluoride (2200 ppm) 4. 0.619% sodium fluoride (2800 ppm)	No non-fluoride comparator	5439	DMFS DMFT % reduction

The results of the analyses of caries prevention are shown in **Table 33** (caries incidence), **Table 34** (caries prevalence) and **Table 35** (proportion of population caries-free). It should be noted that all included studies presented a completer's analysis, in which only subjects who provided both baseline and follow-up data were included. This has the potential to introduce significant bias into the results; however, in most cases the attrition rate was similar between treatment arms. The proportion of randomised subjects included in the analysis ranged from 57% to 96%. Studies differed in a number of ways: (i) measured caries prevalence either by teeth or surfaces; (ii) assessed different types of tooth surfaces (eg, approximal, smooth, occlusal or pits); (iii) assessed different types of lesions (eg, dentin or enamel); (iv) used different diagnostic methods (ie, clinical vs radiographic); and (v) had caries assessed by multiple examiners. Due to the differences between included studies, pooling of results has not been carried out for this review. Where study results are presented for multiple tooth surfaces or lesion types, the most comprehensive assessment will be shown. In a number of studies, separate results have been presented for all outcome assessors. Where this has occurred, and where results are generally consistent between assessors, only the results of the first assessor will be presented.

Table 33 presents the results of the analyses of caries increment/incidence in the included studies. In most cases, topical fluorides were shown to be more effective at preventing caries than no topical fluorides. There was no clear benefit of any one type of topical agent or regimen over another, while there was mixed evidence as to the benefit of higher doses of fluoridated toothpaste.

Three studies assessed caries prevention in subjects receiving fluoridated toothpaste compared with no fluoridated toothpaste. In addition, one study compared the effectiveness of fluoride toothpaste plus an educational programme with no fluoride toothpaste or educational programme. For all four analyses, fluoridated toothpaste was shown to be effective.

Two studies assessed the use of a fluoride gel with no fluoride gel. Both studies were conducted in children with low caries risk (ie, D3MFS/d3mfs score of 0) and used the same treatment regimen; however, one study was conducted in children aged approximately 5.5 while the other was conducted in children aged approximately 10.5. The study by Rijkom et al (2003), found a significant benefit of fluoride gel over placebo (P=0.03) while the study by Truin and van't Hof (2005) found no difference (P=0.30). The authors note that the children in this study had a fluoride history having regularly attended the dental clinics from the age of 5 or 6. However, they also note that there is evidence that past use of fluoride does not always prevent new caries.

Four studies compared fluoride agents with each other and no fluoride agent. Madléna et al (2002) showed a significant benefit of toothpaste plus gel, and toothpaste alone over no toothpaste or gel when measuring caries per tooth (DMFT), and toothpaste plus gel over no toothpaste or gel when measuring caries per surface (DMFS). Sköld et al (2005a, 2005b) showed that both fluoride varnish and fluoride mouthrinse were more effective at preventing caries than no varnish or mouthrinse. The most effective varnish regimen was treatment 8 times per year (during school terms with one monthly intervals). Jiang et al (2005) compared a combination of fluoride toothpaste and gel with toothpaste alone, and no toothpaste or gel. There was no significant difference between the three regimens.

Four studies have compared various doses of fluoride toothpaste with each other, with mixed results. Three studies showed no difference between lower vs higher doses (ie, 500 ppm vs 1100 ppm, 500 ppm vs 1450 ppm and 1100 ppm vs 2800 ppm), while two studies showed higher doses to be more effective than lower doses (ie, 2200 ppm and 2800 ppm vs 1100 ppm). It should be noted that the possible harms of using higher dose fluoride toothpaste such as increased tooth staining were not assessed in these studies.

Finally, one study assessed the benefits of different fluoridation programmes with each other (Kallestäl et al, 2005). The programmes examined included a toothbrushing programme, a fluoride lozenge programme, a fluoride varnish programme and a programme tailored to the individual. There was no significant difference between any of these programmes.

Table 33 Caries increment/incidence (change in caries score from baseline)

Citation	Age at baseline (years)	Treatment[a]	Follow-up	Outcome	Percent randomised population analysed	Caries increment/ incidence	Comparison (P value)[b]
Placebo/no treatment-controlled trials							
Toothpaste vs no toothpaste							
Al-Jundi et al (2006)	6.3	Toothpaste	4 years	DMFT/deft	Not stated	0.43%	RR 0.32 P = 0.001
	6.3	No toothpaste	4 years	DMFT/deft	Not stated	5.2%	
	11.7	Toothpaste	4 years	DMFT/deft	Not stated	0.59%	RR 0.16 P = 0.001
	11.7	No toothpaste	4 years	DMFT/deft	Not stated	17.6%	
Jackson et al (2005)	5	Toothpaste	21 months	DMFS/dmfs	70%	2.60 (1.84, 3.36)	P = 0.001
	5	No toothpaste	21 months	DMFS/dmfs	73%	2.92 (2.18, 3.66)	
Rong et al (2003)	3	Toothpaste + education	2 years	dmfs	71%	2.47 ± SD 4.09	Difference -1.09 (- 1.91, -0.27)[c] P = 0.009
	3	No toothpaste or education	2 years	dmfs	69%	3.56 ± SD 5.30	
You et al (2002)	3	Toothpaste + education	2 years	dmfs[d]	57%	4.21 ± SE 0.23	Difference 14.4% P = 0.03
	3	No toothpaste or education	2 years	dmfs[d]	68%	4.92 ± SE 0.24	
Gel vs no gel							
Truin and van't Hof (2005)	9.5-11.5	Gel	4 years	D_3MFS	88%	0.94 ± SD 1.57	P = 0.30
	9.5-11.5	Placebo	4 years	D_3MFS	90%	1.18 ± SD 2.17	
Van Rijkom et al (2004)	4.5–6.5	Gel	4 years	D_3MFS/dmfs	96%	0.23 ± SD 0.72	P = 0.03
	4.5–6.5	Placebo	4 years	D_3MFS/dmfs	93%	0.34 ± SD 0.85	

Citation	Age at baseline (years)	Treatment[a]	Follow-up	Outcome	Percent randomised population analysed	Caries increment/ incidence	Comparison (P value)[b]
Active- and placebo/no treatment-controlled trials							
Toothpaste vs other/no toothpaste							
Madléna et al (2002)	14-16	Toothpaste + gel	2 years	DMFT[e]	81%	1.2 ± SD 2.8	37% P < 0.05
	14-16	Toothpaste +placebo	2 years	DMFT[e]	75%	1.2 ± SD 2.7	36% P < 0.05
	14-16	No toothpaste or gel	2 years	DMFT[e]	58%	1.9 ± SD 2.5	-
	14-16	Toothpaste + gel	2 years	DMFS[e]	81%	2.0 ± SD 4.0	34% P < 0.05
	14-16	Toothpaste +placebo	2 years	DMFS[e]	75%	2.7 ± SD 4.7	13% ns
	14-16	No toothpaste or gel	2 years	DMFS[e]	58%	3.0 ± SD 3.9	-
Varnish vs other/no varnish							
Sköld et al (2005b)	13-16	Varnish group 1	3 years	Total	Not stated	0.79 ± SD 1.67	P < 0.001
	13-16	Varnish group 2	3 years	Total	Not stated	0.98 ± SD 2.16	
	13-16	Varnish group 3	3 years	Total	Not stated	0.45 ± SD 1.28	
	13-16	No varnish	3 years	Total	Not stated	1.85 ± SD 2.89	
Mouthrinse vs other/no mouthrinse							
Sköld et al (2005a)	13-16	Mouthrinse group 1	3 years	Total	73%	1.12 ± SD 2.10	P < 0.01
	13-16	Mouthrinse group 2	3 years	Total	82%	0.65 ± SD 1.57	
	13-16	Mouthrinse group 3	3 years	Total	84%	0.84 ± SD 1.62	
	13-16	Mouthrinse group 4	3 years	Total	65%	0.94 ± SD 1.81	
	13-16	No mouthrinse	3 years	Total	100%	1.59 ± SD 2.61	
Gel vs other/ no gel							
Jiang et al (2005)	6-7	AFP foam	2 years	DMFS[f]	93%	0.39 ± SD 0.65	ns
	6-7	AFP gel	2 years	DMFS[f]	95%	0.38 ± SD 0.69	
	6-7	No gel/foam	2 years	DMFS[f]	90%	0.50 ± SD 0.87	

Citation	Age at baseline (years)	Treatment[a]	Follow-up	Outcome	Percent randomised population analysed	Caries increment/ incidence	Comparison (P value)[b]
Active-controlled trials							
Toothpaste							
Biesbrock et al (2003a)	9-12	Toothpaste plac/500 ppm	21 months	DMFS	84%	1.90 ± SE 0.40	-
	9-12	Toothpaste plac/1450 ppm	21 months	DMFS		1.75 ± SE 0.43	7.3%
	9-12	Toothpaste 500 ppm	21 months	DMFS	77%	0.26 ± SE 0.31	86.3% P < 0.05
	9-12	Toothpaste 1450 ppm	21 months	DMFS	83%	0.21 ± SE 0.30	88.9% P < 0.05
Biesbrock et al (2003b)	9-12	Toothpaste plac/1100 ppm	21 months	DMFS	80%	3.05 ± SE 0.38	-
	9-12	Toothpaste plac/2800 ppm	21 months	DMFS		2.52 ± SE 0.38	17.4% ns
	9-12	Toothpaste 1100 ppm	21 months	DMFS	78%	1.47 ± SE 0.27	51.8% P < 0.05
	9-12	Toothpaste 2800 ppm	21 months	DMFS	72%	1.25 ± SEM 0.29	59.0% P < 0.05
Biesbrock et al (2001)	6-15	Toothpaste 1100 ppm	1 year[g]	DMFS[h]	83%	1.71 ± SE 0.10	-
	6-15	Toothpaste 1700 ppm	1 year[g]	DMFS[h]	83%	1.53 ± SE 0.10	ns
	6-15	Toothpaste 2200 ppm	1 year[g]	DMFS[h]	80%	1.37 ± SE 0.10	P < 0.05
	6-15	Toothpaste 2800 ppm	1 year[g]	DMFS[h]	80%	1.41 ± SE 0.10	P < 0.05
Stookey et al (2004)	9-12	Toothpaste 500 ppm (NaF)	2 years	DMFS[i]	84%	6.24 ± SE 0.35	0.4% P = 0.52
	9-12	Toothpaste 1100 ppm (NaF)	2 years	DMFS[i]	85%	6.27 ± SE 0.34	-
	9-12	Toothpaste 2800 ppm (NaF)	2 years	DMFS [i]	89%	5.45 ± SE 0.34	13.0% P = 0.045
	9-12	Toothpaste 1100 ppm (SF)	2 years	DMFS[i]	77%	5.52 ± SE 0.36	11.9% P = 0.065
Various programmes							
Källestål (2005)	12	Toothbrushing programme	5 years	DMFS	82%	4.06 ± SD 4.83	ns[j]
	12	Fluoride lozenge programme	5 years	DMFS		4.21 ± SD 4.38	
	12	Fluoride varnish programme	5 years	DMFS		3.93 ± SD 5.67	
	12	Individual programme	5 years	DMFS		3.64 ± SD 4.04	

Abbreviations: DSa; approximal dentin lesions; DFSa+DeSa, total approximal caries score; NaF, sodium fluoride; nr, not reported; ns, not significant; SF, stannous fluoride; Total, total caries incidence and new enamel lesions.

[a] Represents only the difference between treatment and control arm. For more detail of the treatment regimens used see **Table 32**.

[b] As reported in the study if a comparison of intervention vs control. If presented as control vs intervention in the study, then reciprocal of risk estimate taken.

[c] Presented as difference between control and test (ie, control – test). Presented here as test – control.

[d] Primary examiner analysis. Adjusted mean dmfs increment score from analysis of covariance. Difference in reduction between fluoride and placebo group was 16.1% for secondary examiner.

[e] Excluding white spot lesions.

[f] Results for all surfaces. Results also presented separately for smooth surfaces and pit and fissure surfaces. Statistically significant difference seen for smooth surfaces (p=0.01) but not for pit and fissure surfaces.

[g] Only one year data shown. Following the one year examination a number of included schools participated in a fluoride rinse program which may have confounded the two and three year results.

[h] Observed (raw) means. One year analyses were also adjusted for age, baseline DMFS score, baseline dental age, baseline surfaces at risk and dental age.

[i] Adjusted means from analysis of covariance. Includes terms for gender, treatment group and gender-by-treatment group interaction, and covariates including age, baseline DMFS, baseline dental age, baseline surfaces at risk, and dental age.

[j] Multivariate analysis comparing programmes B, C and D to programme A (toothbrushing programme), showed programme C (varnish programme) to be significantly more effective (RR 0.88; 0.79, 0.97) after adjusting for other factors including demographic variables, earlier preventive programmes, use of sealants, self-administered fluoride, eating sweets and toothbrushing interval.

One study did not provide any data regarding the change in caries score over the course of the study (Davies et al, 2002; **Table 34**). However, as the study was conducted in children aged 12 months at baseline, it is likely that caries prevalence at endpoint approximates the caries incidence over the 5 years of the study. While approximately 30% of subjects did not complete the study, the authors have used data from the control group to impute the mean caries score at endpoint in the missing subjects. Including the imputed data, the results show that the use of fluoridated toothpaste at a concentration of 1450 ppm resulted in a significantly lower caries prevalence compared with no fluoridated toothpaste. When the imputed data was not included, a similar result was seen.

Table 34 Caries prevalence (mean caries score at endpoint)

Citation	Age (years)	Treatment	Follow-up	Outcome	Percent randomised population analysed	Caries score at endpoint	Comparison (P value)
Active- and placebo/no treatment-controlled trials							
Toothpaste vs other/no toothpaste							
Davies et al (2002)	1	Toothpaste 440 ppm	5 years	dmft	68%	2.51 ± SD 3.19[a]	ns
	1	Toothpaste 1450 ppm	5 years	dmft	68%	2.33 ± SD 3.06[a]	P = 0.009
	1	No toothpaste	5 years	dmft	67%	2.60 ± SD 3.20[a]	-

Abbreviations: DeSa; approximal enamel lesions; DFSa+DeSa, total approximal caries score; nr, not reported; ns, not significant;

[a] Includes all children who underwent clinical examination (completers and withdrawals) and imputing mean and SD from control group for children not examined.

Table 35 presents the results of the analysis of percent caries-free population or percent change in caries free population at study endpoint. A caries score = 0 designated a subject was caries-free. In the study by Al-Jundi et al (2006), the percentage of caries-free children in the younger group (mean age 6.3 years) was reduced by only 5% (14.7% to 14.0%) for those who received fluoridated toothpaste compared with 25.9% (12.7% to 9.4%) in those who did not receive fluoridated toothpaste. A similar result was seen in the older group (mean age 11.7 years) with no change in the percent of subjects who were caries free in the fluoridated toothpaste group (43.6%) and a reduction of 22.8% (42.8% to 33.0%) in the group who did not receive fluoridated toothpaste. After controlling for potential confounders including age, gender and the age-gender interaction, the results remained statistically significant (P < 0.001 for both age groups).

In the study by Davies et al (2002) the proportion of caries-free children after 5 years was significantly greater in the 1450 ppm toothpaste group (50%) compared with the 440 ppm toothpaste and no toothpaste groups. This comparison was based only on subjects who completed the study. In a post-hoc analysis conducted for this review, missing subjects were assumed to have developed caries. This resulted in caries-free percentages of 24%, 20% and 24% in the 1450 ppm, 440 ppm and control groups respectively. The lack of a difference between the 1450 ppm and control groups is the result of a lesser withdrawal rate in the control group.

Table 35 Percentage caries free population at endpoint

Citation	Age (years)	Fluoride treatment	Follow-up (years)	Outcome	Percent randomised population analysed	Percent (% change)	Comparison (P value)
Placebo/no treatment-controlled trials							
Toothpaste vs no toothpaste							
Al-Jundi et al (2006)	6.3	Toothpaste	4	DMFT/deft	Not stated	14.0 (–5)	RR 6.1 P < 0.001
	6.3	No toothpaste	4	DMFT/deft	Not stated	9.4 (–25.9)	
	11.7	Toothpaste	4	DMFT	Not stated	43.6 (0)	RR 3.1 P < 0.001
	11.7	No toothpaste	4	DMFT	Not stated	33.0 (–22.8)	
Active- and placebo/no treatment-controlled trials							
Toothpaste vs other/no toothpaste							
Davies et al (2002)	1	Toothpaste 440 ppm	5	dmft	48%	42%	P < 0.01
	1	Toothpaste 1450 ppm	5	dmft	48%	50%	
	1	No toothpaste	5	dmft	56%	42%	

5.2 DENTAL FLUOROSIS

The following section will include an examination of the effect of different forms of fluoride on fluorosis. In addition, it will include a section describing the results of studies which have assessed the impact of various risk factors, and the specific contributions of various fluoride types, on fluorosis. Where possible, fluorosis will be categorised into two groups: 'any fluorosis' and 'fluorosis of aesthetic concern'. Any fluorosis includes very mild and questionable diagnoses which are unlikely to represent any real impact on public health or aesthetic appearance.

The types of evidence considered appropriate to answer the clinical question of whether fluoride causes dental fluorosis varied depending on the nature of the intervention. For topical agents, which are implemented at the individual level, RCTs were considered to be the most appropriate. However, water fluoridation, milk fluoridation and salt fluoridation occur at the population level, and as such lower levels of evidence were allowable, including cohort studies, case-control studies and cross-sectional studies which met specific pre-defined criteria, as noted below.

5.2.1 WATER FLUORIDATION

Summary

Research question: ***Does intentional <u>water fluoridation</u> result in dental fluorosis over and above no intentional water fluoridation?***

There is consistent Level III/IV evidence from existing systematic reviews that water fluoridation results in the development of dental fluorosis. However, the majority of dental fluorosis is mild and is not considered to be of 'aesthetic concern'. The number needed to harm (NNH) with water fluoridation at an optimal level compared with no fluoridation to get one additional person with 'any fluorosis' is approximately 6. The corresponding NNH to get one additional person with 'fluorosis of aesthetic concern' is approximately 22. Meta-analysis of additional original studies provides results consistent with those seen in the existing systematic reviews.

5.2.1.1 Identification of relevant studies

The literature search identified 86 citations related to water fluoridation and fluorosis. From these, two systematic reviews were identified (3 citations). The review by McDonagh et al (2000a) was considered to be the most comprehensive, and as such was chosen to form the basis of this section. Therefore, the search for original studies was conducted for the period 2000-2007 to identify studies not included in the McDonagh review. To be included, studies had to meet similar criteria as that required in the McDonagh review, as well as an additional criterion for this review. The inclusion criteria were: (i) the study had to compare groups with different fluoridation levels and (ii) the different levels of fluoridation had to include at least one low fluoride region (ie, < 0.4 ppm fluoride) and one optimal fluoride region (ie, 0.8 to 1.2 ppm fluoride). Following assessment of the identified citations, 10 cross-sectional original studies were included. No higher level studies (ie, RCTs, cohort studies or case-control studies) were identified. The exclusion of citations for this section is summarised in **Table 36**.

Table 36 Exclusion of citations: dental fluorosis and water fluoridation

Reason for exclusion	Number of citations
Potentially relevant citations	86
Not a clinical study	1
Wrong outcomes	2
Original study published pre-2000	35
No low/optimal fluoride group	27
Duplicate data	6
Wrong outcome measure	1
Article not available	1
Remaining relevant citations	13

5.2.1.2 Systematic reviews

The literature search identified two systematic reviews which examined the effect of water fluoridation on the development of dental fluorosis. A summary of the systematic reviews is presented in **Table 37**. A detailed assessment of these reviews is provided in **Appendix A.2.1**.

Table 37 Systematic reviews of the effect of water fluoridation on dental fluorosis

Citation NHMRC Level of Evidence Study Quality	Number and type of included studies	Intervention	Comparator	Outcomes
Khan et al (2005) Level III/IV Poor	55 (type not reported)	Different categories of water fluoridation (ie, fluoridated, intermediate fluoride levels)	No water fluoridation	Fluorosis measured using any index
McDonagh et al (2000a) Level III/IV Good	88 studies (4 before-after, 1 case-control, 83 single time-point cross-sectional studies)	Water fluoridation	No water fluoridation	Prevalence of fluorosis

The review by Khan et al (2005) aimed to determine trends in the prevalence of fluorosis at different water fluoride levels: ≤ 0.3 ppm (non-fluoridated), 0.3 to ≤ 0.7 ppm (intermediate) and > 0.7 to ≤ 1.4 ppm (fluoridated). A literature search was conducted between 1980 and 2000 and studies were eligible for inclusion if they met the following criteria: included subjects aged 0-19 (population or school samples); lifelong residents of the area, or have spend the first seven years in the area; be in an area with water fluoride up to 1.4 ppm; have a specified sample size; and report on fluorosis using any index. Fifty-five publications were included in the review. After quality assessment, this review was considered to be of poor methodological quality.

The results of the analysis of the included studies are shown in **Table 38**. An increase in the prevalence of fluorosis was seen with increasing water fluoride concentration ($p<0.05$).

Table 38 Fluorosis resulting from water fluoridation (Khan et al, 2005)

Fluoride concentration	No. of publications	Mean percent ± SD
0 to < 0.3 ppm	49	16.7 ± 17.9
>0.3 to < 0.7 ppm	9	27.4 ± 32.2
>0.7 to <1.4 ppm	37	32.2 ± 23.5

One of the aims of the review by McDonagh et al (2000a) was to examine whether water fluoridation has any negative effects. One of the negative effects assessed was dental fluorosis. Studies were considered for inclusion in this review if they considered fluoride within the water supply up to 5 ppm and involved two groups with different water concentrations. The literature search was conducted up until 2000. A total of 88 studies were considered relevant to the review, including four before-and-after studies, one case-control study and 83 single time-point cross-sectional studies. Two levels of dental fluorosis were assessed in the review: (i) 'any fluorosis' as defined by any fluorosis scale; and (ii) 'fluorosis of aesthetic concern', which was defined according to a previous study. In the McDonagh review, 'fluorosis of aesthetic concern' was defined as a score of ≥ 3 on the TF index, a Dean's score of mild or worse, or a TSIF score of ≥ 2.

This review was considered to be of good methodological quality. As the best quality and most comprehensive of the two reviews, the McDonagh et al (2000a) review will form the basis of this section. The results will be divided into two sections: (i) assessing any level of fluorosis ('any fluorosis'; and (ii) assessing levels of fluorosis considered to be of aesthetic concern 'fluorosis of aesthetic concern'.

The results of the analysis of 'any fluorosis' conducted in the McDonagh review are shown in Table 39. These results show a significant relationship between level of water fluoride and fluorosis prevalence, with prevalence increasing with increasing fluoride concentration. Results of the multivariate analysis and univariate analysis were the same. It should be noted that apart from fluoride concentration, two other variables were also shown to be significantly related to fluorosis prevalence: method of assessment (ie, clinical, photograph, both or not stated) and type of teeth (ie, primary, permanent, both or not stated).

Table 39 Water fluoridation: estimated proportion of the population with 'any fluorosis' (McDonagh et al, 2000)

Fluoride level (ppm)	Percent prevalence of fluorosis (95% CI)
0.1	15 (10, 22)
0.2	23 (17, 30)
0.4	33 (26, 41)
0.7	42 (34, 51)
1	48 (40, 57)
1.2	52 (43, 60)
2	61 (51, 69)
4	72 (62, 80)
Univariate analysis	Odds 2.05 (1.75, 2.39)
Multivariate analysis[a]	Odds 2.05 (1.77, 2.38)

a Adjusted for fluorosis index, average age, source of fluoridated water, mean altitude, average temperature, type of teeth, method of assessment, study location, water source, year of study report and study validity score.

Based on the results of the multivariate model, the following predictions were made regarding the prevalence of 'any fluorosis' in the presence of different fluoride levels, different methods of assessment and different tooth types (Table 40).

Table 40 Water fluoridation: prediction of the prevalence of 'any fluorosis' at different fluoride levels, diagnosis methods and tooth types (McDonagh et al, 2000)

Fluoride level	Percent prevalence of fluorosis (95% CI)
0.2 ppm fluoride, identified clinically, both teeth types	2 (0, 11)
0.4 ppm fluoride, identified clinically, both teeth types	3 (1, 17)
0.7 ppm fluoride, identified using photograph, permanent teeth	61 (31, 85)
1.0 ppm fluoride, identified using photograph, permanent teeth	67 (37, 88)
1.0 ppm, identified using both methods of assessment, both teeth types	44 (12, 81)
2.0 ppm fluoride, identified clinically, permanent teeth	54 (45, 62)

A sensitivity analysis was conducted in which fluoride concentration levels of > 1.5 ppm were excluded. This was conducted due to a concern that inclusion of data on the higher levels of fluoride were forcing the regression line to show a relationship that did not exist at lower fluoride levels (that would be more typical of modern fluoridation targets). The results of this analysis are shown in Table 41 and were similar to the result of the primary analysis.

Table 41 Water fluoridation: estimated proportion of the population with 'any fluorosis' excluding > 1.5 ppm fluoride (McDonagh et al, 2000)

Fluoride level	Percent prevalence of fluorosis (95% CI)
0.1	18 (12, 26)
0.2	25 (18, 33)
0.4	33 (26, 41)
0.7	41 (33, 49)
1	46 (37, 55)
1.2	49 (40, 58)
Univariate analysis	Odds 1.80 (1.53, 2.12)

A comparison of fluorosis prevalence at different fluoride levels (0.7, 1.0 and 1.2 ppm) with a reference level of 0.4 ppm was evaluated. These results (shown in Table 42) indicate that approximately six people would need to consume water fluoridated to a level of 1.0 ppm to result in one additional person with fluorosis.

Table 42 Water fluoridation: estimated difference in the proportion of the population with 'any fluorosis' and the NNH in fluoridated water vs low fluoride (McDonagh et al, 2000)

Fluoride level	Difference in proportions (95% CI)	NNH
0.7 ppm vs 0.4 ppm	9.3 (-1.9, 20.6)	11
1.0 ppm vs 0.4 ppm	15.7 (4.1, 27.2)	6
1.2 ppm vs 0.4 ppm	18.9 (7.2, 30.6)	5

The results of the analysis of 'fluorosis of aesthetic concern' conducted in the McDonagh review are shown in Table 43. These results also show a significant relationship between level of water fluoride and fluorosis prevalence. The results of the univariate analysis were similar to that of 'any fluorosis' with an odds ratio of 2.29 (95% CI 1.69, 3.12). In the multivariate analysis, four variables were found to be significantly associated with fluoride prevalence. These included fluoride level, method of assessment (ie, clinical or photographic), method of fluoridation (natural or artificial), and the interaction between fluoride level and method of fluoridation.

Table 43 Water fluoridation: estimated proportion of the population with 'fluorosis of aesthetic concern' (McDonagh et al, 2000)

Fluoride level (ppm)	Percent prevalence of fluorosis (95% CI)
0.1	6.3 (3.2, 12.4)
0.2	6.9 (3.5, 13.1)
0.4	8.2 (4.2, 14.9)
0.7	10.0 (5.0, 17.9)
1	12.5 (7.0, 21.5)
1.2	14.5 (8.2, 24.4)
2	24.7 (14.3, 39.4)
4	63.4 (37.9, 8.3)
Univariate analysis	Odds 2.29 (1.69, 3.12)

[a] Adjusted for fluorosis index, average age, source of fluoridated water, mean altitude, average temperature, type of teeth, method of assessment, study location, water source, year of study report and study validity score.

As was the case with the analysis of 'any fluorosis', a sensitivity analysis was conducted in which levels of >1.5 ppm were excluded. The results of this analysis are shown in **Table 44**. This was similar to the result of the primary analysis.

Table 44 Water fluoridation: estimated proportion of the population with 'fluorosis of aesthetic concern' excluding > 1.5 ppm fluoride (McDonagh et al, 2000)

Fluoride level	Percent prevalence of fluorosis (95% CI)
0.1	6 (2, 14)
0.2	6 (3, 14)
0.4	7 (3, 15)
0.7	9 (4, 17)
1	10 (5, 20)
1.2	12 96, 22)
Univariate analysis	Odds 2.04 (1.16, 3.58)

A comparison of fluorosis prevalence at different fluoride levels (0.7, 1.0 and 1.2 ppm) with a reference level of 0.4 ppm was evaluated. These results (shown in **Table 45**) indicate that an increase in water fluoride level from 0.4 ppm to 1.0 ppm would lead to one additional person with fluorosis of aesthetic concern for every 22 people consuming fluoridated water. However, it should be noted that as the confidence interval includes zero, there is the potential that there is no increased risk.

Table 45 Water fluoridation: estimated difference in the proportion of the population with 'fluorosis of aesthetic concern' and the NNH in fluoridated water vs low fluoride (McDonagh et al, 2000)

Fluoride level	Difference in proportions (95% CI)	NNH
0.7 ppm vs 0.4 ppm	2.0 (-6, 10)	50
1.0 ppm vs 0.4 ppm	4.5 (-4.5, 13.6)	22
1.2 ppm vs 0.4 ppm	6.5 (-3.3, 16.2)	15

5.2.1.3 Additional original studies

The review by McDonagh et al (2000a) will form the basis of this section. For inclusion in the McDonagh review, studies had to compare the prevalence of fluorosis between two populations, with at least one non-fluoridated population and one fluoridated population. This inclusion criterion was applied to this current review, with non-fluoridated water defined as a fluoride concentration of < 0.4 ppm. In order to make the review most relevant to the Australian setting, in which non-fluoridated water has a very low concentrations of fluoride and water is generally artificially fluoridated to a level of approximately 1.0 ppm (depending on climate; cooler areas will have a higher concentration while warmer areas will have lower concentration), an additional criterion was added. Studies could only be included if they included at least one area with sub-optimal fluoridation (ie, ≤ 0.4 ppm) and one area with optimal fluoridation (ie, 0.7 – 1.2 ppm). Ten studies met the inclusion criteria and were included in this section.

The included studies measured fluorosis using the following fluorosis indices: Dean's Index, the Thylstrup and Fejerskov (TF) Index and the Tooth Surface Index of Fluorosis (TSIF). The criteria for scoring these indices can be found in **Table 5**, **Table 6** and **Table 7**.

The results of the included studies will be presented in two parts: (i) an assessment of 'any fluorosis' and (ii) an assessment of 'fluorosis of aesthetic concern'. The definitions of these categories are based on the review by McDonagh et al (2000a). For 'any fluorosis' a Dean's Index score > 0 and a TF score > 0 was included. With regards to 'fluorosis is aesthetic concern', a Dean's score of ≥ 3, a TF score of ≥ 3 and a TSIF score of ≥ 2 were included. McDonagh et al note that the fluorosis indices used by these studies also measure opacities that may not be caused by fluoride, and as such, are likely to provide an overestimate of the true prevalence of fluorosis. For each category, a comparison of fluorosis prevalence in areas with water fluoride levels considered to be optimal (ie, 0.8-1.2 ppm) vs suboptimal (≤0.4 ppm) will be made.

In addition to the data regarding the prevalence of fluorosis, studies which have estimated the risk of fluorosis in the presence of water fluoridation (either unadjusted or adjusted for potential confounders) will be examined. Adjustment for potential confounders is an important issue as there are many factors and other types of agents which can affect the overall amount of fluoride exposure. These will be discussed in detail below.

A summary of the studies included in this section is presented in **Table 46**. A detailed assessment of these studies is provided in **Appendix A.2.1**.

Table 46 Summary of characteristics of included original studies assessing effect of fluoridation on dental fluorosis

Citation NHMRC Level of Evidence Study Quality	Study type/ location	Population	Fluoride levels assessed	Fluoridation type	N	Outcomes presented	Comments
Harding et al (2005) Aetiology/harms Level IV Fair	Cross-sectional study (selected schools) Ireland	School children aged 5	Non-fluoridated vs fluoridated	Natural and artificial		Fluorosis prevalence	Data collected including age, gender medical card, toothbrushing age, toothpaste age, toothbrushing frequency, rinsing after brushing, swallowing toothpaste, breastfeeding, infant formula, tea drinking. Variables used in logistic regression analysis.
Ruan et al (2005) Aetiology/harms Level IV Good	Cross-sectional study (schools selected, all children invited to participate) Shaanxi province, China	School children aged 12-13	0.5 to 5.6 ppm	Natural	477	Fluorosis prevalence Mean TF score	Authors note that the selected schools served communities with comparable socioeconomic standards. Additional data collected included storage of water (ie, whether stored and if stored, whether clay pots were used).
Cochrane et al (2004) Aetiology/harms Level IV Good	Cross-sectional study (towns selected based on convenience; subjects selected from schools) Towns in 7 European countries	School children aged 8	<0.01 to 1.00	Natural and artificial	2046	Fluorosis prevalence Fluorosis risk (fluoridated vs not fluoridated)	Data collected on factors which might cause fluorosis including use of fluoride supplements, history of living in a fluoridated area, age at which toothpaste was first used and the amount and type of toothpaste used. Data used in analyses.
Whelton et al (2004) Aetiology/harms Level IV Fair	Cross-sectional study (cluster sampling of schools) Ireland	School children aged 8, 12 and 15[a]	Non-fluoridated vs fluoridated	Natural and artificial	8553	Fluorosis prevalence	Data collected included possession of medical care (surrogate for disadvantage), details of water supply to current/past residence and use of fluoride supplements. Full fluoridation group had been exposed to home fluoridated water supply continuously since birth and may have been exposed to school fluoridation, fluoride tablets or fluoride mouthrinse. Non-fluoridation group has never had any exposure from home, school or tablets/mouthrinses. Data not used in analyses.

Citation NHMRC Level of Evidence Study Quality	Study type/ location	Population	Fluoride levels assessed	Fluoridation type	N	Outcomes presented	Comments
Hamdan (2003) Aetiology/harms Level IV Poor	Cross-sectional study (cluster sampling of schools)	School children aged 12	~0.35 to 8.24 ppm	Natural	1878	Fluorosis prevalence	No data collected on potential confounders.
Griffin et al (2002) Aetiology/harms Level IV Fair	Analysis of data from National Survey of Oral Health in US School Children US	School children aged 12-14	Low (≤ 0.3 ppm) and optimal (0.7 to 1.2 ppm)	Unknown	1839[b]	Fluorosis prevalence	Included only children who had never been exposed to fluoride drops or tablets. No data on other exposures such as toothpaste or infant formula although authors suggest that they would be likely to be similar between groups.
Louw et al (2002) Aetiology/harms Level IV Poor	Cross-sectional study South Africa	Children aged 11-13 with similar nutrition and dietary habits and ethnic and socioeconomic status	0.19 ppm to 2.64 ppm	Natural	387	Fluorosis prevalence	Children living in low-socioeconomic areas, had been living in region continuously since birth, little dental care or fluoride therapy.
Stephen et al (2002) Aetiology/harms Level IV Good	Cross-sectional study (neighbouring towns chosen on the basis of fluoridation status, no details of how school children selected for participation) Scotland	School children aged 8, 9, 10 and 11-12	Low (0.03 ppm) and optimal (1 ppm)	Natural	317	Fluorosis prevalence	Included 249 children with lifetime exposure no fluoride/no fluoride however only approximately 194 included in fluorosis analysis. Assessed fluorosis using TF index and direct question to students. Additional data collected included supplement and dentifrice use (age and brands) and socioeconomic data.

Citation NHMRC Level of Evidence Study Quality	Study type/ location	Population	Fluoride levels assessed	Fluoridation type	N	Outcomes presented	Comments
Tabari et al (2000) Aetiology/harms Level IV Fair	Cross-sectional study (schools chosen to provide children from a spectrum of socioeconomic background) UK	School children aged 8-9	0.1 ppm and 1.0 ppm	Natural and artificial	812	Fluoride prevalence	Data was collected on the use of fluoride drops and tablets, as well as age at which tooth brushing began, frequency of brushing, type of toothpaste sued and quantity of toothpaste used. Data used in analyses.
Tsutsui et al (2000) Aetiology/harms Level IV Fair	Cross-sectional study (schools) Japan	School children aged 10-12	0.0 to 1.4 ppm	Natural	1060	Fluoride prevalence Fluorosis risk (fluoridated vs not fluoridated)	Data collected included child's residence history, lifetime sources of drinking water, tooth brushing frequency, mother's attitude about reducing frequency of sweets consumption, use of fluoride mouthrinse and history of use of other topical agents. Data not used in analysis.

[a] Study also included 5 year olds however they were not used in the analysis of fluorosis.

[b] Includes a 0.3 to 0.7 category for which results are not presented.

Ten studies provided data on 'any fluorosis' at various levels of water fluoridation. These studies used three of the commonly used fluorosis indices: Dean's index , the TF score and the TSIF score. Data for these studies came from the US, UK, Japan, Jordan, Ireland, Finland, Iceland, Greece, Portugal, China and the Netherlands. The results, presented in **Table 47**, show a general increase of fluorosis prevalence associated with increasing fluoride concentration.

Table 47 Water fluoridation: summary of 'any fluorosis' prevalence in relation to different fluoride levels in original studies

Fluoride level	Location	Number of subjects	Age range	Fluoridation type	Fluorosis index/definition	Percent prevalence (95% CI)
Dean's index						
Whelton et al (2004)						
Non-fluoridated	Ireland	814	8	Natural	Dean's score > 0	10
Non-fluoridated	Ireland	747	12	Natural	Dean's score > 0	18
Non-fluoridated	Ireland	632	15	Natural	Dean's score > 0	19
Fluoridated	Ireland	2208	8	Artificial	Dean's score > 0	23
Fluoridated	Ireland	2090	12	Artificial	Dean's score > 0	28
Fluoridated	Ireland	2062	15	Artificial	Dean's score > 0	39
Griffin et al (2002)						
≤ 0.3	US	609	12-14	Unknown	Dean's score > 0	36
0.7 –1.2	US	968	12-14	Unknown	Dean's score > 0	70
Louw et al (2002)						
0.19	South Africa	37	11-13	Natural	Dean's score > 0	59.5
0.36	South Africa	43	11-13	Natural	Dean's score > 0	90.7
0.48	South Africa	68	11-13	Natural	Dean's score > 0	61.8
1.00	South Africa	74	11-13	Natural	Dean's score > 0	94.6
Tsutsui et al (2000)						
0.0 – 0.2	Japan	412	10-12	Natural	Dean's score > 0	5.3
0.2 – 0.4	Japan	209	10-12	Natural	Dean's score > 0	11.3
0.4 – 0.6	Japan	119	10-12	Natural	Dean's score > 0	15.6
0.6 – 0.8	Japan	128	10-12	Natural	Dean's score > 0	22.6
0.8 – 1.0	Japan	76	10-12	Natural	Dean's score > 0	31.2
1.1 – 1.4	Japan	116	10-12	Natural	Dean's score > 0	41.1
TF score						
Ruan et al (2005)[a]						
0.4	China	95	12-13	Natural	TF score > 0	13.7
1.0	China	116	12-13	Natural	TF score > 0	64.4
Cochran et al (2004)						
<0.01	Finland	315	8	Natural	TF score > 0	82
<0.01	Greece	283	8	Natural	TF score > 0	53
<0.1	England	314	8	Natural	TF score > 0	66
0.05	Iceland	296	8	Natural	TF score > 0	68
0.08	Portugal	210	8	Natural	TF score > 0	51
0.13	Netherlands	303	8	Natural	TF score > 0	80
1.0	Ireland	325	8	Artificial	TF score > 0	89

Fluoride level	Location	Number of subjects	Age range	Fluoridation type	Fluorosis index/definition	Percent prevalence (95% CI)
Hamdan (2003)[a]						
0.3	Jordan	407	12	Natural	TF score > 0	9.1
0.5	Jordan	302	12	Natural	TF score > 0	9.9
0.5	Jordan	299	12	Natural	TF score > 0	11.0
0.5	Jordan	205	12	Natural	TF score > 0	7.6
0.6	Jordan	151	12	Natural	TF score > 0	8.5
0.7	Jordan	153	12	Natural	TF score > 0	28.1
0.7	Jordan	200	12	Natural	TF score > 0	39.0
0.8	Jordan	161	12	Natural	TF score > 0	39.1
Stephen et al (2002)						
0.03	Scotland	139[b]	8-12	Natural	TF score > 0	18
1.0	Scotland	55[b]	8-12	Natural	TF score > 0	33
Tabari et al (2000)						
<0.1	UK	428	8-9	Natural	TF score >0	22.9
1.0	UK	439	8-9	Artificial	TF score >0	54.0
TSIF score						
Harding et al (2005)						
Non-fluoridated	Ireland	121	5	Artificial	TSIF score >0	1.2
Fluoridated	Ireland	208	5	Natural	TSIF score >0	32.2

a Fluoride concentration data or results read off graph.

b Number of subjects included in analysis estimated from percentages provided. Number is substantially lower than number for whom lifetime fluoride data was available (ie, 217).

In some cases there was a substantial difference in the prevalence of ‘any fluorosis’ both between different countries and within different counties. For example, four studies showed levels of fluorosis of approximately 1-15% in low or non-fluoridated areas, and 30-40% in optimally fluoridated areas (Harding et al, 2005; Whelton et al, 2004; Tsutsui et al, 2000; Hamdan, 2003). On the other hand, very high levels of ‘any fluorosis’ were seen in the European countries examined in the Cochran study and in South Africa in the Louw study. In the Cochran study, areas with low fluoride levels (< 0.15 ppm) had a fluorosis prevalence of 50 – 80%, while the region with optimal fluoridation had a prevalence of 89%. In the Louw study, regions with water fluoride levels ranging from 0.19 ppm to 1.0 ppm had levels of any fluorosis of 60% to 95%.

These differences in levels between and within different countries may be a result of a number of factors including methodological factors as well as environmental factors. With regards to methodological factors, the fluorosis indices used require subjective assessment of teeth. It is possible that differences in the way investigators were trained to use the instruments may have impacted on the scoring of levels of fluorosis. In addition, the number and types of teeth examined may have differed between studies. The way in which environmental and lifestyle factors may impact on fluorosis is highlighted in the Hamdan study conducted in Jordan. Hamdan notes that the three regions with the highest prevalence of fluorosis are situated in the south of Jordan which has a higher average temperature than the other regions. While fluoride concentration is not much higher in these regions, water intake is likely to be greater than in the north. Therefore, total exposure may be a relevant consideration, as well as exposure concentration. This is also an issue in the Louw study, conducted in regions of South Africa with high daily temperatures. In addition, Hamdan notes that the presence of phosphate mines in this region of Jordan may result in increased exposure to fluoride via the food chain and air particles, as phosphate rocks contain 2-4% fluorine. While lifestyle factors which may effect the development of fluorosis can include the use of topical and other systemic fluoride agents, these agents are not used in the southern, rural regions of Jordan. However, Hamdan notes that children in the southern rural regions are known to have a higher tea consumption that in other regions which may also result in increased fluoride intake.

It is important to note that very few of the included studies assessed the impact of these potential confounding variables on the relationship between water fluoridation and fluorosis. In the Harding et al (2005), Cochran et al (2004) and Tabari et al (2000) studies (**Table 48**), multiple logistic regression analyses were carried out to determine which of the variables examined in the studies were significantly associated with the development of fluorosis. It should be noted that fluorosis was defined as a TF score ≥ 2 in the Cochran study and ≥ 1 in the Tabari study. In addition, the Tabari study assessed the risk of developing fluorosis defined as a TF score ≥ 2. These three studies found that after adjustment for a number of different potential confounders, water fluoridation to a level considered to be optimal was still associated with an increased risk of developing fluorosis.

In the Harding study, only water fluoridation (OR 38) and starting toothbrushing with toothpaste aged 12-18 months (OR 2.1) were significantly associated with fluorosis prevalence. It should be noted that the very high risk estimate reflects the very low prevalence seen in the non-fluoridated group (1.2%); the prevalence seen in the fluoridated group (32.2%) was similar to that seen in a number of other studies. In the Cochran study, only two of the variables examined were significantly associated with fluorosis: water fluoridation (OR 3.53) and use of fluoride tablets for > 2 years (OR 2.17). In the study by Tabari, three variables were significantly associated with 'any fluorosis': place of residence (ie, fluoridated vs non-fluoridated; OR 4.5), type of toothpaste used (ie, adult fluoridated toothpaste or children's toothpaste; OR 1.6) and Jarman (underprivileged area) score (OR not reported). However, when fluorosis was defined as a TF score ≥ 2, only place of residence remained statistically significant (OR 7.1).

Table 48 Estimates of risk of 'any fluorosis' associated with water fluoridation

Citation	Location	Fluoride range (ppm)	Statistically significant variables	Risk	Additional variable/s included in model
Harding et al (2005)	Ireland	Non-fluoridated to 0.8–1.0 ppm	*Water fluoridation* Fluoridated vs non-fluoridated *Age began toothbrushing with toothpaste* 12-18 months vs older	OR 38 (5, 281) OR 2.1 (1.1, 3.8)	Adjusted odds ratios. No other variables statistically significant.
Cochran et al (2004)	Europe	<0.01 to 1.0	*Water fluoridation* 1.0 ppm vs <0.02 ppm *Fluoride tablets* > 2 years use vs < 2 years use	OR 3.53 (2.52, 4.93)[c] OR 2.17 (1.60, 2.95)[c]	Only water fluoridation and fluoride tablet use entered in model as these were the only variables found to be associated with fluorosis.
Tabari et al (2000)	UK	0.1 to 1.0	*Water fluoridation* 1.0 ppm vs 0.1 ppm *Toothpaste* Adult's vs children's *Jarman score* Higher vs lower	OR 4.5 (3.3, 6.1)[b] OR 7.1 (3.4, 14.7)[c] OR 1.6 (1.06, 2.27)[b] OR > 1[b,d]	Age brushing started, brushing frequency, weight of paste used, type of toothpaste used, area of residence and Jarrman score

a Reciprocal of result presented in article.
b Risk of having TF grade ≥ 1.
c Risk of having TF grade ≥ 2.
d Higher Jarman scores associated with increased fluorosis. Number not reported.

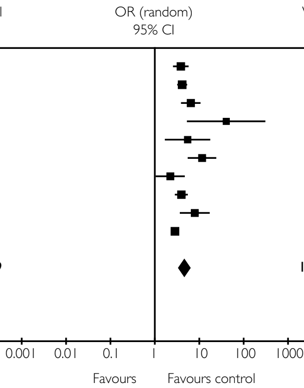
A meta-analysis of the fluorosis prevalence rates found in studies which included the assessment of sub-optimally (ie, ≤ 0.4 ppm fluoride) and optimally fluoridated (ie, 0.8 – 1.2 ppm fluoride) water is presented in **Figure 4**. Three types of effect measure are presented: odds ratio (OR), relative risk (RR) and risk difference (RD). Despite the presence of substantial heterogeneity, the individual study results were consistent, with the RR of developing 'any fluorosis' with optimal fluoridation compared with suboptimal fluoridation all being statistically significant and ranging from 1.31 to 27.7 (pooled RR 2.54; 1.52, 3.56, p<0.001). Therefore, fluoridation to optimal levels is strongly associated with an increased risk in the development of any level of fluorosis. The RD associated with this analysis was 0.26 (0.19, 0.32). This equates to a NNH of 4 (3, 5) people receiving optimal fluoridation to result in one additional person with any level of fluorosis. This is consistent with the results of the McDonagh analysis presented in **Section 5.2.1.2**, in which the NNH with a water fluoride level of 1.0 ppm compared with 0.4 ppm in order to result in one additional person with 'any fluorosis' was 6.

Figure 4 Meta-analysis of the prevalence of 'any fluorosis' in areas with optimal water fluoridation vs sub-optimal water fluoridation

Review: Fluorosis
Comparison: 01 Fluorosis
Outcome: 01 Prevalence of 'any fluorosis'

Study or sub-category	Optimal n/N	Sub-optimal n/N	Weight %	OR (random) 95% CI
Cochran 2004	289/325	1165/1721	13.04	3.83 [2.67, 5.50]
Griffin 2002	677/968	220/609	15.15	4.11 [3.32, 5.10]
Hamdan 2003	63/161	37/407	11.45	6.43 [4.05, 10.21]
Harding 2005	67/208	1/86	1.77	40.39 [5.51, 296.30]
Louw 2002	70/74	61/80	4.49	5.45 [1.76, 16.90]
Ruan 2005	75/116	13/95	8.19	11.54 [5.74, 23.19]
Stephen 2002	18/55	25/139	8.05	2.22 [1.09, 4.51]
Tabari 2000	237/439	98/428	14.07	3.95 [2.95, 5.30]
Tsutsui 2000	24/192	11/621	7.78	7.92 [3.80, 16.50]
Whelton 2004	1879/6360	284/2193	16.01	2.82 [2.46, 3.23]
Total (95% CI)	**8898**	**6379**	**100.00**	**4.61 [3.48, 6.11]**

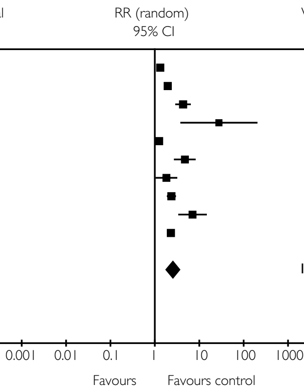
Total events: 3399 (Optimal), 1915 (Sub-optimal)
Test for heterogeneity: Chi² = 43.38, df = 9 (P < 0.00001), I² = 79.3%
Test for overall effect: Z = 10.68 (P < 0.00001)

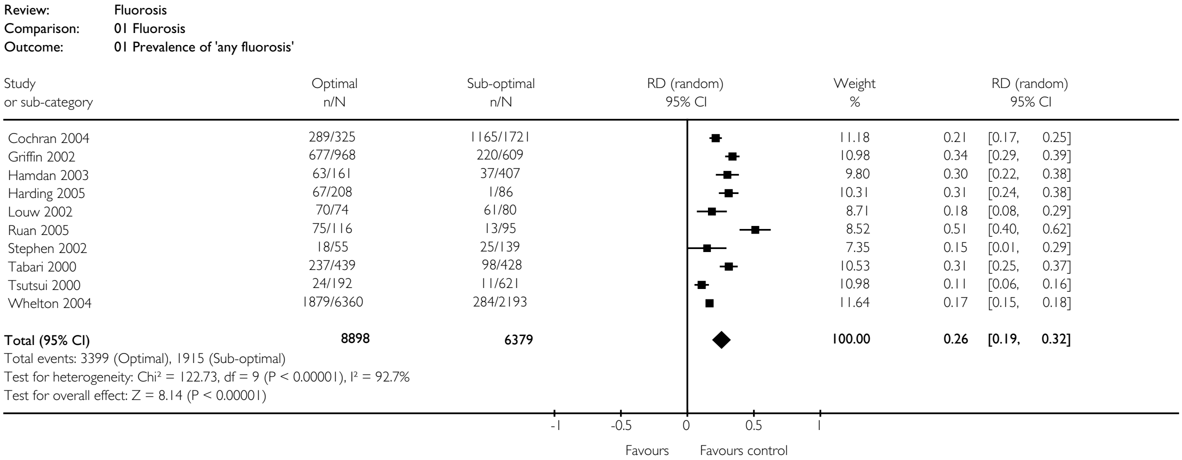


Review: Fluorosis
Comparison: 01 Fluorosis
Outcome: 01 Prevalence of 'any fluorosis'

Study or sub-category	Optimal n/N	Sub-optimal n/N	Weight %	RR (random) 95% CI
Cochran 2004	289/325	1165/1721	12.18	1.31 [1.25, 1.38]
Griffin 2002	677/968	220/609	12.05	1.94 [1.73, 2.17]
Hamdan 2003	63/161	37/407	10.70	4.30 [3.00, 6.19]
Harding 2005	67/208	1/86	2.38	27.70 [3.91, 196.37]
Louw 2002	70/74	61/80	11.98	1.24 [1.09, 1.42]
Ruan 2005	75/116	13/95	9.44	4.72 [2.80, 7.97]
Stephen 2002	18/55	25/139	9.47	1.82 [1.08, 3.06]
Tabari 2000	237/439	98/428	11.74	2.36 [1.94, 2.86]
Tsutsui 2000	24/192	11/621	8.03	7.06 [3.52, 14.14]
Whelton 2004	1879/6360	284/2193	12.04	2.28 [2.03, 2.56]
Total (95% CI)	**8898**	**6379**	**100.00**	**2.54 [1.82, 3.56]**

Total events: 3399 (Optimal), 1915 (Sub-optimal)
Test for heterogeneity: Chi² = 364.61, df = 9 (P < 0.00001), I² = 97.5%
Test for overall effect: Z = 5.44 (P < 0.00001)





In summary, there is a clear increase in the risk of developing 'any fluorosis' associated with water fluoridation. However, it should be noted that this definition includes questionable and very mild fluorosis which may not be considered to be an issue.

Eight studies provided data on 'fluorosis of aesthetic concern' at various levels of water fluoridation. These studies used two of the commonly used fluorosis indices: Dean's index and the TF score. Data for these studies came from the UK, US, Japan, Ireland, Finland, Iceland, Greece, Portugal, China, South Africa and the Netherlands. This data is presented in **Table 49**.

Table 49 Water fluoridation: summary of 'fluorosis of aesthetic concern' prevalence in relation to different fluoride levels in original studies

Fluoride level	Location	Number of subjects	Age range	Fluoridation type	Fluorosis index/ definition	Percent prevalence (95% CI)
Dean's index						
Whelton et al (2004)						
Non-fluoridated	Ireland	814	8	Natural	Dean's ≥ mild	0
Non-fluoridated	Ireland	747	12	Natural	Dean's ≥ mild	2
Non-fluoridated	Ireland	632	15	Natural	Dean's ≥ mild	3
Fluoridated	Ireland	2208	8	Artificial	Dean's ≥ mild	4
Fluoridated	Ireland	2090	12	Artificial	Dean's ≥ mild	7
Fluoridated	Ireland	2062	15	Artificial	Dean's ≥ mild	7
Griffin et al (2002)						
≤ 0.3	US	609	12-14	Unknown	Dean's ≥ mild	0
0.7 to 1.2	US	968	12-14	Unknown	Dean's ≥ mild	7
Louw et al (2002)						
0.19	South Africa	37	11-13	Natural	Dean's ≥ mild	18.9
0.36	South Africa	43	11-13	Natural	Dean's ≥ mild	14.0
0.48	South Africa	68	11-13	Natural	Dean's ≥ mild	16.2
1.00	South Africa	74	11-13	Natural	Dean's ≥ mild	85.1
Tsutsui et al (2000)						
0.0 – 0.2	Japan	412	10-12	Natural	Dean's ≥ mild	0.2
0.2 – 0.4	Japan	209	10-12	Natural	Dean's ≥ mild	0.5
0.4 – 0.6	Japan	119	10-12	Natural	Dean's ≥ mild	0

Fluoride level	Location	Number of subjects	Age range	Fluoridation type	Fluorosis index/ definition	Percent prevalence (95% CI)
0.6 – 0.8	Japan	128	10-12	Natural	Dean's ≥ mild	2.3
0.8 – 1.0	Japan	76	10-12	Natural	Dean's ≥ mild	1.3
1.1 – 1.4	Japan	116	10-12	Natural	Dean's ≥ mild	1.7
TF Index						
Ruan et al (2005)[a]						
0.4	China	95	12-13	Natural	TF score ≥ 3	2.4
1.0	China	116	12-13	Natural	TF score ≥ 3	18.4
Cochran et al (2004)						
<0.01	Finland	315	8	Natural	TF score ≥ 3	0
<0.01	Greece	283	8	Natural	TF score ≥ 3	0
<0.1	England	314	8	Natural	TF score ≥ 3	1
0.05	Iceland	296	8	Natural	TF score ≥ 3	1
0.08	Portugal	210	8	Natural	TF score ≥ 3	1
0.13	Netherlands	303	8	Natural	TF score ≥ 3	4
1.0	Ireland	325	8	Artificial	TF score ≥ 3	4
Stephen et al (2002)						
0.03	Scotland	139[b]	8-12	Natural	TF score ≥ 3	3
1.0	Scotland	55[b]	8-12	Natural	TF score ≥ 3	7
Tabari et al (2000)						
<0.1	UK	428	8-9	Natural	TF score ≥ 3	0.47
1.0	UK	439	8-9	Artificial	TF score ≥ 3	3.42
TSIF Index						
Harding et al (2005)						
Non-fluoridated	Ireland	86	5	Natural	TSIF score ≥2	0
Fluoridated	Ireland	208	5	Artificial	TSIF score ≥2	2.9

As shown in the table above, the prevalence of fluorosis of 'aesthetic concern' was generally very low in areas with optimal fluoridation levels, with levels of less than 10%. Exceptions to this were the Ruan study and Louw studies, where optimal fluoride levels resulted in a prevalence of fluorosis of 'aesthetic concern' of 18.4% and 85.1% respectively. It should be noted that the populations in both studies come from rural regions (in China and South Africa respectively), and that there is little dental care provided in these regions. It should be noted that the study by Louw was conducted in a region of South Africa with high daily temperatures. This is likely to result in increased water consumption, and hence total water consumption, rather than fluoride level itself, may be a factor in the high prevalence of fluorosis seen in this region.

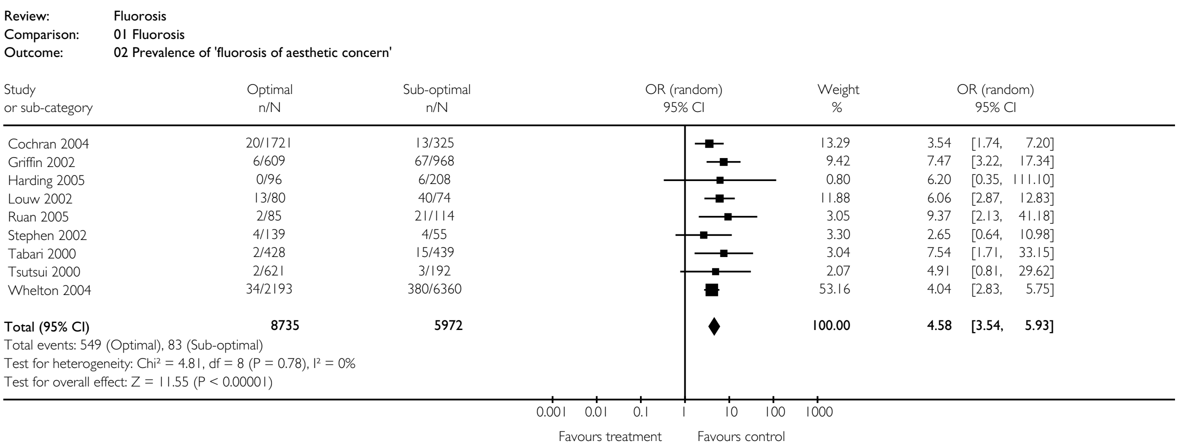
A univariate analysis of a number of potentially relevant variables (water fluoridation, storage of water in clay pots and age) was performed in the study by Ruan et al (2005), as shown in Table 50. In the Ruan study, the storage of water in clay pots resulted in a significantly increased risk of 'fluorosis of aesthetic concern' (OR 4.7; 2.4, 9.0). Mean TF scores associated with optimal and suboptimal fluoridation were 1.40 (1.15, 1.65) and 0.30 (0.02, 0.57) respectively. When the analysis was limited to children living in an optimally fluoridated region who had not used clay pots (82% of children), the mean TF score was 1.13 (0.86, 1.40). When the analysis was limited to children living in a sub-optimally fluoridated region who had not used clay pots (31% of children), the mean TF score was 0.14 (0.09, 0.37).

Table 50 Estimates of risk of 'fluorosis of aesthetic concern' associated with water fluoridation

Citation	Location	Fluoride range (ppm)	Statistically significant variables	Risk	Additional variable/s included in model
Ruan et al (2005)	China	0.04 to 5.6	Water fluoridation		Univariate analyses
			1.0 ppm v 0.4 ppm	OR 23.3 (5.0, 19.5)	
			Storage of water		
			Clay pots vs no clay pots	OR 4.7 (2.4, 9.0)	
			Age		
			13 year-olds vs 12 year-olds	OR 2.3 (1.3, 4.2)	

A meta-analysis of the prevalence of 'fluorosis of aesthetic concern' found in studies which included the assessment of sub-optimally (ie, ≤ 0.4 ppm fluoride) and optimally fluoridated (ie, 0.8 – 1.2 ppm fluoride) water is presented in **Figure 5**. Three types of effect measure are presented: OR, RR and RD. There was less heterogeneity associated with this analysis compared with the previous meta-analysis of 'any fluorosis', with only the analysis of RD showing statistically significant heterogeneity. Once again, the RR of developing 'fluorosis of aesthetic concern' with optimal fluoridation compared with suboptimal fluoridation was statistically significant (RR 4.01; 3.15, 5.10, p<0.001). Therefore, fluoridation to optimal levels is strongly associated with an increased risk in the development of 'fluorosis of aesthetic concern'. However, the risk difference (RD) associated with this analysis was small (RD 0.05; 0.03, 0.07). This equates to a NNH of 20 (14, 33) people receiving optimal fluoridation to result in one additional person with any level of fluorosis. This is consistent with the results of the McDonagh analysis, in which the NNH with a water fluoride level of 1.0 ppm compared with 0.4 ppm in order to result in one additional person with 'fluorosis of aesthetic concern' was 22. Due to the higher than average levels of fluorosis seen in the Ruan and Louw studies, sensitivity analyses excluding these studies were conducted. Exclusion of the Louw study only, and the Louw and Ruan studies, resulted in a RD of 0.04 (0.02, 0.05), which slightly increased the NNH to 25 (20, 50).

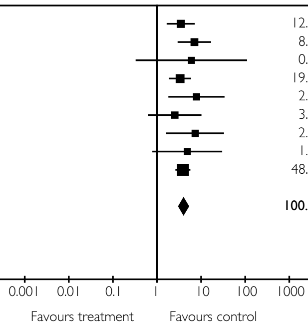
Figure 5 Meta-analysis of the prevalence of 'fluorosis of aesthetic concern' in areas with optimal water fluoridation vs sub-optimal water fluoridation



Review: Fluorosis
Comparison: 01 Fluorosis
Outcome: 02 Prevalence of 'fluorosis of aesthetic concern'

Study or sub-category	Optimal n/N	Sub-optimal n/N	Weight %	RR (random) 95% CI
Cochran 2004	20/1721	13/325	12.26	3.44 [1.73, 6.85]
Griffin 2002	6/609	67/968	8.45	7.03 [3.07, 16.10]
Harding 2005	0/96	6/208	0.71	6.03 [0.34, 106.02]
Louw 2002	13/80	40/74	19.91	3.33 [1.94, 5.71]
Ruan 2005	2/85	21/114	2.87	7.83 [1.89, 32.48]
Stephen 2002	4/139	4/55	3.18	2.53 [0.65, 9.75]
Tabari 2000	2/428	15/439	2.69	7.31 [1.68, 31.78]
Tsutsui 2000	2/621	3/192	1.83	4.85 [0.82, 28.82]
Whelton 2004	34/2193	380/6360	48.10	3.85 [2.72, 5.45]
Total (95% CI)	**8735**	**5972**	**100.00**	**4.01 [3.15, 5.10]**

Total events: 549 (Optimal), 83 (Sub-optimal)
Test for heterogeneity: Chi² = 4.67, df = 8 (P = 0.79), I² = 0%
Test for overall effect: Z = 11.29 (P < 0.00001)



Review: Fluorosis
Comparison: 01 Fluorosis
Outcome: 02 Prevalence of 'fluorosis of aesthetic concern'

Study or sub-category	Optimal n/N	Sub-optimal n/N	Weight %	RD (random) 95% CI
Cochran 2004	20/1721	13/325	14.09	0.03 [0.01, 0.05]
Griffin 2002	6/609	67/968	14.90	0.06 [0.04, 0.08]
Harding 2005	0/96	6/208	12.89	0.03 [0.00, 0.06]
Louw 2002	13/80	40/74	1.92	0.38 [0.24, 0.52]
Ruan 2005	2/85	21/114	4.89	0.16 [0.08, 0.24]
Stephen 2002	4/139	4/55	5.26	0.04 [-0.03, 0.12]
Tabari 2000	2/428	15/439	14.83	0.03 [0.01, 0.05]
Tsutsui 2000	2/621	3/192	14.84	0.01 [-0.01, 0.03]
Whelton 2004	34/2193	380/6360	16.39	0.04 [0.04, 0.05]
Total (95% CI)	**8735**	**5972**	**100.00**	**0.05 [0.03, 0.07]**

Total events: 549 (Optimal), 83 (Sub-optimal)
Test for heterogeneity: Chi² = 55.96, df = 8 (P < 0.00001), I² = 85.7%
Test for overall effect: Z = 4.53 (P < 0.00001)

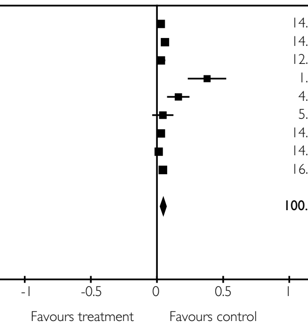
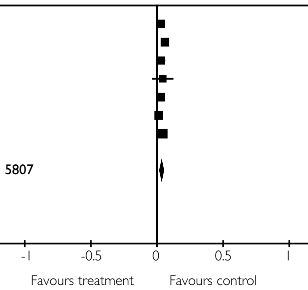


Figure 6 Sensitivity analysis of the RD estimate 'any fluorosis' in areas with optimal water fluoridation vs sub-optimal water fluoridation

Review: Fluorosis
Comparison: 01 Fluorosis
Outcome: 02 Prevalence of 'fluorosis of aesthetic concern'

Study or sub-category	Optimal n/N	Sub-optimal n/N	Weight %	RD (random) 95% CI
Cochran 2004	13/325	20/1721	14.17	0.03 [0.01, 0.05]
Griffin 2002	67/968	6/609	16.56	0.06 [0.04, 0.08]
Harding 2005	6/208	0/96	11.36	0.03 [0.00, 0.06]
Stephen 2002	4/55	4/139	2.60	0.04 [-0.03, 0.12]
Tabari 2000	15/439	2/428	16.33	0.03 [0.01, 0.05]
Tsutsui 2000	3/192	2/621	16.38	0.01 [-0.01, 0.03]
Whelton 2004	380/6360	34/2193	22.59	0.04 [0.04, 0.05]
Total (95% CI)	**8547**	**5807**	**100.00**	**0.04 [0.02, 0.05]**

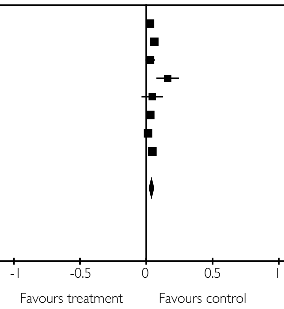
Total events: 488 (Optimal), 68 (Sub-optimal)
Test for heterogeneity: Chi² = 18.13, df = 6 (P = 0.006), I² = 66.9%
Test for overall effect: Z = 5.46 (P < 0.00001)



Review: Fluorosis
Comparison: 01 Fluorosis
Outcome: 02 Prevalence of 'fluorosis of aesthetic concern'

Study or sub-category	Optimal n/N	Sub-optimal n/N	Weight %	RD (random)	RD (random) 95% CI
Cochran 2004	13/325	20/1721	14.30	0.03	[0.01, 0.05]
Griffin 2002	67/968	6/609	15.92	0.06	[0.04, 0.08]
Harding 2005	6/208	0/96	12.19	0.03	[0.00, 0.06]
Ruan 2005	21/114	2/85	3.16	0.16	[0.08, 0.24]
Stephen 2002	4/55	4/139	3.46	0.04	[-0.03, 0.12]
Tabari 2000	15/439	2/428	15.77	0.03	[0.01, 0.05]
Tsutsui 2000	3/192	2/621	15.81	0.01	[-0.01, 0.03]
Whelton 2004	380/6360	34/2193	19.39	0.04	[0.04, 0.05]
Total (95% CI)	**8661**	**5892**	**100.00**	**0.04**	**[0.02, 0.05]**

Total events: 509 (Optimal), 70 (Sub-optimal)
Test for heterogeneity: Chi² = 28.32, df = 7 (P = 0.0002), I² = 75.3%
Test for overall effect: Z = 5.03 (P < 0.00001)



In summary, while there is a four-fold risk of developing 'fluorosis of aesthetic concern' with optimal water fluoridation compared with suboptimal water fluoridation, the absolute increase in prevalence is small, increasing by approximately 4-5%.

5.2.2 MILK FLUORIDATION

Summary

Research question: ***Does intentional milk fluoridation result in dental fluorosis over and above no intentional milk fluoridation?***

One study provided Level IV evidence that milk fluoridation is not associated with significant levels of fluorosis. A statistically significant increase in fluorosis was seen in a number of age groups following the introduction of milk fluoridation; however, the majority of this fluorosis was mild and would not be considered to be of aesthetic concern.

5.2.2.1 Identification of relevant studies

Only one citation related to the effect of milk fluoridation on dental fluorosis was identified by the literature search and this was included in the review.

5.2.2.2 Systematic reviews

No systematic reviews were identified which assessed the association between milk fluoridation and fluorosis.

5.2.2.3 Additional original studies

One study was identified which provided evidence regarding the development of fluorosis following participation in a milk fluoridation programme. This study was a multiple time-point cross-sectional study (Level IV, poor methodological quality; see **Appendix A.2.2**). This study, by Mariño et al (2003) was conducted in two communities in Chile: one which received fluoridated milk between 1995 and 1999 (Codegua) and one which received no fluoridated milk (La Punta). Four age cohorts were examined at both 1994 (pre-fluoridation) and 2002 (3 years post-fluoridation). The timeframe of the study ensured that children in all cohorts received fluoridated milk during the period considered critical for the development of fluorosis (ie, 22 ± 4 months).

The results of the study are summarised in **Table 51**. It should be noted that the results shown below refer to 'any fluorosis', in this case defined as a score > 0 on Dean's Index (ie, includes the categories questionable, very mild, mild, moderate and severe). The difference in fluorosis prevalence from 1994 to 2002 was not statistically significant for any age cohort, or all age cohorts combined in the control community La Punta. In 6 and 7 year olds, prevalence of fluorosis decreased between 1994 and 2002, while only small increases were seen in 8 and 9 year olds. On the other hand, in Codegua, larger increases in fluorosis prevalence were seen in 6 and 9 year olds (from 9.4% to 19.6% and from 11.5% to 44.2% respectively); the increase in 9 year olds was highly statistically significant ($p<0.001$). In the combined age cohort, this resulted in an increase of fluorosis prevalence of 109% in the combined 6-9 year age cohort.

Data regarding the severity of fluorosis showed that very few subjects had ‘fluorosis of aesthetic concern’ (ie, Dean’s score ≥ mild). Based on data provided in graphical form, it appears that there was <1% of subjects with mild fluorosis in 1994 and approximately 2% with mild fluorosis and < 1% with moderate fluorosis in 2002 in Codegua. In La Punta there were no subjects with ≥ mild fluorosis in 1994 and < 1% subjects with mild fluorosis in 2002.

The results of this study suggest that milk fluoridation is not associated with significant levels of fluorosis.

Table 51 Milk fluoridation: fluorosis (Mariño et al, 2003)

Age	Year	Outcome	Codegua Fluoridated 1995 Ceased fluoridation 1999		La Punta Never fluoridated	
			Fluorosis prevalence	P value	Fluorosis prevalence	P value
6	1994	Any fluorosis	9.4%	ns	25.0	ns
6	2002		19.6%		19.6	
7	1994	Any fluorosis	8.7%	ns	19.2	ns
7	2002		12.3%		17.0	
8	1994	Any fluorosis	17.0%	ns	21.4	ns
8	2002		22.2%		30.0	
9	1994	Any fluorosis	11.5%	<0.001	26.8	ns
9	2002		44.2%		37.3	
6-9	1994	Any fluorosis	11.6%	0.01	23.6	ns
6-9	2002		24.3%		25.9	

5.2.3 SALT FLUORIDATION

Summary

Research question: ***Does intentional salt fluoridation result in dental fluorosis over and above no intentional salt fluoridation?***

One level IV study provided evidence of a significantly increased risk of ‘any fluorosis’ associated with salt fluoridation. Two additional supportive studies which did not strictly meet the inclusion criteria were in agreement with the included study. There was no data relating to the risk of ‘fluorosis of aesthetic concern’.

5.2.3.1 Identification of relevant studies

Three citations related to the effect of milk fluoridation on dental fluorosis were identified by the literature search and all three were included in the review.

5.2.3.2 Systematic reviews

No systematic reviews of the effect of salt fluoridation on dental fluorosis were identified by the literature search.

5.2.3.3 Additional original studies

Three relevant studies were identified via the literature. Only one of three studies strictly met the criteria for this review (Stephen et al, 1999). However, the additional two studies provide useful information and as such, they are not formally included in the review and are briefly described only (Vallejos-Sánchez et al, 2006; Estupiñán-Day et al, 2001).

The study by Stephen et al (1999) was a cross-sectional study which assessed fluorosis in children who had or had not resided in a region with fluoridated salt (see **Appendix A.2.3**). Three out of 40 subjects (6%) in the fluoridated group and two out of 59 subjects (3%) in the control group had ‘any fluorosis’, as measured by the TF and TSIF scales. No subjects in the test or control groups had fluorosis of ‘aesthetic concern’ as measured by the TF scale, while two out of 40 subjects (0.05%) in the test group and no subjects in the control group had fluorosis not considered to be of ‘aesthetic concern’.

The two additional studies were cross-sectional in design, and measured fluorosis in a single location prior to, and following, the introduction of salt fluoridation. As these studies do not strictly meet the inclusion criteria for this review (ie, they do not compare one region with salt fluoridation compared with another region without), The study by Vallejos-Sánchez et al (2006) aimed to assess the risk of developing fluorosis in cohorts of children before, during and after the introduction of a national salt fluoridation program in Mexico in 1991. Cohorts were ordered chronologically (date of birth ranged from 1986 to 1992) and the relationship between birth year and the time of the introduction of fluoridated salt was examined. The seven included cohorts were examined in 1998. Fluorosis prevalence in the cohorts ranged from 38.4% in the 1986 cohort to 86.7% in the 1992 cohort. The results showed that with increasing exposure to salt fluoridation over time, the risk of developing fluorosis increased, with a statistically significant increase in risk seen in cohorts born in 1990, 1991 and 1992 (OR 1.76, 4.00 and 10.47 respectively) when compared with the earliest born cohort. A multivariate analysis was conducted which included year of birth, tooth brushing frequency, additional fluoride sources, beginning of toothpaste use, mother’s schooling and main fluoride source. After adjustment for these variables, the year of birth remained a significant risk factor for the development of fluorosis (ie, cohorts born around the time of, or after, the introduction of salt fluoridation, had a significantly increased risk of developing dental fluorosis. It should be noted that in this study, fluorosis was defined as a Dean’s score > 0 (ie, ‘any fluorosis’ and as such is likely to be an overestimate of the true prevalence of fluorosis.

The study by Estupiñán-Day et al (2001) was a cross-sectional study conducted in Jamaica, in which the prevalence of fluorosis following the introduction of salt fluoridation was compared with the prevalence of fluorosis prior to salt fluoridation. The study shows that in 1995 the prevalence of ‘any fluorosis’ (as measured by a Dean’s score > 0 was 4.2% (29/695). Fluorosis as measured by a score of > 1 was 0.7%. While previous data collected in 1984 is not presented, the authors note in the abstract that in 1984, 23 subjects were scored as having very mild/mild fluorosis (ie, Dean’s score > 1). This equates to a prevalence of 1.9%. Therefore, the authors state that fluorosis remained at negligible levels after the introduction of salt fluoridation.

5.2.4 TOPICAL FLUORIDE

Summary

Research question: *Does topical fluoride supplementation result in dental fluorosis over and above no topical fluoride supplementation?*

Research question: *Does a combination of topical fluoride supplementation products result in dental fluorosis over and above a single topical fluoride supplementation product?*

Two level IV studies provide evidence regarding the impact of the use of topical fluorides on dental fluorosis. One study showed that fluoridated toothpaste may be associated with 'any fluorosis'. However, when 'fluorosis of aesthetic concern' was examined, no statistically significant difference between the higher fluoride dose group and the control group was found, and the prevalence of fluorosis in the higher dose toothpaste group was low (< 2%). One poor quality study in which fluorosis was measured after a campaign was implemented to reduce the amount of topical fluoride use in children suggested that a decrease in fluorosis was seen.

5.2.4.1 Identification of relevant studies

The literatures search identified seven potentially relevant citations assessing salt fluoridation and fluorosis. Of these, two were included in the review. The exclusion of citations for this section is summarised in **Table 52**. One of these represented a reanalysis of RCT data, while the other was a cross-sectional study.

Table 52 Exclusion of citations: dental fluorosis topical fluorides

Reason for exclusion	Number of citations
Potentially relevant citations	7
Wrong outcomes	1
No/wrong comparator	1
Duplicate data	2
Article not available	1
Remaining relevant citations	2

5.2.4.2 Systematic reviews

No systematic reviews of the effect of topical fluorides on dental fluorosis were identified by the literature search.

5.2.4.3 Additional original studies

Two studies were identified which provided information relevant to this section. These included (i) an analysis of RCT data in which fluorosis was assessed in subjects receiving two doses of fluoridated toothpaste compared with no fluoridated toothpaste (Tavener et al, 2004; Level II, poor methodological quality); and (ii) an analysis of the decrease in fluorosis following a campaign to discourage use of fluoride supplements and encourage the use of low fluoride toothpaste in children aged < 6 years (Riordan et al, 2002). A detailed assessment of these studies is provided in **Appendix A.2.4**.

The results of the Tavener et al (2004) study are summarised in **Table 53**. The results for 'any fluorosis' were similar between treatment groups, whether teeth were wet or dry when examined, as this may influence the detection of fluorosis. There was a significant difference between the three treatment arms for 'fluorosis of aesthetic concern' for both wet and dry examinations (p=0.03 and p<0.01 respectively), although the prevalence in the 1450 ppm toothpaste group was low (1.4% and 1.8% respectively). However, when the 1450 ppm arm was compared only to the control arm there was no statistically significant difference (p>0.05).

Table 53 'Any fluorosis': topical fluoride (Tavener et al, 2004)

Fluoride level	Location	Number of subjects	Age range	Measurement type	Fluorosis index/ definition	Percent prevalence (95% CI)
'Any fluorosis'						
1450 ppm	UK	218	8-9	Wet	TF score > 0	17.4
440 ppm	UK	226	8-9	Wet	TF score > 0	15.0
No fluoride	UK	259	8-9	Wet	TF score > 0	12.4
1450 ppm	UK	218	8-9	Dry	TF score > 0	25.7
440 ppm	UK	226	8-9	Dry	TF score > 0	24.3
No fluoride	UK	259	8-9	Dry	TF score > 0	25.0
'Fluorosis of aesthetic concern'						
1450 ppm	UK	218	8-9	Wet	TF score ≥ 3	1.4
440 ppm	UK	226	8-9	Wet	TF score ≥ 3	0
No fluoride	UK	259	8-9	Wet	TF score ≥ 3	0
1450 ppm	UK	218	8-9	Dry	TF score ≥ 3	1.8
440 ppm	UK	226	8-9	Dry	TF score ≥ 3	0
No fluoride	UK	259	8-9	Dry	TF score ≥ 3	0

In an earlier study, Riordan and Banks (1991) had shown that fluorosis prevalence (defined as a TF score > 0) was 40.2% in Perth and 33.0% in Bunbury. The concentration of fluoride in the water supply in these regions was 0.8 ppm and ~0.25 ppm respectively. Following this the School Dental Services in Western Australia recommended the cessation of fluoride supplementation, and produced a new dosage schedule for use in children < 8 years. In addition, new recommendations were made regarding the use of low fluoride toothpastes in children < 6. A follow-up assessment of fluorosis was carried out in children in Perth and Bunbury in 2000. The results showed that there had been a significant decrease in the use of fluoride supplements between 1989/1990 and 2000 ($p<0.001$) and that low fluoride toothpaste which had been unavailable in 1989/1990 was used by 24.5% of subjects in 2000. In 2000, fluorosis prevalence was 22.0% in Perth and 10.8% in Bunbury.

5.2.5 ADDITIONAL STUDIES ASSESSING THE RISK FACTORS ASSOCIATED WITH DEVELOPMENT OF FLUOROSIS

The literature search identified five studies which did not strictly meet the inclusion criteria for this review but which were useful as supportive evidence. While they are not formally included in the review, they are described briefly here. They were not included in any of the previous sections, as they did not specifically aim to assess any one particular type of fluoride exposure. These studies did not assess any particular type of fluoride intervention but rather assessed the impact of various fluoride types and other related factors on the development of fluorosis. Four studies were cross-sectional and one was a case-control. The characteristics and results of these studies are summarised in **Table 54**.

Four studies carried out multivariate analyses in which results were adjusted for different types of fluoride exposures and/or demographic characteristics (Conway et al, 2005; Bottenberg et al, 2004; Kumar et al, 2000; Mascarenhas et al, 1998; Wang et al, 1997). The results of these studies were mostly consistent with three of the four studies showing a statistically significantly increased risk of fluorosis associated with use of fluoride. In the case of the study by Kumar et al (2000), all types and combinations of fluoride used resulted in an increased fluoride risk compared with no fluoride. Odds ratios ranged from 1.7 for early toothbrushing to 3.1 for fluoride supplements combined with early toothbrushing. Water fluoridation alone and water fluoridation plus early brushing or supplements resulted in odds ratios of 2.2 and 2.8 respectively. In the study by Mascarenhas et al (1998), the use of fluoride toothpaste resulted in an increased risk of fluorosis after adjustment for other variables (OR 1.94; 1.07, 3.35). Wang et al (1997) showed that in a selected group of 8-year old children in Norway, the development of any fluorosis was significantly associated with the use of fluoridated toothpaste before 14 months and regular fluoride supplement use for greater than one year. On the other hand, the results of the Conway study conducted in Sweden showed that water fluoridation, higher concentration of toothpaste and use fluoride tablets were not associated with an increased risk of fluorosis.

The remaining study by Bottenberg et al (2004) conducted only univariate analyses of the effect of different risk factors on fluorosis. Variables significantly associated with fluorosis included toothbrushing frequency (2 or more times a day vs < 2 times a day), use of systemic fluoride supplements (ever vs never), use of fluoride supplements taken in milk (vs not in milk) and water fluoride concentration (> 0.7 ppm vs < 0.3 ppm and > 0.7 ppm vs 0.3 ppm to 0.7 ppm).

It should be noted that all of these studies assessed the risk of 'any fluorosis', including fluorosis that is unlikely to be of aesthetic concern.

Table 54 Fluorosis: assessment of various risk factors

Citation	Study type/ location	Subjects	Outcome	Relevant variables examined	Risk estimate	P value
Conway et al (2005)	Cross-sectional Sweden	Cluster sample of 7 to 9-year olds via random selection of 13 schools from a total of 31 in the region N=1039 (analysis carried out on 413 children with complete data)	TF score > 0	Univariate analyses Water fluoride: yes Concentration of toothpaste: ≥ 1000 ppm Fluoride tablets: yes Multivariate analyses Water fluoride: yes Concentration of toothpaste: ≥ 1000 ppm Fluoride tablets: yes Note: other variables examined included age, sex, Swedish birth, SES, education, amount of toothpaste, brushing frequency, age brushing began. Only education significant in the univariate analyses, and none significant in the multivariate analyses.	OR (95% CI) 0.67 (0.16, 2.82) 1.01 (0.50, 2.03) 1.29 (0.82, 2.02) nr 1.19 (0.57, 2.47) 1.40 (0.87, 2.23)	 0.58 0.99 0.27 nr 0.64 0.16

Citation	Study type/ location	Subjects	Outcome	Relevant variables examined	Risk estimate	P value
Bottenberg et al (2004)	Cross-sectional Belgium	Cohort of schoolchildren born in 1989 from Department of Education data. N=5071 (analysis carried out on ~4000 7 and 11 year-olds in 1996 and 2000 respectively)	TF score > 0	Univariate analyses Fluoride toothpaste: never use vs continuous use Fluoride-reduced toothpaste: never use vs continuous use Systemic fluoride supplements: ever vs never Systemic fluoride supplements: not in milk vs in milk Water fluoride: < 0.3 ppm vs >0.7 ppm Note: other variables examined included sex, medical history and toothbrushing habits	OR (95% CI) 0.90 (0.58, 1.42) 0.88 (0.58, 1.32) 1.31 (1.03, 2.68) 1.69 (1.03, 2.68) 0.51 (0.38, 0.69)	 ns ns 0.03 0.02 <0.001
Kumar et al (2000)	Cross-sectional US	4-14 year-old lifelong residents of two school districts in New York N=2193	Dean's score > 1 Incisors and first molars Canines, premolars and second molars	Multivariate analyses Fluoridation and early brushing or supplements Fluoridation alone Fluoride supplements and early brushing Early brushing Fluoride supplements None of the above exposures Fluoridation and early brushing or supplements Fluoridation alone Fluoride supplements and early brushing Early brushing Fluoride supplements None of the above exposures Note: Other variables included in the analysis were race, age, gender, college education, school lunch type. Statistically significant results were seen for African-Americans relative to whites and others (OR 2.2 and 1.9 for the two tooth types) and college education vs no college education (OR 1.4 and 1.6 for the two tooth types).	OR (95% CI) 2.8 (1.7, 4.5) 2.2 (1.3, 3.6) 3.1 (1.7, 5.4) 1.7 (1.0, 3.0) 2.3 (1.2, 4.6) 1.0 3.8 (2.1, 6.6) 2.6 (1.5, 4.6) 4.1 (2.0, 8.3) 2.3 (1.3, 4.3) 2.2 (0.9, 5.0) 1.0	

Citation	Study type/ location	Subjects	Outcome	Relevant variables examined	Risk estimate	P value
Mascarenhas et al (1998)	Case-control India	Children from eleven most affluent schools in the region under investigation. N=1189	TF score > 0	Multivariate analysis Fluoride toothpaste Note: Other variables included in the model were age started toothbrushing, frequency of toothbrushing, amount of toothpaste, eating toothpaste, residence outside Goa, well water, well and tap water, tea, diet consisting of fish and gender. Other significant variables were residence outside Goa (OR 2.12; 1.20, 3.74) and gender/male (OR 1.77 (1.17, 2.67).	OR (95% CI) 1.94 (1.07, 3.35)	 0.027
Wang et al (1997)	Cross-sectional Norway	Children born in 1988 in Asker, a municipality of Norway	TF>0	Multivariate analysis Fluoride supplements > 1 year vs < 1 year Fluoride toothpaste ≤ 14 months of age vs > 14 months of age Note: Other variables examined included weight at birth, place of residence, regularity and duration of fluoride supplement use, toothbrushing practices including who put toothpaste on brush at different ages, whether child swallowed toothpaste, if the child liked the taste of toothpaste, schooling.	OR (95% CI) 1.84 (1.43, 2.35) 2.44 (1.07, 5.55)	 <0.001 0.03

5.3 FRACTURE

The following section reports the impact of fluoridation upon bone mineral density (BMD) and fracture. If included studies contained both BMD and fracture results, fracture was reported preferentially, as this represents the most patient relevant outcome. Extraction of fracture data was not limited to any specific location or fracture type.

This section also contains a brief discussion on skeletal malformations that may occur at excessive fluoride intakes.

5.3.1 WATER FLUORIDATION

Summary

Research question: ***Does intentional water fluoridation result in fracture over and above no intentional water fluoridation?***

The authors of the three existing systematic review concur that water fluoridation at levels aimed at preventing dental caries has little effect on fracture risk - either protective or deleterious. The results of the subsequent original studies support this conclusion, although suggest that optimal fluoridation levels of 1 ppm may indeed result in a lower risk of fracture when compared to excessively high levels (well beyond those experienced in Australia). One study also indicated that optimal fluoridation levels may also lower overall fracture risk when compared to no fluoridation (the latter was not the case when hip fractures were considered in isolation).

5.3.1.1 Identification of relevant studies

The literature search identified 20 potentially relevant citations which examined the possible association between water fluoridation and fracture. Of these, four citations related to three systematic reviews. The review by McDonagh et al (2000a) was chosen to form the basis of this section. As such, the aim was to identify original studies published between 2000 and 2007. An additional 3 original studies were identified. The exclusion of citations for this section is summarised in **Table 55**.

Table 55 Exclusion of citations: fracture and water fluoridation

Reason for exclusion	Number of citations
Potentially relevant citations	20
Original study published pre-2000	9
No low/optimal fluoride group	3
Duplicate data	2
Remaining relevant citations	6

5.3.1.2 Systematic reviews

The literature search identified three systematic reviews which examined the effect of water fluoridation on the bone mineral density or fracture. A summary of the systematic reviews is presented in **Table 37**. A more detailed assessment of these reviews is provided in **Appendix A.3.1**.

Table 56 Systematic reviews of the effect of water fluoridation on fracture

Citation Level of Evidence Study Quality	Number and type of included studies	Intervention	Comparator	Outcomes
Jones et al (1999) Level III/IV Fair/good	21 observational studies (10 ecological, 11 cross-sectional and 3 cohort)	Water fluoridation	Lower level of water fluoridation (generally but not always no fluoridation)	Fracture (also BMD and diagnosis of osteoporosis)
McDonagh et al (2000a,b) Level III/IV Good	27 studies (4 prospective cohort, 6 retrospective cohort, 15 ecological, 1 case-control, 1 case-control & ecological). 2 other studies were excluded from analyses.	Water fluoridation (or level nearest to 1 ppm)	No water fluoridation (or lowest water fluoride level)	Fracture
Demos et al (2001) Level III/IV Poor	27 human studies (6 ecological, 4 cross-sectional, 1 ecological & cross-sectional, 3 cohort, 12 clinical trials, 1 case-control)	Water fluoridation (also fluoride for osteoporosis treatment but not included here)	Non-fluoridation of low concentration	Fracture (also BMD and bone strength)

The review by Jones et al (1999) aimed to determine whether water fluoridation is associated with altered fracture risk at the population level. Broadly speaking they included studies that had compared fluoridation with no fluoridation, although some of the studies included fluoridation up to 4 or 5 ppm (higher than recommended with intentional water fluoridation). A literature search was conducted covering 1966 to Nov 1997. Only English language papers were included, but other inclusion and exclusion criteria were not explicitly stated. After quality assessment, this systematic review was considered to be of fair/good methodological quality. The pooled results of the included studies lead to a relative risk of 1.02 (95%CI 0.96–1.09) indicating no effect of fluoride upon fracture risk, although there was considerable heterogeneity between studies. The authors concluded that water fluoridation at levels aimed at preventing dental caries, and possibly at somewhat higher naturally occurring levels, appears to have little effect on fracture risk - either protective or deleterious.

The review by Demos et al (2001) did not state a specific research question, however reviewed papers published since the 1991 NHMRC report, up to December 1998. Only English language papers were included. Both animal (n=6) and human studies (n=27) were included, however only human results are discussed here. Twelve of the studies related to the therapeutic use of fluoride in patients with osteoporosis, not a subject of the current review. After quality assessment, this systematic review was considered to be of poor methodological quality. Data were not formally pooled. The authors conclude that the studies indicate that the addition of fluoride to drinking water at level of approximately 1 ppm, does not increase the incidence of fracture or decrease BMD, when compared to drinking unfluoridated water. The authors suggest that the body of epidemiological evidence suggests either no association or a slight beneficial effect of water fluoridation upon bone strength, bone density and fracture risk.

One of the aims of the review by McDonagh et al (2000a) was to examine whether water fluoridation has any negative effects, including upon bone, specifically fracture. Studies were considered for inclusion in this review if they reported data for two different levels of fluoride, one of which was indicative of a population receiving non-fluoridated water. The literature search was conducted up until 2000. A total of 29 studies were considered relevant to the review. This included four prospective cohort studies, six retrospective cohort studies, fifteen ecological investigations, one case-control study, and one study that was both case-control & ecological that were ultimately included in the analyses. Two studies were excluded from analyses (one because the control group fluoride level was more similar to a intentional water fluoridation level, and the other as it was only available in abstract form. This review was considered to be of good methodological quality. As the best quality and most comprehensive of the three systematic reviews, the McDonagh et al (2000a) review will form the basis of this section.

Data for various fracture types and locations was extracted, although hip fracture was the most commonly reported within the included studies. Several studies included data for more than two fluoride levels. All calculations undertaken by the authors compared the area with the water fluoride level closest to 1 ppm, with the lowest water fluoride level.

When considered in toto (Figure 8.1 of McDonagh, 2000), the majority of the measures of effects from the included studies and their confidence intervals are distributed around 1 (the line of no effect). Although there are studies with broad confidence intervals, there is no consistent indication of either a harmful or protective effect of water fluoridation upon fracture risk.

Eighteen studies investigated the association between water fluoridation and hip fracture. When subgroups of men, women or both were considered, a total of 30 analyses were presented. Five individual analyses showed a statistically significant protective effect, four found a statistically significant harmful effect and the remaining 21 studies found no effect. A univariate analysis that included no adjustment for covariates was undertaken by the authors. This analysis (analogous to a standard meta-analysis) resulted in a pooled estimate of 1.00 (95%CI, 0.94–1.06), however the between studies heterogeneity was statistically significant. A multi-variate analysis indicated that the duration of the study has the potential to influence the relationship between fluoridation and fracture.

5.3.1.3 Additional original studies

In keeping with the inclusion and exclusion criteria used in the McDonagh 2000 review, any subsequent studies that included two different levels of fluoride exposure, and that reported the outcomes of BMD or fracture, were included. As fracture is potentially a serious harmful effect of fluoride supplementation, the inclusion criteria were broadened somewhat so that even data for excessively high levels of fluoride were included. However, the reader is reminded that these levels are considerably higher than what would be experienced in Australia. These data typically came from developing countries where the local population consumed water from ground water wells with excessive fluoride concentrations.

There were three additional studies included since the McDonagh review (all Level IV evidence; see **Appendix A.3.1**). Two of these compared a control exposure representative of optimal fluoridation (~1 ppm) with higher exposures that would be considered unlikely to ever occur in Australia (Alarcon-Herrera et al, 2001; Sowers et al, 2005). The third study compared an optimal exposure with multiple other exposures, some that were lower and some that were higher (Li et al, 2001). Study design characteristics are explained in more detail in **Appendix A**. All three studies presented data for adults. The Alarcon-Herrera study also presented data for children, but the sample size is too small to provide meaningful results and **Table 57** presents the fracture prevalence for different fluoride exposures within the three additional studies. The reader should be aware that all three studies are small when considered in the context of their cross-sectional design and the rarity of fracture.

Table 57 Fracture (original studies): fracture prevalence

Fluoride level	Location	Number of subjects	Age range	Fluoride source	Fracture outcome	Percent fracture prevalence, odds ratio, p value relative to control
Li et al (2001)						
0.25–0.34 ppm	China	1363	> 50	Natural	Overall fractures	7.41%, OR 1.50, p=0.01[a]
0.58–0.73 ppm	China	1407	> 50	Natural	Overall fractures	6.40%, OR 1.25, p=0.17
1.00–1.06 ppm (control)	China	1370	> 50	Natural	Overall fractures	5.11%, reference
1.45–2.19 ppm	China	1574	> 50	Natural	Overall fractures	6.04%, OR 1.17, p=0.33
2.62–3.56 ppm	China	1051	> 50	Natural	Overall fractures	6.09%, OR 1.18, p=0.35
4.32–7.97 ppm	China	1363	> 50	Natural	Overall fractures	7.40%, OR 1.47, p=0.01 [a]
0.25–0.34 ppm	China	1407	> 50	Natural	Hip fracture	0.37%, OR 0.99, p=0.99
0.58–0.73 ppm	China	1370	> 50	Natural	Hip fracture	0.43%, OR 1.12, p=0.85
1.00–1.06 ppm (control)	China	1574	> 50	Natural	Hip fracture	0.37%, reference
1.45–2.19 ppm	China	1051	> 50	Natural	Hip fracture	0.89%, OR 2.13, p=0.15
2.62–3.56 ppm	China	1501	> 50	Natural	Hip fracture	0.76%, OR 1.73, p=0.34
4.32–7.97 ppm	China	1363	> 50	Natural	Hip fracture	1.20%, OR 3.26, p=0.02 [a]
Alarcon-Herrera et al (2001)						
<1.5 mg/l (control)	Mexico	192	13–60	Natural	'Unexpected' fracture	3.1%, reference
1.51–4.99 mg/l	Mexico	330	13–60	Natural	'Unexpected' fracture	7.9%, p<0.05
5.00–8.49 mg/l	Mexico	146	13–60	Natural	'Unexpected' fracture	8.9%, p<0.05
8.50–11.99 mg/l	Mexico	138	13–60	Natural	'Unexpected' fracture	7.2%, NS
12.00–16.00 mg/l	Mexico	96	13–60	Natural	'Unexpected' fracture	6.3%, NS
Sowers et al (2005)						
1 ppm (control)	USA	368	> 18	Natural	Osteoporotic fractures	1.4%, reference
4 ppm	USA	526	> 18	Natural	Osteoporotic fractures	2.9%, p=0.01 (unadjusted) however lost significance when adjusted for BMD in logistic regression
1 ppm (control)	USA	368	> 18	Natural	Non-osteoporotic fractures	3.2%, reference
4 ppm	USA	526	> 18	Natural	Non-osteoporotic fractures	3.1%, NS (unadjusted)

[a] Odds ratio and p value results are relative to the 1.00–1.06 ppm control group, adjusted for age and BMI using logistic regression

The results of Li et al (2001) support that conclusion of the previous systematic reviews that intentional water fluoridation (at levels recommended and achieved in Australia) has no negative effect upon fracture risk. In fact, the results of Li et al (2001) provide some suggestion of 'U-shaped' relationship, whereby fluoridation to optimal levels (~1 ppm) may be preferable to no fluoridation or extreme high concentrations. However, as this study represents a low level of evidence, in the face of many potentially confounding factors, this relationship should be interpreted with caution.

However, the higher fluoride exposures of both Li et al (2001) and Alarcon-Herrera et al (2001) both suggest that levels above 1.5 ppm may be associated with an increased risk of fracture. The reader is reminded that these data are sourced from developing countries with drinking water wells that contain excessive endemic ground water fluoride concentrations. Such levels are unlikely to be encountered in Australia, and are well above the target levels for artificial water fluoridation.

Although not specifically included within the scope of the current review, the literature search identified a number of recent studies reporting skeletal malformations (rather than fracture). These four studies published since 2000 were all from India, and reported the prevalence of malformations such as genuvalgum (knock-knee), scoliosis and kyphosis (Choubisa et al, 2001; Choubisa 2001; Dubey 2004; Khandare et al, 2005). Chronic fluoride toxicity was prevalent in these communities with fluoride concentration in well water up to 11 ppm, with the prevalence of abnormalities related to the extent of fluoride exposure. Exposures were considerably above those likely to occur in Australia or in artificially fluoridated water. These observations are also complicated by the presence of calcium and vitamin D deficiency (rickets) in some of these communities.

5.3.2 MILK FLUORIDATION

Summary

Research question: *Does intentional milk fluoridation result in osteoporosis or fracture over and above no intentional milk fluoridation?*

There is currently no evidence available to determine the impact of milk fluoridation upon fracture risk.

5.3.2.1 Identification of relevant studies

No relevant citations were identified by the literature search.

5.3.2.2 Systematic reviews

No systematic reviews have investigated the impact of milk fluoridation upon fracture risk.

5.3.2.3 Additional original studies

No original studies, meeting the inclusion criteria of the current review, have investigated the impact of milk fluoridation upon fracture risk.

5.3.3 SALT FLUORIDATION

Summary

Research question: *Does intentional salt fluoridation result in osteoporosis or fracture over and above no intentional salt fluoridation?*

There is currently no evidence available to determine the impact of salt fluoridation upon fracture risk.

5.3.3.1 Identification of relevant studies

No relevant citations were identified by the literature search.

5.3.3.2 Systematic reviews

No systematic reviews have investigated the impact of salt fluoridation upon fracture risk.

5.3.3.3 Additional original studies

No original studies, meeting the inclusion criteria of the current review, have investigated the impact of salt fluoridation upon fracture risk.

5.3.4 TOPICAL FLUORIDES

Summary

Research question: ***Does <u>topical fluoride supplementation</u> result in osteoporosis or fracture over and above no topical fluoride supplementation?***

Does a combination of topical fluoride supplementation products result in osteoporosis or fracture over and above a single topical fluoride supplementation product?

There is currently no evidence available to determine the impact of topical fluoride supplementation upon fracture risk.

5.3.4.1 Identification of relevant studies

No relevant citations were identified by the literature search.

5.3.4.2 Systematic reviews

No systematic reviews have investigated the impact of topical fluoride supplementation upon fracture risk.

5.3.4.3 Additional original studies

No original studies, meeting the inclusion criteria of the current review, have investigated the impact of topical fluoride supplementation upon fracture risk.

5.4 CANCER

The following section will assess the risk of any cancer type (both incidence and mortality) associated with any extent of fluoride exposure.

5.4.1 WATER FLUORIDATION

Summary

Research question: ***Does intentional water fluoridation increase the risk of cancer over and above no intentional water fluoridation?***

The existing systematic review by McDonagh et al (2000a) concluded that there is no clear association between water fluoridation and overall cancer incidence or mortality (for 'all cause' cancer, and specifically for bone cancer and osteosarcoma). The authors state that the evidence relating fluoridation to cancer incidence or mortality is mixed, with small variations on either side of the effect.

The current literature review identified four additional studies that investigated the relationship between water fluoridation and cancer incidence or mortality, including three Level IV ecological studies and one Level II-3 matched case-control study (Bassin et al, 2006). The latter study compares the fluoride exposure of histologically-confirmed osteosarcoma cases with that of matched controls - a sub-set of patients from a larger case-control study initiated by the Harvard School of Dental Medicine that is yet to report its findings. After adjusting for significant differences at baseline between the cases and controls, the results of Bassin et al (2006) suggest an increased risk of osteosarcoma amongst young males (but not females) with water fluoridation. However, the attention of the reader is drawn to a Letter to the Editor by co-investigators of Bassin in which the letter authors point out that they have not been able to replicate these findings in the broader Harvard study, that included prospective cases from the same 11 hospitals. Furthermore, the bone samples that were taken in the broader study corroborate a lack of association between the fluoride content in drinking water and osteosarcoma in the new cases. The final publication of the full study is not yet available, and the authors of the Letter caution readers not to over-interpret the results of Bassin and colleagues in the interim.

5.4.1.1 Identification of relevant studies

The literature search identified six potentially relevant citations assessing the association between water fluoridation and cancer. Of these, one was a systematic review by McDonagh et al (2000a). As the McDonagh review was to form the basis of this section, only original studies published from 2000-2007 were to be included. One study was excluded as it was published prior to 2000, resulting in five included original studies.

5.4.1.2 Systematic reviews

The literature search identified one systematic review that examined the effect of water fluoridation on cancer incidence and mortality. The review by McDonagh et al (2000a) examined a total of 26 studies. A detailed assessment of this study is provided in **Appendix A.4.1**. For the cancer outcome, the McDonagh review included studies that compared a non-fluoridated control area with an area (or areas) with fluoridation of any level, ie, natural or artificial. Therefore in many cases the included studies related to fluoridation levels many times the optimal level for intentional water fluoridation. The review included 10 before and after studies, 11 ecological studies, and 3 case-control studies. A further two studies were not included in the analyses because they had mixed control groups (ie, not entirely unfluoridated control areas). The included studies were generally of poor quality (5 moderate quality, 21 low quality evidence). None of the included studies involved prospective follow-up or reported any form of blinding. The McDonagh review focuses on the outcomes for all-cause cancer, bone cancer and thyroid cancer.

Table 58 presents the data for all cause cancer incidence and mortality. A total of 10 studies reported these outcomes, using 22 analyses.

Table 58 Effect of fluoridation on cancer incidence and mortality (McDonagh et al, 2000)

Author (Year)	Age	Sex	Summary measure	Results (95% CI)	Validity score/8
Smith (1980)	All ages	Both	Mean difference of change in SMRs	-4.4 (-7.5, -1.3)	4.8
Lynch (1985)	All ages	Male	Mean difference in SIRs	9.00 (p < 0.001)	4.2
				2.10 (p = 0.592)	
				-6.80 (p = 0.057)	
		Female		-1.10 (p = 0.500)	
				5.9 (p < 0.001)	
				2.3 (p = 0.565)	
				0.1 (p = 1.000)	
				2 (p = 0.630)	
Chilvers (1983)	All ages	Both	Mean difference of change in SMRs	-0.1 (-3.8, 3.6)	3.8
Hoover (1976)	All ages	Male	Mean difference in SMRs	0 (-3.5, 3.5)	.3.8
		Female		0 (-3.8, 3.8)	
Chilvers (1985)	All ages	Male	Mean difference in SMRs	-0.49 (-5.7, 4.8)	3.5
	All ages	Female		-1.56 (-7.4, 4.3)	
Goodall (1980)	Not Stated	Male	Ratio of crude rate ratios	0.85	3.5
		Female		0.90	
Raman (1977)	All ages	Male	Mean difference of change in SMRs	6.9	3.3
	All ages	Female		18.9	
Cook-Mozaffari (1981)	All ages	Male	Ratio of rate-ratios	0.99	3.3
Richards (1979)	All ages	Both	Mean difference in SMRs	-3.3 (-18.7, 12.1)	3.1
Schlesinger (1956)	All ages	Male	Ratio of crude rate ratios	0.6	2.8
		Female		1.01	

The authors conclude that there is no clear association between water fluoridation and overall cancer incidence or mortality (for 'all cause' cancer). When considering all of the analyses, 11 found the direction of the association to be positive (fewer cancers with fluoridation), 2 found no association, and 9 found the direction to be negative (more cancers with fluoridation). Only two studies reported statistically significant associations - one study reporting a decrease in cancer mortality (Smith et al ,1980) and one reporting an increase in cancer incidence in two of the eight subgroups they investigated (Lynch et al, 1985).

The McDonagh review also discusses in more detail the controversy surrounding various published analyses of data from the same set of US cities (10 fluoridated and 10 non-fluoridated). These data have been published by at least four authors. All of the studies used a before and after study design, simply comparing cancer incidence or mortality before and after the introduction of water fluoridation in half of the cities. McDonagh et al report that the original US study by Yiamouyiannis in 1977 found an association between fluoridation and cancer incidence that suggested more cancers, however this study did not take into account demographic differences between the cities at baseline and across the time period of interest. For example, the proportion of the population who were non-white and over 65 years of age increased more rapidly in the fluoridated areas - which may have contributed to the increased cancer incidence. When the later studies standardised for age, gender and ethnic group, there was no association between fluoride and cancer mortality. The study with the highest validity and corrected data (Smith et al, 1980) was included by the McDonagh reviewer in their main analyses (see above). This study showed a mean difference in the change in SMRs of –4.4 (95%CI –7.5, –1.3). A discussed above, the results of this study indicate a statistically significant protective effect. This comparison of publications relating to essentially the same dataset, reiterates the importance of controlling for potential confounding factors.

Table 59 provides the results for bone cancer and osteosarcoma incidence and mortality for 11 studies using 20 analyses. Where studies had reported an adjusted measure this is presented, given the known importance of adjusting for confounders such as age, gender, menopausal status and smoking status in cancer epidemiological studies.

Table 59 Association of osteosarcoma, bone and joint cancer incidence and mortality with water fluoride level (McDonagh et al, 2000)

Author (Year)	Age	Sex	Cancer	Summary measure	Results (95% CI)	Validity score/8
Kinlen (1975)	All ages	Both	Bone	Mean difference in SMRs	6 (-50.8, 62.8)	4.0
Hoover (1976)	All ages	Male Female	Bone	Mean difference in SMRs	0 (-35.9, 35.9) 20 (-22.6, 62.6)	3.8
Hoover (1991)	All ages		Bone and joint	Mean difference of change in SIRs	1 (-30.2, 32.2)	3.3
Mahoney (1991)	<30 <30 30+ 30+	Male Female Male Female	Bone	Crude RR	0.93 0.96 0.84 1.1	2.8
Moss (1995)	Not stated	Both	Osteosarcoma	OR	1.0 (0.6, 1.5)	6.0
Gelberg (1995)	<24 <24		Osteosarcoma	OR OR	2.07 (0.5, 8.0) 1.84 (0.8,4.2)	4.3
Hrudey (1990)	All ages		Osteosarcoma	Crude RR	0.93 (0.6, 1.6)	4.0
Hoover (1991)	All ages		Osteosarcoma	Mean difference of change in SIRs	-11 (-44.6, 22.6)	3.8
McGuire (1991)	0-40	Both	Osteosarcoma	OR	0.33 (0.0, 2.5)	3.5
Mahoney (1991)	<30 <30 30+ 30+	Male Female Male Female	Osteosarcoma	Crude RR	0.98 0.78 0.88 0.91	2.8
Cohn (1992)	0-20	Male Female	Osteosarcoma	Crude RR	3.4 (1.4, 8.1) 1.0 (0.3, 3.5)	2.5

With respect to bone cancer generally, the results show the direction of the association to be positive (fewer cancers) in three analyses, no association in one analyses, and negative in four analyses. None found a statistically significant relationship.

With respect to osteosarcoma specifically, the direction of the association was positive (fewer cancers) in seven analyses, no association in two, and negative (more cancers) in three analyses. One study reported a statistically significant result - Cohn et al, 1992 reported a statistically significant increased prevalence of osteosarcoma in males. However, this study had the lowest validity score (2.5 out of 8). The study was based on census data comparing crude osteosarcoma rates from areas where >85% or <10% of the population received fluoridated water - although there is no information regarding the level of fluoridation. There was no correction for confounding factors, although the results are presented in age and gender categories.

The McDonagh review included two studies that investigated the impact of water fluoridation upon thyroid cancer. Both of these studies indicated a lack of association between fluoride and thyroid cancer.

In summary, McDonagh et al (2000a) conclude that the evidence relating fluoridation to cancer incidence or mortality is mixed, with small variations on either side of the effect.

5.4.1.3 Additional original studies

The literature review identified four additional studies that investigated the relationship between water fluoridation and cancer incidence or mortality, including three ecological studies (Takahashi et al, 2001; Yang et al, 2000; Steiner 2002) and one match case-control study (Bassin et al, 2006). A detailed assessment of these studies is provided in **Appendix A.4.1**.

The study by Takahashi et al (2001; Level IV) is an ecological study regressing the rate of various cancers for the period 1978–1992 against a 'fluoridation index'. The study has a low level of validity as there is no adjustment for potential confounding factors and no discussion of how potential confounding factors may have varied across the nine areas being compared. Furthermore the fluoridation index is purely an expression of the proportion of persons receiving fluoridated water, without consideration of the level of fluoridation. The results suggest an association between fluoridation and increased cancer incidence in 23 of the 36 bodily sites investigated, and between fluoridation and decreased cancer incidence in 4 sites. In the 9 remaining sites, there was no significant association. Given the low level of evidence that this study represents, the results should be interpreted with extreme caution.

The ecological study of Yang et al (2000; Level IV) compares cancer mortality in 10 municipalities with unfluoridated water with 10 municipalities with naturally fluoridated water. However, the reader should be aware that the municipalities with naturally fluoridated water all had fluoride concentrations well below those targeted by intentional fluoridation in Australia (all < 0.28 ppm). The two groups of municipalities were matched according to their urbanisation index and their socioeconomic characteristics. The results indicate that cancer mortality rates were generally similar between unfluoridated and naturally fluoridated areas, both for males and females, except for significantly higher female bladder cancer mortality in naturally fluoridated areas. In the absence of biological reasoning, the authors suggest that this is a chance finding as a function of the large number of comparisons.

The ecological study of Steiner (2002; Level IV) presents international age-standardised cancer incidence data relative to each country's fluoridation, latitude and temperature. The authors argue that the results show that fluoride concentration in drinking water was inversely correlated with cancer incidence ($r = -0.75$, ie, lower the fluoride, higher the cancer incidence). The results should be interpreted with extreme caution as the analysis is overly simplistic. There remain a multitude of probable confounding factors that have not been accounted for, such as socioeconomic/ development status, smoking prevalence, and nutritional status. All of these factors are known to impact upon cancer incidence.

The recent hospital based case-control study of Bassin et al (2006; Level III-3) compares the fluoride exposure of histologically-confirmed osteosarcoma cases with that of matched controls. This publication reports a sub-set of patients from a larger case-control study initiated by the Harvard School of Dental Medicine that is yet to report its findings. The Bassin publication reports data from the retrospectively-obtained cases and their control (n=103 and 215, respectively). Cases were identified from the orthopaedic departments of 11 teaching hospitals across the United States. Controls were age-matched patients from the same orthopaedic departments seen within 6 months of the cases diagnosis. The analysis presented by Bassin (2006) is limited to the patients under 20 years of age.

For the primary analyses, fluoride exposure was climate-standardised into three categories (<30%, 30–99%, >99%) based on the CDC target fluoride levels for areas with differing climates. A secondary analyses used non-climate standardised categories (<0.3, 0.3–0.69, and ≥0.7 ppm).

Adjustments were made in the logistic regression for socioeconomic status, (using a crude measure of median family income for their residential postcode, categorised into quartiles), age, county population, use of well or bottled water, fluoride supplements or mouth-rinses. The results are presented in **Table 60** with and without adjustment.

Table 60 Sex-specific associations between fluoride exposure at age 7 years and osteosarcoma, estimated by conditional logistic regression (Bassin et al, 2006)

Fluoride exposure category at age 7 years	Odds ratio (95% CI)[a]
Males:	
> 30% of target	1.00 (reference)
30–99% of target	3.36 (0.99, 11.42)
>99% of target	5.46 (1.50, 19.90)
Females:	
> 30% of target	1.0 (reference)
30–99% of target	1.39 (0.41, 4.76)
>99% of target	1.75 (048, 6.35)

[a] Adjusted for age, zip code median income, county population, use of well water by age 7, use of bottle water by age 7, any use of fluoride supplements

Whilst the study is a fair/good case-control study, there are several possible limitations of which the reader should be aware. Whilst cases and controls were theoretically part of same broader population, it is not clear to what extent additional cases could have been present in other hospitals (eg, non-teaching, and to what extent these cases may have differed from those included. Furthermore, cases had a statistically significantly lower socioeconomic status than controls ($p<0.01$), and fewer of them used bottled water ($p=0.002$).

Residential history (and therefore fluoride exposure level) was determined for each patient by interview with the patient, their parent or a proxy. Each individual's fluoride exposure was assumed to be that indicated by the CDC fluoridation data for their locality (ie, individual residence fluoride concentration and consumption of water not accounted for). The exception was where well water was used and actual measurements were made. Therefore exposure for the purposes of analyses was the exposure in each individual year in isolation, rather than cumulative or total exposure. Similarly, there was no biological confirmation of fluoride (eg. bone fluoride concentration) to confirm the validity of the exposure variable.

The attention of the reader is drawn to a Letter to the Editor that appeared in the same issue of Cancer Causes and Controls by co-investigators on the larger Harvard study (Douglass & Joshipura, 2006). The authors point out that they have not been able to replicate the findings of Bassin and colleagues in the larger study that included prospective cases from the same 11 hospitals. Furthermore, the bone samples that were taken in the broader study corroborate a lack of association between the fluoride content in drinking water and osteosarcoma in the new cases. As Bassin and colleagues acknowledged, the shortcomings of their study mean that their results should be interpreted with caution pending publication of the larger study results.

5.4.2 MILK FLUORIDATION

Summary
Research question: *Does intentional milk fluoridation increase the risk of cancer over and above no intentional milk fluoridation?*
There is currently no evidence available to determine the impact of milk fluoridation upon cancer risk.

5.4.2.1 Identification of relevant studies

No relevant citations were identified by the literature search.

5.4.2.2 Systematic reviews

No systematic reviews have investigated the impact of milk fluoridation upon cancer risk.

5.4.2.3 Additional original studies

No original studies, meeting the inclusion criteria of the current review, have investigated the impact of milk fluoridation upon cancer risk.

5.4.3 SALT FLUORIDATION

Summary
Research question: *Does intentional salt fluoridation increase the risk of cancer over and above no intentional salt fluoridation?*
There is currently no evidence available to determine the impact of salt fluoridation upon cancer risk.

5.4.3.1 Identification of relevant studies

No relevant citations were identified by the literature search.

5.4.3.2 Systematic reviews

No systematic reviews have investigated the impact of salt fluoridation upon cancer risk.

5.4.3.3 Additional original studies

No original studies, meeting the inclusion criteria of the current review, have investigated the impact of salt fluoridation upon cancer risk.

5.4.4 TOPICAL FLUORIDES

Summary
Research question: *Does topical fluoride supplementation increase the risk of cancer over and above no topical fluoride supplementation?*
Research question: Does a combination of topical fluoride supplementation products increase the risk of cancer over and above a single topical fluoride supplementation product?
There is currently no evidence available to determine the impact of topical fluoride supplementation upon cancer risk.

5.4.4.1 Identification of relevant studies

No relevant citations were identified by the literature search.

5.4.4.2 Systematic reviews

No systematic reviews have investigated the impact of topical fluoride supplementation upon cancer risk.

5.4.4.3 Additional original studies

No original studies, meeting the inclusion criteria of the current review, have investigated the impact of topical fluoride supplementation upon cancer risk.

5.5 OTHER HARMS

The following section includes an assessment of other possible negative effects associated with fluoridation.

5.5.1 WATER FLUORIDATION

Summary

Research question: *Is intentional water fluoridation associated with other adverse effects over and above no intentional water fluoridation?*

The authors of previous systematic reviews concluded that the studies examining other possible negative effects of water fluoridation provide insufficient evidence to reach a conclusion.

5.5.1.1 Identification of relevant studies

The literature search identified 12 citations potentially related to other harms of water fluoridation. Of these, two were systematic reviews. As the most comprehensive of these reviews (McDonagh et al, 2000) was conducted in 2000, the search of additional original studies encompassed the period 2000-2007. The exclusion of citations for this section is summarised in **Table 61**.

Table 61 Exclusion of citations: other harms and water fluoridation

Reason for exclusion	Number of citations
Potentially relevant citations	12
Original study published pre-2000	3
No low/optimal fluoride group	3
Duplicate data	1
Remaining relevant citations	5

5.5.1.2 Systematic reviews

The literature search identified two systematic reviews of other potentially negative effects of water fluoridation. One of these covered any other negative effects (other than fluorosis, fracture and cancer (McDonagh et al, 2000; Level III/IV), whilst the other focused upon Down's syndrome (Whiting et al, 2001; Level IV). Detailed assessments of these reviews are presented in **Appendix A.3**.

The McDonagh systematic review investigated whether water fluoridation was associated with other negative effects. They included 25 studies comprising six before and after studies, one retrospective cohort study, 12 ecological studies, five cross-sectional studies, and one case control study. They also briefly report on an additional eight studies that met the inclusion criteria but were not included in the main analyses for various methodological reasons. The quality of the studies was low, with all studies assigned the lowest level of evidence by the reviewers. None of the studies had a prospective follow-up and none incorporated any form of blinding.

The results are presented in **Table 62**. Where studies reported an adjusted measure, this is presented. For studies reporting a difference measure (eg. mean difference) a negative result suggests a benefit of fluoridation and a positive result suggests harm. For ratio measurements, a ratio less than one suggests a benefit whilst a ratio greater than one suggests harm.

Table 62 Other potential harms of water fluoridation (McDonagh et al, 2000)

Citation	Outcome	Age	Sex	Summary measure	Results (95% CI)	Validity Score
Forbes (1997)	Alzheimer's disease Impaired mental functioning	76	Both	Adjusted odds ratio	1.22 (1.0–1.5) 0.49 (0.3–0.9)	4.0
Still (1980)	Primary degenerative dementia	55+	Both	Crude RR	0.18	3.0
Jacqmin-Gadda (1994)	Cognitive impairment	≥ 65	Both	Crude RR	0.93	4.5
Griffith (1963)	Anaemia during pregnancy	Not stated	Women	Rate difference	2.03 (-5.0–9.0)	2.3
Farkas (1983)	Age at menarche	7–18	Girls	Mean difference	0	1.5
Erickson (1976)	Congenital malformations Down's syndrome		Both	Crude RR	1.08 (p>0.05) 0.95 (p<0.05) 1.16 (p>1.05) 0.96 (p>0.05)	3.5
Erickson (1980)	Congenital malformations Down's syndrome		Both	Crude RR	1.00 (0.9–1.1) 0.93 (0.7–1.2)	3.5
Berry (1958)	Down's syndrome		Both	Crude RR	0.84–1.48	1.8
Needleman (1974)	Down's syndrome		Both	Crude RR	1.14	2.0
Rapaport (1957)[a]	Down's syndrome		Both	Crude RR	1.5 2.3 2.2 2.2	2.0
Rapaport (1963)	Down's syndrome Infant mortality		Both	Crude RR	3.0 1.3	2.0
Dick (1999)	Sudden infant death syndrome	Not stated	Both	Odds ratio	1.19 (0.8–1.7)	7 (of 9)
Overton (1954)	Infant mortality		Both	Difference in RR	0.06	2.8
Erickson (1978)	Mortality	All	Both	Adjusted rate-ratio	1.01	3.8
Hagan (1954)	Mortality	Not stated	Both	Adjusted rate-ratio	1.01	3.5
Rogot (1978)	Mortality	Not stated	Both	Difference in RR	0	4.1
Schatz (1976)[b]	Mortality Infant Mortality	Not stated	Both	Difference in RR	-0.1 0.5	2.8
Weaver (1944)	Mortality	Not stated	Both	Difference in RR	0	1.8
Zhao (1996)	IQ	7–14	Both	Mean difference	-7.7	2.5
Lin (1991)	IQ Mental retardation	7–14	Not stated	Mean difference Crude RR	-6 1.6 (1.15–2.34)	1.5
Jolly (1971)	Skeletal fluorosis	Not stated	Both	Prevalence	Increased prevalence of skeletal fluorosis at higher fluoride concentrations	2.7
Gedalia (1963)	Goitre	7–18	Female	Crude RR	0.16–1.80	2.5
Jooste (1999)	Goitre	6, 12 & 15	Both	Crude RR	0.3–1.2	1.8
Lin (1991)	Goitre	7–14	Not stated	Crude RR	1.11 (1.04–1.20)	1.5

[a] Multiple areas studied.

[b] Briner (1966) reported data from the same areas and some of the same years but is not presented here because Schatz reported more years and included infant mortality.

Only three of the studies showed a statistically significant result. Forbes (1997) found a significant negative effect of water fluoride on Alzheimer's disease (increased incidence) but a significant positive effect on impaired mental functioning (decreased incidence). Erickson (1976) found a positive association with congenital malformations in one of two sets of data but not in the other. Lin (1991) found a significant negative association of combined low iodine and high fluoride with goitre and mental retardation.

All of the studies investigating other possible negative effects used study designs that measured population level fluoride exposure, rather than individual level exposure. Because of this they are susceptible to confounding by exposure. If the populations differ in other respects, that may influence the outcome measure in question, then confounding is likely. As a result, these studies represent low level and poor quality evidence. In summary, the authors conclude that the studies examining other possible negative effects provide insufficient evidence on any particular outcome to reach a conclusion.

The systematic review of Whiting et al (2001) was commissioned by the UK Department of Health to investigate whether water fluoridation had any impact upon the incidence of Down's syndrome. six ecological studies were included in the review, all with low validity scores. The studies were published between 1957 and 1980. None of the studies had prospective follow-up, incorporated blinding, had a baseline survey or stated how the level of water fluoride was calculated. Confounding factors such as maternal age and race were discussed in most papers but only adjusted for in the studies of Erickson. Table 63 presents the results of these six studies.

Table 63 Association of Down's syndrome with water fluoridation (Whiting, 2001)

Citation	Crude relative risk	Factors controlled
Erickson (1976)	1.16 (p>0.05) 0.96 (p>0.05)	Maternal age, race
Erickson (1980)	0.93 (0.7–1.2)	Maternal age, race
Needleman (1974)	1.14	None
Rapaport (1957)	2.3 (p<0.01) 2.9 (p<0.01) 2.4 (p<0.05)	None
Rapaport (1963)	3.0 (p<0.001)	None
Berry (1958)	0.84–1.48	None

The reviewers conclude that the evidence for an association between water fluoride level and the incidence of Down's syndrome is weak, and that all the identified studies were of poor quality, in particular the older studies of Rapaport (1957 and 1963) that reported a significant association.

5.5.1.3 Additional original studies

The literature search identified three additional original studies published since the McDonagh (2000) and Whiting (2001) reviews that related to other potentially negative effects of fluoride. These studies are summarised in Table 64, while a more detailed assessment is presented in Appendix A.3.

Table 64 Other potential harms (original studies)

Citation Level of Evidence Study Quality	Study design Country	N	Exposure	Outcome	Results (95%CI)
Singh et al, 2001 Level IV Poor	Cross-sectional India	8,270 10,436	Endemic area: 3.5–4.9 ppm Non-endemic area: 0.5 ppm (reference)	Urinary stone disease	Kidney stone prevalence: Endemic: 750/100,000 Non-endemic: 163/100,000 OR 4.63 (2.07–7.92)
Lowry et al, 2003 Level IV Poor[a]	Ecological Short report only [a] England	Population of 3 million in total	Areas with full fluoridation: >0.9 ppm Areas with no fluoridation: <0.3 ppm (reference)	Still births and congenital abnormalities	Still births: OR 1.06 (0.91–1.24) All trisomies: OR 1.11 (0.86–1.43) Downs syndrome: OR 1.05 (0.79–1.41) Neural tube defect: OR 0.82 (0.62–1.09) Clefts: OR 0.63 (0.46–0.86)
Kaipio et al, 2004 Level IV Fair	Ecological Rural Finland	365 rural communities with average population of 5400 (range 120–30,400) in 1995. In total these communities had 188,888 deaths in period 1961–1995	Quintiles: V: 0.3–2.15 ppm IV: 0.15–0.30 ppm III: 0.10–0.15 ppm II: 0.064–0.10 ppm I: 0.00–0.064 ppm (reference) NB. Fluoride concentration primarily determined in 1958.	Coronary heart disease mortality	Adjusted risk ratio results for 1961–1995, relative to reference[b]: 35–64 years: V: 0.80 (0.77–0.83) IV: 0.76 (0.74–0.79) III: 0.86 (0.83–0.89) II: 0.90 (0.87–0.93) 65+ years: V: 0.93 (0.90–0.95) IV: 0.90 (0.88–0.93) III: 0.94 (0.92–0.96) II: 0.95 (0.93–0.97) NB. Data for later period, 1991–95 is shown in graph form only. In this period, magnitude of difference decreases and only quintiles IV and V remain significantly different from quintile I.

[a] Short report only therefore minimal methodological information available

[b] Adjusted for age, period, drinking water magnesium and calcium, and average income.

In summary, the additional studies do not suggest an increased risk of other adverse events with the level of fluoridation used in Australia (~1 ppm). The study of Singh et al (2001) involved fluoride concentrations that would not be observed in water in Australia. The results of Lowry support the findings of the Whiting systematic review, indicating no difference in stillbirths and congenital abnormalities in fluoridated and non-fluoridated areas (with the exception of clefts, which were significantly lower in the fluoridated areas). The data of Kaipio et al, 2004 suggest a small protective effect with respect to coronary heart disease mortality. However this ecological study remains subject to many potential biases and therefore the results should be interpreted with extreme caution. If there is an effect of fluoridation upon coronary heart disease it is possible that the mechanism is indirect, via a reduction in dental infections.

5.5.2 MILK FLUORIDATION

Summary

Research question: *Is intentional milk fluoridation associated with other adverse effects over and above no intentional milk fluoridation?*

There is currently no evidence available to determine the impact of milk fluoridation upon other harms.

5.5.2.1 Identification of relevant studies

No relevant citations were identified by the literature search.

5.5.2.2 Systematic reviews

No systematic reviews have investigated the impact of milk fluoridation upon other harms.

5.5.2.3 Additional original studies

No original studies, meeting the inclusion criteria of the current review, have investigated the impact of milk fluoridation upon other harms.

5.5.3 SALT FLUORIDATION

Summary

Research question: *Is intentional salt fluoridation associated with other adverse effects over and above no intentional salt fluoridation?*

There is currently no evidence available to determine the impact of salt fluoridation upon other harms.

5.5.3.1 Identification of relevant studies

No relevant citations were identified by the literature search.

5.5.3.2 Systematic reviews

No systematic reviews have investigated the impact of salt fluoridation upon other harms.

5.5.3.3 Additional original studies

No original studies, meeting the inclusion criteria of the current review, have investigated the impact of salt fluoridation upon other harms.

5.5.4 TOPICAL FLUORIDES

Summary

Research question: *Is topical fluoride supplementation associated with other adverse effects over and above no topical fluoride supplementation?*

Research question: *Is a combination of topical fluoride supplementation products associated with other adverse effects over and above a single topical fluoride supplementation product?*

There is currently no evidence available to determine the impact of topical fluorides upon other harms.

5.5.4.1 Identification of relevant studies

No relevant citations were identified by the literature search.

5.5.4.2 Systematic reviews

No systematic reviews have investigated the impact of topical fluorides upon other harms.

5.5.4.3 Additional original studies

No original studies, meeting the inclusion criteria of the current review, have investigated the impact of topical fluorides upon other harms.

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7 APPENDIX A: DATA EXTRACTION FORMS: STUDY CHARACTERISTICS AND QUALITY

The following section includes tables for each of the studies included in this systematic review. They include details regarding the characteristics of the study and also a quality assessment of each study.

A.1 CARIES PREVENTION

A.1.1 FLUORIDATED WATER

Level III/IV evidence (Intervention) Truman et al (2002)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
30 studies (not including those addressing other questions) Any study type Arnold 1956; Ast 1962; Attwood 1988; Backer-Dirks 1961; Beal 1971; Beal 1981; Blayney 1964; Booth 1992; Brown 1965; Campagna 1995; Ellwood 1995; Evans 1995; Fanning 1980; Guo 1984; Hardwick 1982; Hawew 1996; Jones 1997; Kalbeek 1993; Kelman 1996; Kunzel 1997; Loh 1996; Margolis 1975; Provart 1995; Rugg-Gunn 1981; Rugg-Gunn 1977; Selwitz 1995; Seppa 1998; Slade 1996; Tsusui 2000; Weerheijm 1997	Not specifically defined	Water fluoridation	No water fluoridation or exposure at a lower concentration	DMFT, DEFT, DMFS, dmfs, percentage of caries-free children	A. While a specific question was not defined, an analytic framework was developed. B. Yes. Electronic search of Medline to Jan 2001, manual searching and contacting experts. C. Specific inclusion criteria applied. No details on number of reviewers assessing citations. D. Yes. Quality assessed by two reviewers. E. Yes. F. Not pooled. G. Not applicable. **Quality rating:** Good.
Comments: The authors conclude there is strong evidence that community water fluoridation is effective in reducing the cumulative experience of dental caries within communities.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level III/IV evidence (Intervention) *McDonagh et al (2000a)*					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
26 studies (73 articles) related to effect of water fluoridation on caries 23 before-after and 3 cohort Adriasola 1959; Ast 1951: Beal 1981; Beal 1971; DHSS 1969; DHSS 1969; Gray 1999; Guo 1984; Kunzel 1997; Brown, 1965; Loh, 1996; Alvarez-Ubilia, 1959; Arnold, 1956; Blayney, 1960; Hardwick, 1982; Backer-Dirks, 1961; Pot, 1974; Wragg, 1992; Kalsbeek, 1993; Attwood, 1988; Hobbs, 1994; Seppä, 1998; Maupome, 2000; Klein, 1946; Holdcroft, 1999; Gray, 2000	Not specifically defined	Water fluoridation	No water fluoridation	DMFT, proportion of children without caries; dental fluorosis	A. Yes. Five specific objectives were stated. B. Yes. Included electronic and manual searching up to Feb 2000. C. Yes. Assessed by three reviewers. D. Yes. Assessed using a NHS CRD checklist. E. Yes. Detailed summary provided in data extraction tables. F. Yes. Data were pooled using the DerSimonian and Laird method when no significant heterogeneity was present. G. Yes. Explored using meta-regression. Quality rating: Good.
Comments: The authors conclude that the evidence of a beneficial reduction in caries should be considered together with the increased prevalence of dental fluorosis. There was no clear evidence of other potential adverse effects.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level IV evidence (Intervention) Seppä et al (2000)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Controlled before-and-after study (population level) Study time-points: 1992, 1995 and 1998 N=688, 1484 and 1530	3, 6, 9, 12 and 15 year olds	Kuopio (Finland) Non-fluoridated (fluoridation ceased in 1992) Fluoride concentration 0.1 ppm	Jyväskyla (Finland) Fluoridated Fluoride concentration 0.1 ppm	Percentage of children caries-free dmfs/DMFS	For the fluoride group, independent random samples of children aged 3, 6, 9, 12 and 15 residing in Kuopia from 1992, 1995 and 1998. For the non-fluoride group random samples of children aged 3, 6, 9, 12 and 15 residing in Jyväskyla from 1992, 1995 and 1998. No further details. No demographic or other potential confounders are adjusted for. The study assesses the number of fluoride varnish and sealant applications over time in both towns and states that they decreased in both towns over time. Measurement of outcomes was not blinded. Two dentists examined children, looking at approximately equal numbers of children in each town. Fluoridation ceased at the end of 1992 and there was a six year time-frame between the baseline and final surveys, although there is the possibility of some residual effect in the older children. **Quality rating:** Poor
Comments: No evidence of increasing caries was found in the previously fluoridated town (Kuopio). DMFS/dmfs levels in both towns stayed the same or decreased over time and the percentage of caries-free children stayed the same or increased over time. The use of fluoride varnish and fissure sealants decreased from 1993-1998 compared with 1990-1992. In addition they noted that a small percentage of children accounted for a large percentage of high DMFT counts. The authors conclude that the "fact that no increase in caries was found in Kuopio despite discontinuation of water fluoridation and decrease in preventive procedures suggests that not all of these measures were necessary for each child."					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

A.1.2 FLUORIDATED MILK

Level I evidence (Intervention) Yeung et al (2005)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
2 studies RCTs or quasi-RCTs Maslak 2004; Stephen 1984	General population irrespective of age or level of risk for dental caries	Fluoridated milk	Non-fluoridated milk	DMFS, dmfs, DMFT, dmft, pain, antibiotic use, general anaesthesia, adverse effects	A. Yes. The hypothesis to be tested was that there is no difference in dental caries experience, or caries increment, in participants who have received fluoridated or non-fluoridated milk B. Yes. Electronic and manual searching was carried out. C. Yes. Citations were assessed by two reviewers. D. Yes, based on randomisation, allocation concealment, blinding and follow-up. E. Yes. Study characteristics and data extraction performed by two reviewers. F. Yes. Results expressed as RR. G. Yes. **Quality rating:** Good
Comments: The authors conclude that there are insufficient studies with good quality evidence examining the effects of fluoridated milk in preventing dental caries. However, the included studies suggest that fluoridated milk was beneficial to school children, especially their permanent dentition. Review was limited only to RCTs/quasi-RCTs and as such lower levels of evidence were excluded.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level IV evidence (Intervention) Mariño et al (2001; 2004)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Controlled before and after study (population level) Study time-points: 1994/1997-1999 (Study 1) 1999-2002 (Study 2) Approximately 200 in each community at each time-point	Children aged 3-6 in each region at each time-point	Codegua, Chile Milk fluoridation programme introduced in 1995 and ceased in 1999	La Punta, Chile No fluoridated milk programme	Measured at baseline (1995 and endpoint (1999) of milk fluoridation programme in Codegua to assess effect of implementation of programme. Measured in 2002 to assess effect of cessation of programme. Measured in 1997 and 1999 and 2002 in La Punta to compare. dmfs, percentage caries free	Codegua was chosen as the test community as a milk fluoridation programme was introduced in 1995. Children aged 3-6 attending public kindergartens and primary schools were included. La Punta was chosen as the control group as it was located near Codegua, had similar caries prevalence and children in both regions had dental care in the same regional capital. No baseline demographic data shown and no adjustments appear to have been made in the analysis. Authors note similar water fluoride levels in both regions and that nearly all children in Chile use fluoridated toothpaste. Outcome assessment not blinded. Inter-examiner and intra-examiner assessments carried out on sample of 25 children with kappa > 0.9. Baseline survey in test group carried out at same time as introduction of milk fluoridation. However, baseline survey in control group not carried out until 1997. Follow-up survey conducted after 4 yeasr in test group, but only 2 years in control group. **Quality rating:** Poor
Comments: This study was considered to be of poor methodological quality due to a lack of detail regarding baseline characteristics of the two populations, a lack of adjustment for potential confounders, and the lack of blinding of outcome assessment. Following introduction of the milk fluoridation programme, significant improvements in dmfs score, and increases in the percentage of caries-free children in Codegua (milk fluoridation) compared with La Punta (no milk fluoridation). Following cessation of the programme in 1999, dental caries increased in Codegua.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

<table>
<tr><td colspan="6">Level IV evidence (Intervention)
Riley et al (2005)</td></tr>
<tr><th>Study type/patient no.</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Outcomes</th><th>Study quality</th></tr>
<tr><td>Controlled cross-sectional study

Study time-point:
2003

N=690(Wirral; test group) and 1835 (Sefton, control group)</td><td>Children aged 5 in 1997/1998 in schools with/without fluoridated milk programmes.</td><td>Wirral, UK
Fluoridated milk programme implemented in nursery and primary schools in the region in 1995/1996</td><td>Sefton, UK
No fluoridated milk programme at schools</td><td>DMFT/DT/DFS
Mean number sealed teeth, percentage of children with fissure sealants, DMFT>0, DT>0 and DFS>0.</td><td>Schools from Wirral could only be included if they had received fluoridated milk for a minimum of 6 years and if the fluoridated milk uptake in each school was at least 50%.
Choice of the comparison district required that a full population dental health survey had been carried out in 1997/98 so that matching of schools could be carried out. Matching based on age and key deprivation indicators. Chosen control region could have no water fluoridation, or fluoridated milk or tablet schemes.
No adjustment for potential confiunders was conducted.
Independent examiner re-examined 12% of children in both regions for inter-examiner comparison and 9% of children re-examined for intra-examiner comparison. Both had high agreement.
Milk fluoridation implemented in Wirral in 1995/1996 and initial survey conducted in 1997/1998. Follow-up survey performed in 2003.
Quality rating
Poor</td></tr>
<tr><td colspan="6">Comments:
This study was considered to be of fair methodological quality. No baseline data is presneted, however analyses were adjusted for clustering, age and IMD 2000 scores (a deprivation index). Based on the results of their study the authors concluded that children in Wirral, the region with a school-based fluoridated milk programme, had better dental health than children residing in Sefton, a region without a fluoridated milk programme. Caries was seen in 13% less children and active decay developed in 16% less children in Wirral compared with Sefton.</td></tr>
</table>

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

A.1.3 TOPICAL FLUORIDES

Level I evidence (Intervention) Petersson et al (2004)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
24 studies RCTs and CTs (≥ 2years duration) Petersson 1998; Grodzka 1982; Holm 1979; Zimmer 2001; Zimmer 1999; Bravo 1997; Borutta 1991; Tewari 1991; Lindquist 1989; Shobha 1987; Clark 1985; Holm 1984; Modeer 1984; van Eck 1984; Schioth 1981; Seppa 1995; Seppa 1994; Skold 1994; Petersson 1991; Seppa 1990; Seppa 1987; Kirkegaard 1986; Bruun 1985; Koch 1979	Not specifically defined	Professionally-applied fluoride varnish	Placebo, no active treatment or fluoride at different concentrations	Change in DMFS/T or dmfs/t	A. A specific clinical question was not defined; however, the objective was stated: to assess the caries preventive effect of topical fluoride varnish applications applied by professionals in patients of various ages. B. Yes. Included electronic and manual searching up to Apr 2003. C. Yes. Relevant papers were selected by two reviewers. D. Yes. Performed by at least two reviewers and scored A-C based on predetermined criteria. E. Yes. Study details and results tabulated. F. Data not pooled. Prevention fraction calculated for each study. G. Not applicable. **Quality** rating: Good
Comments: The authors note that there was limited evidence (evidence level 3) that professional fluoride varnish treatment has a caries preventive effect in permanent teeth in children and adolescents. In primary dentition as well as for adults, the evidence for using fluoride varnish was inconclusive (evidence level 4). The evidence was also inconclusive for the efficacy of different fluoride varnishes as well as for various application frequencies.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level I evidence (Intervention) Marinho et al (2004a)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
17 studies RCTs or quasi-RCTs Ashley 1977; Axelsson 1987; Blinkhorn 1983; Bruun 1985; DePaola 1980; Kirkegaard 1986; Koch 1967; Koch 1979; Mainwaring 1978; Marthaler 1970; Marthaler 1970a; Petersson 1985; Ran 1991; Ringelberg 1979; Seppa 1987; Seppa 1995; Torell 1965	Children or adolescents aged 16 or less at the start of the study (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where intervention is received or time when it started). Studies where participants were selected on the basis of special (general or oral) health conditions were excluded	Topical fluoride in the form of toothpastes, mouthrinses, gels or varnishes at any concentration, amount or duration of application. Application must have been at least once a year	Any of the six possible pair-wise comparisons of the four topical fluoride agents	Included outcomes: change from baseline in DMFS, dmfs, DMFT, proportion of children developing new caries, study withdrawals. Note: other outcomes defined but not assessed included other efficacy measures and safety outcomes	A. Yes. Five specific objectives were defined. B. Yes. A comprehensive electronic and hand search was conducted spanning 1965 to 2001. Non-English articles were not excluded. C. Yes. Inclusion of studies was performed by one reviewer and a 30% sample was checked by a second reviewer. Disagreements were resolved by a third reviewer. D. Yes. Quality assessment of included RCTs was based on concealment allocation and blinding. E. Yes. Data was extracted by one reviewer and about 30% was checked by a second reviewer. F. Yes. Results for caries prevention expressed as a prevented fraction. Withdrawal results expressed as RR. G. Yes. Heterogeneity examined and metaregression used. **Quality rating:** Good
Comments: The authors conclude that fluoride toothpastes in comparison with mouthrinses or gels appear to have a similar degree of effectiveness for the prevention of dental caries in children. There is no clear suggestion that fluoride varnish is more effective than mouthrinses and the evidence for the comparative effectiveness of fluoride varnishes and gels, and mouthrinses and gels is inconclusive. No conclusions about adverse effects could be reached, because no data were reported on in the trials. Acceptance is likely to be greater for fluoride toothpaste.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level I evidence (Intervention) Marinho et al (2004b)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
12 studies RCTs and quasi-RCTs Arcieri 1988; Ashley 1977; Axelsson 1987; Axelsson 1987a; Blinkhorn 1983; DePaola 1980; Mainwaring 1978; Marthaler 1970; Marthaler 1970a; Petersson 1985; Ringelberg 1979; Triol 1980	Children or adolescents aged 16 or less at the start of the study (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where intervention is received or time when it started). Studies where participants were selected on the basis of special (general or oral) health conditions were excluded	Topical fluoride in the form of toothpastes, mouthrinses, gels or varnishes at any concentration, amount or duration of application. Application must have been at least once a year. Any combinations of the above.	Single-topical fluoride agents.	Included outcomes: change from baseline in DMFS, dmfs, DMFT, proportion of children developing new caries, study withdrawals. Note: other outcomes defined but not assessed included other efficacy measures and safety outcomes	*A. Yes. Five specific objectives were defined.* *B. Yes. A comprehensive electronic and hand search was conducted spanning 1965 to 2001. Non-English articles were not excluded.* *C. Yes. Inclusion of studies was performed by one reviewer and a 30% sample was checked by a second reviewer. Disagreements were resolved by a third reviewer.* *D. Yes. Quality assessment of included RCTs was based on concealment allocation and blinding.* *E. Yes. Data was extracted by one reviewer and about 30% was checked by a second reviewer.* *F. Yes. Results for caries prevention expressed as a prevented fraction. Withdrawal results expressed as RR.* *G. Yes. Heterogeneity examined and metaregression used.* Quality rating: *Good*
Comments: The authors conclude that topical fluorides (mouthrinses, gels or varnishes) used in addition to fluoride toothpaste achieve a modest reduction in caries compared to toothpaste used alone. No conclusions about any adverse effects could be reached, because data were scarcely reported in the trials.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level I evidence (Intervention) Steiner et al (2004)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
4 studies RCTs/CCTs Koch 1982; Koch 1990; Reed 1973; Mitropoulos 1984	Not specifically defined	Fluoride toothpaste 1000 ppm	Fluoride toothpaste 250 ppm	DFS/DMFS	A. Yes. The aim was to estimate the overall effect of 1000 ppm F relative to 250 ppm F toothpaste B. Unclear. Search encompassed Medline and CCTR databases but only uncovered 2/6 potentially relevant studies. C. Unclear. Only inclusion criteria stated were trial type and English language. D. No formal assessment of quality was undertaken although certain quality indicators were extracted. E. Yes. F. Yes. Data calculated as prevention fraction and pooled using Bayesian technique. Fixed and random effects models both used. G. Test for heterogeneity non-significant. Quality rating: Fair
Comments: Caries reduction using 1000 ppm F toothpaste was significantly greater compared with 250 ppm F toothpaste. Using the FEM the PF was 0.14 (0.07, 0.21) and using the REM was 0.13 (0.02, 0.23). The authors conclude that the caries increment was low when increasing from 250 ppm F toothpaste to 1000 ppm toothpaste. Due to increased fluorosis associated with higher concentrations of fluoride (not assessed in this study) the authors conclude that 250 ppm F toothpaste should remain in use in Swiss preschools.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level I evidence (Intervention) Twetman et al (2004)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
25 studies RCTs and CTs (≥ 2years duration) Van Wyk 1986; Bilnkhorn 1983; Ringelberg 1979; Ashley 1977; De Paola 1977; Gallagher 1974; Heifitz 1973; Rugg-Gunn 1973; Petersson 1998; Driscoll 1992; Heidmann 1992; deLiefde 1989; Axelsson 1987; Heifetz 1987; Ruiken 1987; Bruun 1985; Poulsen 1984; Driscoll 1992; Heifetz 1982; Ringelberg 1982; DePaola 1980; Luoma 1978	Not specifically defined	Fluoride mouthrinse	Placebo, no active treatment or fluoride at different concentrations	Change in DMFS/T	A. A specific clinical question was not defined; however, the aim was stated: to report the findings concerning the caries-preventive effect of fluoride mouthrinses in various age groups, with special reference to background fluorides. B. Yes. Included electronic and manual searching up to Aug 2003. C. Yes. Relevant papers were selected by two reviewers. D. Yes. Performed by at least two reviewers and scored A-C based on predetermined criteria. E. Yes. Study details and results tabulated. F. Data not pooled. Prevention fraction calculated for each study. G. Not applicable. **Quality rating:** Good
Comments: The authors conclude that there was limited evidence (evidence level 3) that fluoride mouthrinse has a caries preventive effect in permanent teeth in children and adolescents (29%). There was inconclusive evidence (evidence level 4) regarding the effect of fluoride mouthrinse in children and adolescents exposed to additional fluoride sources such as fluoride toothpaste.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level I evidence (Intervention) Ammari et al (2003)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
7 studies RCTs Reed 1973; Forsman 1974; Kocg 1982; Mitropoulos 1984; Winter 1989; Koch 1990; Petersson 1991	Not specifically defined	Toothpaste with ≤ 600 ppm F	Toothpaste with ≥ 1000 ppm F	DMFT/dmft; DMFS, dmfs	A. Yes. The objective was to determine the clinical effectiveness of low fluoride toothpaste containing 600 or less ppm F with toothpaste containing 1000 or more ppm F in preventing dental caries B. Yes. Comprehensive electronic and manual search up to Jan 2001 C. Unclear. Specific criteria not listed and unclear if more than one reviewer assessed citations. D. Yes. Assessed using the Jadad Quality Scale. Only studies with a score of ≥ 3/5 were included. E. Yes. F. Yes. G. Only one analysis showed significant heterogeneity however as this was borderline it was not explored further. **Quality** rating: Fair
Comments: The authors conclude that 250 ppm fluoride toothpaste was not as effective in caries prevention in permanent dentition as toothpaste containing at least 1000 ppm F. More studies required to test difference between 500 ppm F toothpaste and 1000 and above ppm F.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level I evidence (Intervention)					
Marinho et al (2003d); encompasses the following Cochrane Reviews: fluoride toothpaste (Marinho et al, 2003b); fluoride gels (Marinho et al, 2003a; fluoride varnishes (Marinho et al, 2002); fluoride mouthrinses (Marinho et al, 2003c)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
144 studies RCTs or quasi-RCTs Abadia 1978; Abrams 1980; Andlaw 1975; Ashley 1977; Ashley 1977a; Bastos 1989; Bijella 1981; Blinkhorn 1983; Blinkhorn 1983a; Borutta 1991; Brandt 1972; Bravo 1997; Brudevold 1966; Bryan 1970; Buhe 1984; Cahen 1982; Clark 1985; Cobb 1980; Cons 1970; Craig 1981; Depaola 1977; Depaola 1980; Depaola 1980a; Di Maggio 1980; Doles 1980; Driscoll 1982; Duany 1981; Englander 1967; Englander 1971; Englander 1978; Fanning 1968; Finn 1975; Fogela 1979; Forsman 1974; Forsman 1974a; Frostell 1991; Gallaghyer 1974; Gish 1966; Gisselsson 1999; Glass 1978; Glass 1983; Hagan 1985; Hanachowicz 1984; Hargreaves 1973; Hargreaves 1973a; Hargreaves 1973b; Heidemann 1992; Heifetz 1970; Heifetz 1973; Heifetz 1982; Held 1968; Held 1968a; Held 1968b; Hidge 1980; Holm 1979; Holm 1984; Homan 1969; Horowitz 1966; Horowitz 1971; Horowitz 1971a; Horowitz 1971b; Horowitz 1974; Howat 1978; Ingraham 1970; Jackson 1967; James 1967; James 1977; Kinkel 1972; Kleber 1996; Koch 1967; Koch 1967a; Koch 1967b; Koch 1967c; Koch 1967d; Koch 1967e; Koch 1967f; Koch 1975; Laswell 1975; Lind 1974; Mainwaring 1978; Mainwaring 1978a;	Children or adolescents aged 16 or less at the start of the study (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where intervention is received or time when it started). Studies where participants were selected on the basis of special (general or oral) health conditions were excluded	Topical fluoride in the form of toothpastes, mouthrinses, gels or varnishes at any concentration, amount or duration of application. Application must have been at least once a year	Placebo or no topical fluoride therapy	Included outcomes: change from baseline in DMFS, dmfs, DMFT, proportion of children developing new caries, study withdrawals. Note: other outcomes defined but not assessed included other efficacy measures and safety outcomes	A. Yes. Five specific objectives were defined. B. Yes. A comprehensive electronic and hand search was conducted spanning 1965 to 2001. Non-English articles were not excluded. C. Yes. Inclusion of studies was performed by one reviewer and a 30% sample was checked by a second reviewer. Disagreements were resolved by a third reviewer. D. Yes. Quality assessment of included RCTs was based on concealment allocation and blinding. E. Yes. Data was extracted by one reviewer and about 30% was checked by a second reviewer. F. Yes. Results for caries prevention expressed as a prevented fraction. Withdrawal results expressed as RR. G. Yes. Heterogeneity examined and metaregression used. **Quality rating:** *Good*

Level I evidence (Intervention)					
Marinho et al (2003d); encompasses the following Cochrane Reviews: fluoride toothpaste (Marinho et al, 2003b); fluoride gels (Marinho et al, 2003a; fluoride varnishes (Marinho et al, 2002); fluoride mouthrinses (Marinho et al, 2003c)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
Mainwaring 1983; Marthaler 1965; Marthaler 1965a; Marthaler 1970; Marthaler 1970a; Marthaler 1970b; Marthaler 1970c; Marthaler 1974; McConchie 1977; Mergele 1968; Mestrinho 1983; Modeer 1984; Molina 1987; Moreira 1972; Moreira 1981; Muhler 1955; Muhler 1970; Murray 1980; Naylor 1967; Naylor 1979; Olivier 1992; Packer 1975; Peterson 1967; Peterson 1979; petersson 1998a; Poulsson 1984; Powell 1981; Radike 1973; Ran 1991; Ran 1991a; Reed 1973; Reed 1975; Ringelberg 1979; Ringelberg 1979a; Ringelberg 1982; Rugg-Gun 1973; Ruiken 1987; Rule 1984; Segal 1967; Shern 1976; Slack 1964; Slack 1967; Slack 1967a; Slack 1971; Spets-Happonen 1991; Szwedja 1972; Tewari 1990; Thomas 1966; Torell 1965; Torell 1965a; Torell 1965b; Torell 1965c; Treide 1988; Trubman 1973; Weisenstein 1972; Zacherl 1970; Zacherl 1970a; Zacherl 1972; Zacherl 1972a; Zacherl 1973; Zacherl 1981; de Liefde 1989; van Wyk 1986					
Comments: The authors conclude that the benefits of topical fluorides have been firmly established on a sizable body of evidence from RCTs. While the formal examination of sources of heterogeneity between studies has been important in the overall conclusions reached, these should be interpreted with caution. We were unable to reach definite conclusions about any adverse effects that might result from the use of topical fluorides, because data reported in the trials are scarce.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level I evidence (Intervention) Twetman et al (2003)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
54 studies RCT or CT (≥ 2 years follow-up) Davies 2002; Winter 1989; Cahen 1982; Heidmann 1997; Bube 1984; Hanachowicz 1984; Andlaw 1983; Mainwaring 1983; Zacherl 1981; Abrams 1980; Murray 1980; Ennever 1980; Fogels 1979; Naylor 1979; Ringelberg 1979; Glass 1978; Mainwaring 1978; James 1977; Kinkel 1977; Lind 1976; Reed 1975; Andlaw 1975; Stookey 1975; Saporito 2000; Glass 1997; O'Mullane 1997; Stephen 1994; DePaola 1993; Marks 1992; Petersson 1991; Koch 1990; Ripa 1990; Beiswanger 1989; Blinkhorn 1988; Ripa 1988; Stephen 1988; Lu 1987; Mitropoulis 1984; Koch 1982; Beiswanger 1981	Not specifically defined	Fluoride toothpaste	Placebo, no fluoride toothpaste or fluoride toothpaste of a different concentration	Change in DMFS/T or dmfs/t	A. A specific clinical question was not defined; however, the aim was stated: to assess the caries preventive effect of fluoride toothpastes in non-selected populations of various ages with emphasis on fluoride concentration and supervised vs non-supervised brushing. B. Yes. Included electronic and manual searching up to Apr 2003. C. Yes. Relevant papers were selected by two reviewers. D. Yes. Performed by at least two reviewers and scored A-C based on predetermined criteria. E. Yes. Study details and results tabulated. F. Data not pooled. Prevention fraction calculated for each study. G. Not applicable. Correlation used to measure relationship between baseline caries and efficacy. **Quality rating** Good
Comments: The authors conclude that they found strong evidence that daily use of fluoride toothpaste had a significant caries-reducing effect in young permanent teeth compared with placebo (evidence level 1). Supervised tooth brushing was more effective than non-supervised brushing (evidence level 1). Moreover, strong evidence suggested a dose-response relationship with enhance caries protection from toothpastes with 1500 ppm of fluoride in young permanent teeth following daily use (evidence level 1).					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level I evidence (Intervention) Van Rijkom et al (1998)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
19 studies RCTs Englander 1967; Bryan 1970; Cons 1970; Englander 1971; Horowitz 1971; Szwejda 1971; Szwedja 1972; Trubman 1973; Mainwaring 1978; Cobb 1980; Hagan 1985; Olivier 1992; Heifetz 1970; Marthaler 1970; Howat 1978; Fogels 1979; Abrams 1980; Rule 1984; Ran 1991	Non-selected population aged 6-15 at start of study	Fluoride gel	Placebo or no treatment	Caries incidence at surface level	A. Yes. The purpose of the meta-analysis was to (i) assess the overall caries-inhibiting effect of clinical fluoride gel treatment studies and (ii) to explore factors potentially modifying the caries-inhibiting effect of fluoride gel. B. No. Only Medline database was searched. C. Yes. Inclusion and exclusion criteria were clearly defined. Unclear if applied by more than one reviewer. D. No. E. Yes. F. Yes. Results expressed as prevention fraction and NNT. G. Not specifically, although analyses were performed on different variables (eg, baseline caries prevalence, fluoride regimen, gel application method and application frequency) Quality rating: Fair
Comments: The authors conclude that a 22% overall caries-inhibiting effect resulted from the included fluoride gel treatment trials. The different variables did not significantly affect the careis-inhibiting effect of fluoride gel. The NNT in a low caries population was 18 while in a high caries population was 3. Therefore, from the standpoint of cost-effectiveness, the additional effect of fluoride gel treatment in current low and even moderate caries incidence child populations must be questioned.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level I evidence (Intervention) Axelsson et al (2004)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
24 studies RCTs and CCTs (≥ 2 years duration) Maltz 2003; Ekstrand 2000; Arrow 1998; Axelsson 1994; lalloo 1994; Stephen 1990; Klimek 1985; Petersson 1985; Zickert 1982; Melsen 1980; Bagramian 1978; Hamp 1978; Fischman 1977; Downer 1876; Powell 1999; Fure 1998; Mojon 1998; Zimmer 2001; hausen 2000; Seppa 1991; Rask 1988; Gisselsson 1983; Kerebel 1985; Zickert 1982	Not specifically defined	Combination of two or more caries-preventive measures (± fluoride)	Placebo, no treatment or different active treatments	Change in DMFS/T or dmfs/t	A. A specific clinical question was not defined; however, the aim was stated: to assess the caries preventive effect of combinations of interventions. B. Yes. Included electronic and manual searching up to Jun 2003. C. Yes. Relevant papers were selected by two reviewers. D. Yes. Performed by at least two reviewers and scored A-C based on predetermined criteria. E. Yes. Study details and results tabulated. F. Data not pooled. No details of analysis given. G. Not applicable. Quality rating: Fair. Not specifically related to fluoride.
Comments: No formal pooled analysis. Provides moderate scientific evidence that combinations of treatments involving fluoride have a preventive effect on caries in children and adolescents (evidence level 2). For elderly patients the evidence was found to be incomplete (evidence level 4) and no conclusion could be drawn for high risk groups as the evidence was conflicting.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

LEVEL I EVIDENCE (INTERVENTION) Bader et al (2001)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
27 studies Study type not defined Included studies relevant to this review: Hamberg 1971; Hennon 1972; Margolis, 1967; Margolis 1975; Hennon 1977; Hu 1998; Lin 2000; Holm 1979; Grodzka 1982; Frostell 1991; Twetman 1996; Petersson 1998; Autio-Gold 2001	Preschool children (aged 0-5)	Various but dietary and topical fluoride relevant to this review	No fluoride	Caries prevention and fluorosis	A. Yes. Five clinical questions were defined of which two were directly relevant to this review: (i) How effective is the prescription of dietary supplemental fluoride by the primary care clinician; and (ii) how effective is application of fluoride by the primary care clinician. B. Yes. Electronic search of Medline and Cochrane database and manual search. C. Unclear. Inclusion criteria were that it addressed clinical question, reported original data and involved primary care practitioners. D. No. E. Yes. F. Data were not pooled. G. Not applicable. Quality rating: Fair. Not specifically related to fluoride.
Comments: No formal pooled analysis. With regards to the use of fluoride, the authors conclude that there is fair evidence of the effectiveness of two fluoride-based interventions (supplementation and varnish).					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level II evidence (Intervention) Al-Jundi et al (2006)					
Study type Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=856	Children in 1st and 6th grades in four schools in Irbid City, Jordan	School-based dental education programme and supervised toothbrushing with fluoridated toothpaste (500 ppm for 1st graders and 1000 ppm for 6th graders)	School-based educational programme only	deft/DMFT	A. Unclear. Described as randomised but no further details given. B. No. C. No demographic details reported. Baseline deft/ DMFT similar across treatment groups for 1st and 6th graders. D. 94% of subjects completed studies. Is assumed that analysis was performed on completers only. Similar proportions lost across age groups and treatments. E. No sample size calculations reported. Analysis of difference included all patients and baseline and only completers at endpoint. Analysis adjusted for gender and age. No assessment of whether completers group differed from baseline group. F. No **Quality rating:** Poor
Comments: This study was considered to be of poor methodological quality due to a lack of assessment of potential confounders and the comparison of potentially non-comparable patients groups (ie, all patients at baseline with only completers at endpoint.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Jackson et al (2005)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cluster-RCT N=517	Children in the first term of their first year of primary school in North West London	Daily toothbrushing at school with a 1450 ppm fluoride toothpaste	No daily toothbrushing at school	dmfs/DMFS	A. Unclear. Cluster-randomised by school. B. Single-blind. Examiner unaware of school treatment assignment. C. Age, gender, assessable surfaces and mean DMFS + dmfs similar between treatment groups at baseline. No other variables assessed. D. No. 72% completed study. Baseline characteristics similar for those completing compared with those randomised. E. Required sample size calculated. Randomised sample large enough however completed sample lower than required sample. F. Yes. Apart from overall analysis, analyses were conducted on those not caries-free at baseline. Quality rating: Fair
Comments: This study was considered to be of fair methodological quality. Data on potential confounders was not collected (eg, use of other fluoride agents outside school) and analyses were not adjusted for these potential confounders. Completers analysis only. Caries increment was less for children in the test group compared with the control group (2.60 vs 2.92). The authors conclude that the study results suggest that "a programme of daily teacher-supervised toothbrushing with fluoride toothpaste can be effectively targeted into socially-deprived communities and a significant reduction in dental caries can thereby be achieved especially among caries-susceptible children".					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Jiang et al (2004)					
Study type Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cluster RCT N=661 1. n=205 APF foam 2. n= 210 APF gel 3. n=246 control	Children 6-7 years old were recruited from primary schools in Wuhan City, China	Professionally applied acidulated phosphate fluoride (APF) (1.23%) in gel or foam form every 6 months for 2 years	No treatment	dmfs/DMFS Assessed at baseline and after 2 years	A. Unclear. Randomised by classroom to one of three treatment groups using block randomisation. B. Yes. C. Yes. Characteristics assessed included age, gender, toothbrushing frequency, use of fluoride toothpaste, dental visits, socioeconomic status and baseline caries. D. No. 93% of randomised subjects included in analysis. No comparison of randomised subjects and completers characteristics is presented. E. Yes. Completers analysis had sufficient power to detect the expected difference. F. No **Quality rating:** Fair
Comments: Study considered to be of fair methodological quality due to only completers analysis being performed and no comparison of demographic and other characteristics of completers and subjects randomised. The study found that there was a significant reduction in caries when comparing fluoride gel and foam with the control group. There was no significant difference between fluoride gel and foam.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) *Källestål (2005)*					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=1134	High risk 12-year old children attending one of 26 Swedish public dental health clinics. Children were considered high-risk for one of a number of reasons (ie, DeMFSa>1; mental or physical disability or chronic disease; CFU>105)	1. Tooth-brushing programme: yearly instruction on tooth brushing technique using fluoridated toothpaste 2. Fluoride lozenge programme: 0.25 mg × 3, daily up to 16 and thereafter 0.25 × 4, daily. 3. Fluoride varnish programme: fluoride varnish (Duraphat®) 3 times during 1 week, 6 monthly. 4. Individual programme: counselling and varnish every 3 months	Active treatments only (see Intervention)	Change in DMFS/DeMFS	A. Unclear. Described as randomised but no further details reported. B. No. C. No baseline demographics reported. Baseline caries levels show some difference but do not appear to be statistically significant. D. No. Completers only. At five years 80% of randomised subjects included in the analysis. E. No sample size calculations performed. Analysis adjusted for significant variables. F. No. **Quality rating:** Poor.
Comments: Study was considered to be of poor methodological quality due to analysis of completing subjects only. No comparison of demographics and other variables for completers vs randomised subjects was carried out. Programme C (semi-annual application of fluoride varnish; RR 0.88 (0.79, 0.97) and RR 0.88 (0.78, 0.98) for dentine increment and dentine + enamel increment respectively).					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Truin and van't Hof (2005)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=594 1. n=305 fluoride 2. n=289 placebo	Low caries-active children aged 9.5-11.5 years who were regular attendees at 3 paediatric clinics in the cities of Oss, Nijmegan and Beuningen in the Netherlands	Fluoride gel (4500 ppm fluoride ion) was professionally applied in a flexible tray for 4 minutes. The protocol was repeated eight times over four years	Placebo	The number of decayed, missing, and filled tooth surfaces in permanent teeth.	A. Probably. Randomised using unmarked envelopes. B. Yes. Placebo gel used. C. Y es. D. Yes. ITT analysis conducted including 95% of randomised patients. E. Yes. F. Yes. Subgroups analysed included per-protocol population and the 'caries-free' subgroup. Quality rating: Good
Comments: The prevention fraction was 18%. The relative mean reduction in dental caries was 0.2. These results were not statistically significant.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Skold et al (2005a)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=788 1. n=173 Group 1 2. n=162 Group 2 3. n=184 Group 3 4. n=175 Group 4 5. n=94 Control	Children 13 years old from five secondary schools in the city of Molndal in Sweden	All groups rinsed with 10 mL of a 0.2% neutral NaF solution Group 1. Rinsed the first three schooldays every semester. Six rinses a year Group 2 rinsed the first three and the last three schooldays of every semester. Twelve rinses every year Group 3 rinsed three consecutive days once a month during the semesters. Twenty-seven rinses a year. Group 4 rinsed once every fortnight during the semesters. Twenty rinses a year	Did not rinse	Caries prevalence, prevented fraction	A. Unclear. Describes as randomised but no further details provided. B. No. C. Not stated. D. No. Analysis included completers only (79%). E. No sample size calculations performed. No adjustment for potential confounders. F. No. Quality rating: Poor
Comments: *The study was considered to be of poor methodological quality due to a lack of description of the randomisation procedure, no blinding, a lack of description of baseline characteristics of the groups and lack of adjustment for potential confounders. Prevented fraction was 30% for Group 1, 59% for Group 2, 47% for Group 3 and 41% for Group 4. These results were statistically significant for Groups 2, 3 and 4.*					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Skold et al (2005b)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=758 1. n=190 Fluoride group 1 2. n=186 Fluoride group 2 3. n=201 Fluoride group 3 4. n=173 Control	Children 13 years of age from nine secondary schools in three different geographical and socioeconomic areas of Sweden	1. Fluoride varnish application twice a year for three years at six month intervals. (6 times total) 2. Fluoride varnish application three times a year, all in one week, for three years. (9 times total) 3. Fluoride varnish application eight times a year with at least a one month interval for three years. (24times total)	No varnish	Caries prevalence	A. Unclear. Described as randomised but no further details given. B. No. C. Not stated. D. No. Analysis based on 89% of randomised subjects. E. No sample size calculations performed and no adjustment for potential confounders. F. Yes. Analyses performed for the whole group and by SES. **Quality rating:** Poor
Comments: The study was considered to be of poor methodological quality due to a lack of description of the randomisation procedure, no blinding, a lack of description of baseline characteristics of the groups and lack of adjustment for potential confounders. Prevented fraction was 30% for Group 1, 59% for Group 2, 47% for Group 3 and 41% for Group 4. These results were statistically significant for Groups 2, 3 and 4.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Stookey et al (2003)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=955 1. n= 242 2. n=235 3. n=238 4. n=240	School children aged 9-12 years recruited from an urban area in Puerto Rico that had a community water supply containing low levels of fluoride (<0.3 ppm)	Supervised tooth brushing twice a day in the classroom using one of the three experimental fluoride containing dentifrices. 1. low sodium fluoride dentifrice 500 ppm 2. high sodium fluoride dentifrice 2800 ppm 3. stabilized stannous fluoride with sodium hexametaphosphate (1100 ppm)	Supervised tooth brushing twice a day in the classroom using one the positive control dentifrice 4. positive control dentifrice 1100 ppm	Decayed, missing and filled surface scores over time	A. Unclear. Randomised but no further details given. B. Yes. C. Yes. D. No. Analysis included 71% of subjects who completed study. E. Sample size calculations carried out however completer's analysis contained fewer than required subjects. F. Yes. Subgroup analysis carried out on completers who attended at least 60% of supervised toothbrushing sessions. **Quality rating:** Fair.
Comments: This study was considered to be of fair methodological quality due to an insufficient sample size and analysis of completer's only. A greater reduction in DMFS was seen for higher concentration sodium fluoride toothpaste, and the experimental toothpaste.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) van Rijkom et al (2004)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=773 1. n=387 fluoride 2. n=386 placebo	Low caries-active children aged 4.5-6.5 years who were regular attendees at 3 paediatric clinics in the cities of Oss, Nijmegan and Beuningen in the Netherlands	Fluoride gel (4500 ppm fluoride ion) was professionally applied in a flexible tray for 4 minutes. The protocol was repeated eight times over four years	Placebo	Caries diagnosis, distinguishing enamel (D2) and dentinal (D3) scores.	A. Unclear. Randomised using unmarked envelopes. B. Yes. C. Yes D. ITT analysis conducted including 97% of randomised subjects. E. Sample size calculations not reported. F. Yes. ITT, per-protocol and caries-free subgroups analysed. Quality rating: Fair
Comments: This study was considered to be of fair methodological quality due to lack of detail regarding randomisation and sample size calculations. Prevention fraction was 26% for permanent teeth and 20% for primary teeth.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Biesbrock et al (2003a)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=657 1. n=218 High fluoride 1450 ppm 2. n= 219 Low fluoride 500 ppm 3. n=220 control	Children aged 9-12 years were recruited from an urban area of Guatemala	Twice daily supervised tooth brushing using toothpaste containing either 1450 ppm fluoride or 500 ppm fluoride	Supervised brushing with a placebo toothpaste; however, randomised and switched to active treatment after 9 months.	Decayed, missing or filled surfaces (DMFS)	A. Unclear. Described as randomised but no further details given. Siblings in same household assigned to same treatment. B. Yes. C. Yes. D. No. Completer's analysis including 81% of randomised subjects. E. No sample size calculations reported. F. No. **Quality rating:** Poor.
Comments: The study was considered to be of poor methodological quality due to lack of description of randomisation, lack of sample size calculations and completer's only analysis. Percent reduction in DMFS was 86% and 89% in the 500 ppm F and 1450 ppm fluoride groups respectively.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Biesbrock et al (2003b)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=644 1. n=212 High fluoride 2800 ppm 2. n= 216 Low fluoride 1100 ppm 3. n=216 control	Children aged 9-12 years were recruited from an urban area of Guatemala	Twice daily supervised tooth brushing using toothpaste containing either 2800 ppm fluoride or 1100 ppm fluoride	Supervised brushing with a placebo toothpaste; however, randomised and switched to active treatment after 9 months.	Decayed, missing or filled surfaces (DMFS)	A. Unclear. Described as randomised but no further details given. Siblings in same household assigned to same treatment. B. Yes. C. Yes. D. No. Completer's analysis including 77% of randomised subjects. E. No sample size calculations reported. F. No. **Quality rating:** Poor.
Comments: The study was considered to be of poor methodological quality due to lack of description of randomisation, lack of sample size calculations and completer's only analysis. Percent reduction in DMFS was 52% and 59% in the 500 ppm F and 1450 ppm fluoride groups respectively.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Rong et al (2003)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cluster-RCT N=731 1. n=361 fluoride 1100 ppm 2. n=370 control	3 year old kindergarten children in the Miyun County of China	Oral health education sessions and supervised teeth brushing twice a day using fluoridated toothpaste, 1100 ppm F New toothpaste and tooth brush was given to each child every 3 months for 2 years	No education and no supervised teeth brushing No supplied toothbrush or toothpaste	dmfs	A. No. Kindergartens randomised by drawing lots. B. No C. Yes. D. No. Analysis includes 70% of randomised children. E. Yes. Sample size calculation not reported. F. No. Quality rating: Poor
Comments: This study was considered to be of poor methodological quality due to the use of a non-secure randomisation procedure, lack of blinding, non-ITT analysis and lack of sample size calculations. Reduction in caries increment was 31% (p=0.009).					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Davies et al (2002)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N = 7422 1. n = 2488, fluoride toothpaste, 1450 ppmF 2. n = 2472, fluoride toothpaste, 440 ppmF 3. n = 2462 Comparison group toothpaste (no intervention)	Male and female children were enrolled at the age of 12 months	At age 12 months children were provided with free "off the shelf" toothpaste (containing either 440 ppm or 1450 ppm fluoride) every 12 weeks until they were 5½ years old. They also received a free toothbrush annually	No intervention	Mean decayed missing and filled teeth (dmft). Caries examination using the standards set by the British Association for the Study of Community Dentistry (BACD)	A. Yes. Treatment group allocated centrally. B. No. Families were aware of treatment allocation but caries examinations were blinded. C. Data not provided D. No, 46.7% of randomised children were unable to be included in the analysis. Generally because they had moved out of the study area during the course of the study. E. Yes. Sample size calculations carried out. F. Yes. Analysis performed on completers subgroup, completers + withdrawals who were examined clinically, and completers + withdrawals + an estimate for those not examined clinically using control data. **Quality rating:** *Fair*
Comments: Children who received 1450 ppm fluoride toothpaste had a statistically significantly lower mean dmft (mean 2.15) than those that received 440 ppm fluoride toothpaste (mean 2.49; P=0.02) and those in the control group (mean 2.57, P=0.002; 16% reduction compared with control). There was no statistical difference between the mean dmft values for the 440 ppm fluoride toothpaste group and the control. The proportion of children with dmft>0 was statistically significantly lower than the 440 ppm fluoride toothpaste and control groups (1450 ppmF, 50%, 440 ppmF 58%, control 58%, P<0.001). Similarly, the proportion of children with more than 0 missing teeth in the 1450 ppm fluoride toothpaste group was statistically significantly lower than the 440 ppm fluoride toothpaste and control groups (1450 ppmF, 12%, 440 ppmF 14%, control 17%, P,0.02).					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Madléna et al (2002)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cluster-RCT N=586 1. n=192; Fluoride toothpaste + fluoride gel 2. n= 157; Fluoride toothpaste + placebo gel 3. n=237; usual care	School pupils aged 14-16 in Budapest and Debrecen, Hungary	Toothpaste and gel 1. Amine fluoride toothpaste and amine fluoride gel 2. Amine fluoride toothpaste and placebo gel	No amine fluoride toothpaste or gel	DMFS DMFT	A. Unclear. Cluster randomised. B. No. C. No difference reported; however, baseline DMFS and DMFT appears lower in control group. D. No. Completers analysis includes 70% of randomised subjects. E. No sample size calculation reported. F. No. Quality rating: Poor
Comments: This study was rated as being of low methodological quality due to a lack of information regarding randomisation, lack of blinding, possible difference between groups in caries prevalence at baseline, analysis of completers only and lack of sample size calculations. There was a significant difference in caries reduction as a percentage of control group for both intervention groups: 37% and 36% when measured using DMFT; and 34% and 13% when measured using DFMS for toothpaste/gel and toothpaste only respectively.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) You et al (2002)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=1334 1. n=682, fluoride toothpaste, 1100 ppmF 2. n=652 Placebo	Preschools children recruited from 24 kindergarten classes. Mean age 3.0 years 54.4 % male	1100 ppm fluoride dentrifice brushed twice daily (morning and afternoon) at school under the supervision of classroom teachers during rhe school week. At each brushing, the teachers applied a pea-sized dose of toothpaste (~0.48 grams). An educational program consisting of video and audio programs supplemented with pictures was provided to children and teachers every two weeks. Children were supplied with toothbrushes and toothpaste (120 g) every three months	Placebo	Visual-tactile caries examinations performed at baseline, one year and two years to provide decayed, missing, and filled surfaces (dmfs) increment scores. Safety measures: time-controlled 24 hour urine samples to determine levels of ingested fluoride in a subgroup of 40 randomly chosen children in each group tested before and after starting the school program	A. Subjects were randomly assigned but no further detail provided. B. No. Examiner-blind only. C. Yes. Baseline age, gender mix, and dmfs were similar in both groups. D. No, there was a 31.1% attrition rate over the two years. Analysis conducted on completers. E. Yes F. Yes. Subgroup analysis performed on completers who complied with study protocol continuance criteria. **Quality rating:** *Fair*
Comments: Study rated as fair methodological quality due to lack of detail of randomisation procedure and analysis of completers only. Both groups demonstrated a reduction in dmfs from baseline to end of study (year 2). However, mean dmfs fell more sharply in the fluoride group compared to the placebo group. The year two results, for all subjects that provided data (Primary examiner), demonstrated that the increment dmfs in the sodium fluoride group was 14.4% lower than the placebo group (P = 0.034). Similarly, the year two results, for all subjects that provided data (secondary examiner), found that the increment dmfs in the sodium fluoride group were 16.1% lower than the placebo group (P = 0.046). Ingestion of fluoride by the young participants was found to be within accepted safe levels.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level II evidence (Intervention) Biesbrock et al (2001)					
Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=5439 1. n=1361, fluoride toothpaste, 1100 ppm F 2. n=1360, fluoride toothpaste, 1700 ppm F 3. n=1359, fluoride toothpaste, 2200 ppm F 4. n=1359, fluoride toothpaste, 2800 ppm F	Elementary school children aged 6-15 years recruited from an urban central Ohio (USA) area. Subjects were stratified by gender, age, and baseline DMFS scores	Fluoride toothpaste: 1. 0.243% sodium fluoride (1100 ppm) 2. 0.376 sodium fluoride (1700 ppm) 3. 0.486% sodium fluoride (2200 ppm) 4. 0.619% sodium fluoride (2800 ppm)	Active treatment of varying fluoride concentrations (see Intervention)	Visual-tactile and radiographic examination were conducted at baseline and after one, two and three years of treatment. DMFS DMFT	A. Unclear. Described as randomised but no further details provided. B. Yes. C. Yes. D. No. Only completers at each time point included in analysis. This included 81% of subjects at year 1, 70% of subjects at year 2 and 62% of subjects at year 3. E. Analyses tested after adjusting for various variables including age and gender. Also included adjustment for baseline DMFS and baseline surfaces at risk. F. No **Quality rating:** Fair
Comments: Study rated as fair methodological quality due to lack of detail of randomisation procedure and analysis of completers only. At year 1, children provided with toothpaste containing 2800 ppmF, 2200 ppmF, and 1700 ppmF had fewer caries than children provided with toothpaste containing 1100 ppmF. These differences were statistically significant in the 2800 ppmF and 2200 ppmF treatment groups. These differences were not maintained throughout year 2 and 3 of the study and the authors note that a concurrent preventive fluoride rinse program may have confounded the results.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

A.2 FLUOROSIS

A.2.1 FLUORIDATED WATER

Level III/IV evidence (Intervention) Khan et al (2000)					
Study/patient number Study type	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
55 studies Population/school studies	Aged 0-19 years from population sample or school sample	Water fluoride concentration up to 1.4 ppm	None	Fluorosis prevalence	A. Yes. The aim was to determine trends in fluorosis prevalence at water fluoride levels < 0.3, >0.3 to <0.7 and > 0.7 to 1.4 ppm from 1980-2000. B. Maybe. Electronic search using PubMed and manual search of reference lists. C. Yes. Specific inclusion criteria stated. Unclear whether inclusion assessed by more than one reviewer. D. No. E. No. No summary of the characteristics or results of the individual studies is provided. F. Yes. G. No. Quality rating: **Poor.**
Comments: This review was considered to be of poor methodological quality due to the lack of detail given regarding each included studies, and the lack of quality assessment. There has been an increase in fluorosis in fluoridated and non-fluoridated communities over time.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level III/IV evidence (Intervention) *McDonagh et al (2000a)*					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
88 studies 4 before-after; 1 case-control; 83 single-time point cross-sectional	Not specifically defined	Water fluoridation (natural or artificial) up to a level of 5 ppm	Other levels of water fluoridation	Fluorosis as defined by any fluorosis scale. Results divided into 'any fluorosis' defined as any degree of fluorosis on any fluorosis scale, or 'fluorosis of aesthetic concern' defined as a score of ≥ 3 on TF index, mild on the Dean's index or ≥ 2 on the TSIF scale	A. Yes. A specific objective was stated as "does water fluoridation have negative effects?" with the specific effect being examined inthis section being dental fluorosis. B. Yes. Included electronic and manual searching up to Feb 2000. C. Yes. Assessed by three reviewers. D. Yes. Assessed using a NHS CRD checklist. E. Yes. Detailed summary provided in data extraction tables. F. Yes. Multilevel regression analysis used to combine studies. G. Yes. Multivariate analysis used to investigate possible sources of heterogeneity by assessing a number of potential confounders. **Quality rating:** Good.
Comments: The NNH for 'any fluorosis' was 6, while the NNH for 'fluorosis of aesthetic concern' was 22. The authors state that a beneficial reduction in caries should be considered together with the increased prevalence of dental fluorosis. There was no clear evidence of other potential adverse effects.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level IV evidence (Intervention) Harding et al (2005)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=294	5-year-old schoolchildren in Cork, Ireland	Fluoridated water supply Concentration 0.8 to 1.0 ppm	Non-fluoridated water supply Concentration not stated	Fluorosis measured using modified TSIF scale	Survey conducted in areas with existing fluoridation. Examinations conducted prospectively. Unclear if extent of the intervention was reliable mesured. Assume that at time of survey, fluoride levels in fluoridated areas would be at optimum levels. Analyses adjusted for demographic variables as well as extent of additional fluoride exposure. . Outcome assessment was not blinded. Survey conducted after sufficient time for outcomes to occur. **Quality rating:** *Fair*
Comments: This study was considered to be of fair methodological quality due to the lack of clear measurement of water fluoride levels in the included areas and the lacking of blinding of outcome assessment. Fluorosis prevalence was 32% in children residing in areas with water fluoridation and 1% in children residing in areas without water fluoridation. Regression analysis showed that water fluoridation and age at which toothbrushing was started were associated with a significantly increased risk of fluorosis. Children who always received a fluoridated water supply were 38 times more likely to have fluorosis, while children who began using toothpaste between 12 and 18 months were 2 times more likely to have fluorosis.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Intervention) Ruan et al (2005)					
Study type/patient no.	**Population**	**Intervention group**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=577	12-13 year-old schoolchildren from selected schools	Villages with same water supply for 13 years Optimal or higher concentration fluoride Concentration 1.0-5.6 ppm	Villages with same water supply for 13 years Low fluoride concentration Concentration 0.4 ppm	Fluorosis measured using TF score	Survey conducted in areas with existing natural fluoride levels. Examinations conducted prospectively. Fluoride concentrations in each region measured using fluoride selective electrodes. Univariate analyses included demographic variables and whether water stored in clay pots (which can increase fluoride concentration). Outcome assessment was blinded as fluoride levels in regions unknown to examiner. Timeframe of study sufficient to allow development of fluorosis. Quality rating: Good
Comments: Only regions A and B were included in this review as they had water fluoride levels considered to be suboptimal (0.4 ppm) and optimal (1.0 ppm). The prevalence of 'any fluorosis' was 64.4% in the optimally fluoridated area and 13.7% in the sub-optimally fluoridated area. The prevalence of fluorosis of aesthetic concern was 18.4 % in the optimally fluoridated area and 2.4% in the sub-optimally fluoridated area. The OR was 23.3 (5.0, 19.5). The clay pots and being 13 rather than 12 were both associated with significantly higher fluorosis. In the optimally fluoridated region, not using clay pots resulted in a mean TF score of 1.13, while in the sub-optimally fluoridated region, not using clay pots for water storage resulted in a mean TF score was 0.14.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Intervention) Cochran et al (2004)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=2051	Schoolchildren aged 8 years in selected European cities (Cork, Knowsley, Athens, Haarlem, Oulu, Reykjavik, Almada and Setubal.	Fluoridated water supply Concentration > 1.0 ppm (Cork)	Non-fluoridated water supply Concentration < 0.13 ppm (Knowsley, Oulu, Athens, Reykjavic, Haarlem, Amada, Setubal)	Fluorosis measured using TF scale	Survey conducted in areas with existing fluoridation (natural and artificial). Examinations conducted prospectively. Records of fluoride levels over 10 year period obtained from towns. Extent of additional fluoride exposure adjusted for in analysis. Examinations performed blinded to fluoride exposure. Quality rating: Good
Comments: Any fluorosis was 89% in fluoridated region and averaged 68% in non-fluoridated areas. Fluorosis of aesthetic concern was 4% in the fluoridated region and averaged 1% in the non-fluoridated regions. After adjustment for use of fluoride tablets, there was a significantly increased risk of any fluorosis associated with water fluoridation (OR 3.53; 2.52, 4.93).					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Intervention) Whelton et al (2004)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=17851	Schoolchildren aged 5, 8, 12 and 15 in Ireland (Fluorosis only reported for 8, 12 and 15 year-olds)	Full fluoridation	No fluoridation	Fluorosis measured using Dean's Index	Survey conducted in areas with existing fluoride levels (natural and artificial). Examinations conducted prospectively. Unclear how fluoride levels were measured. Extent of additional fluoride exposure measured included but not adjusted for in analysis. Unclear id blinded outcome assessment. Quality rating: Fair
Comments: This study was considered to be of fair methodological quality due to the lack of (i) method of measurement of fluoride levels, (ii) adjustment for other factors and (iii) blinding of outcomes assessment. Any fluorosis was found in 30% of subjects in fluoridated areas and 13% of subjects in non-fluoridated areas. Fluorosis of 'aesthetic concern' was found in 6% of subjects in fluoridated regions and 2% in non-fluoridated regions.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Intervention) Hamdan (2003)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=1878	Schoolchildren aged 12 in Jordan	Various levels of fluoride in drinking water (up to 0.8 ppm)	Various levels (as low as 0.4 ppm)	Fluorosis measured using TF scale	Survey conducted in areas with existing fluoride levels. Examinations conducted prospectively. Unclear how fluoride measurements made. No measurement of potential confounders, or adjustment for confounders in analysis. Outcome assessment not blinded. **Quality rating:** Poor
Comments: This study was considered to be of poor methodological quality due to the lack of (i) method of measurement of fluoride levels, (ii) measurement and adjustment for potential confounders and (iii) blinding of outcomes assessment. The proportion of children with fluorosis was significantly higher in children in the regions with higher fluoride levels. However, these were also situated in the southern, warmer regions of Jordan, and as such water intake may play a role in level of fluorosis.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Intervention) Griffin et al (2002)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=1839	School children aged 12-14 with at least one tooth scored for fluorosis who took part in the 1986-1987 National Survey of Oral Health in US School Children	Optimal fluoride (0.7 ppm to 1.2 ppm)	Optimal fluoride (< 0.3 ppm)	Fluorosis measured using Dean's Index	Survey conducted in areas with existing fluoride levels. Analysis of retrospectively collected data carried out prospectively. Fluoride levels measured at participating schools. Used as a proxy for subjects intake. Children whose residential fluoridation status was not consistent with the school fluoridation status were excluded. Demographic and other variables measured as part of original survey. No adjustment for these variables made in the analysis, although analysis conducted on children who had not received fluoride tablets or drops. Blinding of outcome assessment not stated. Quality rating: Fair
Comments: This study was considered to be of fair methodological quality due to the retrospective nature of the study and the lack of (i) adjustment for potential confounders and (ii)information regarding the blinding of outcomes assessment. Any fluorosis was seen in 70% of subjects exposed to optimal fluoridation and 36% of subjects exposed to low fluoride. Fluorosis of 'aesthetic concern' was seen in 7% of subjects with optimal fluoride exposure and 1% of subjects exposed to low levels of fluoride in water.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Intervention) Louw et al (2002)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=387	Children aged 11-13 in a number of regions of rural south-western South Africa with different natural fluoride levels.	Optimal fluoride (0.7 ppm to 1.2 ppm)	Optimal fluoride (< 0.4 ppm)	Fluorosis measured using Dean's Index	Survey conducted in areas with existing fluoride levels. Examinations carried out prospectively. Fluoride concentration measured potentiometrically over a period of 10 years. No t of optential confounders and no adjustment in analysis. Outcome assessment not blinded. **Quality rating:** Poor
Comments: This study was considered to be of poor methodological quality due to a lack of assessment of potential confounding factors and a lack of blinding.The results of the study show high levels of fluorosis across all regions.The authors note that the regions examined have high temperatures which may result in increased water consumption.This in turn may halp explain the high levels of fluorosis in regions with optimal or suboptimal fluoride levels.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Intervention) Stephen et al (2002)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=317	Schoolchildren aged 5/6 (Grade 1) and 8-12 (Grade 4-7)	3 regions with naturally fluoridated water (concentration 2.4 ppm diluted to 1ppm)	2 regions naturally non-fluoridated (0.03 ppm)	Fluorosis measured using TF Index	Survey conducted in areas with existing fluoride levels. Data collected prospectively. Method of measuring fluoride levels not stated. Demographic and other data collected and fluorosis associated with fluoridation status measured according to other fluoride exposures. Outcome assessment blinded. **Quality rating:** Good
Comments: Any fluorosis was seen in 33% of subjects exposed to optimal fluoridation and 18% of subjects exposed to low fluoride. Fluorosis of 'aesthetic concern' was seen in 7% of subjects with optimal fluoride exposure and 3% of subjects exposed to low levels of fluoride in water.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Intervention) Tabari et al (2002)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=812	Schoolchildren aged 8-9 who were lifetime residents of a fluoridated (Newcastle) or non-fluoridated (Northumberland) region.	Water fluoridation to 1.0 ppm (Newcastle)	Natural water fluoridation of 0.1 ppm (Northumberland)	Fluorosis measured using TF Index	*Survey cond*ucted in areas with existing fluoride levels. Data collected prospectively. Method of measuring fluoride levels not stated. Demographic and other data collected and fluorosis associated with fluoridation status measured according to other fluoride exposures. Outcome *assessment not blinded.* **Quality rating:** Fair
Comments: This study was considered to be of fair methodological quality due to a lack of (i) descriptions of measurement of fluoride levels, and (ii) blinding of outcome assessment. Any fluorosis was seen in 54% of subjects exposed to optimal fluoridation and 23% of subjects exposed to low fluoride. Fluorosis of 'aesthetic concern' was seen in 3% of subjects with optimal fluoride exposure and 0.5% of subjects exposed to low levels of fluoride in water.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Intervention) Tsutsui et al (2000)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=1060	Schoolchildren aged 10-12 who were lifetime residents chosen regions of Japan. Regions chosen due to stable fluoride concentrations, large populations and agreement to participate.	Regions with water fluoridation 1.0ppm to 1.4 ppm	Regions with water fluoridation < 0.4 ppm	Fluorosis measured using Dean's Index	Survey conducted in areas with existing fluoride levels. Data collected prospectively. Fluoride levels identified via government office and then tested monthly for 12 months to observe seasonal fluctuations using a fluoride-sensitive electrode. Demographic and potential confounders adjusted for in analysis. Outcome assessment not blind. **Quality rating:** Fair
Comments: This study was considered to be of fair methodological quality due to a lack of blinding of outcome assessment. Any fluorosis was seen in 38% of subjects exposed to optimal fluoridation and 7% of subjects exposed to low fluoride. Fluorosis of 'aesthetic concern' was seen in 2% of subjects with optimal fluoride exposure and 0.3% of subjects exposed to low levels of fluoride in water.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

A.2.2 FLUORIDATED MILK

Level IV evidence (Intervention) Mariño et al (2003)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Controlled before-and-after study (population level) Study time-points: 1994 and 2002 N=283 and 419	Children born between 1993 and 1996 (6-9 year olds)	Codegua (Chile) Milk fluoridated between 1994 and 1999	La Punta (Chile) Milk not fluoridated	Fluorosis measured using Dean's Index	*Codegua was chosen as the test comm*unity as a milk fluoridation programme was introduced in 1995. Children aged 3-6 attending public kindergartens and primary schools were included. La Punta was chosen as the control group as it was located near Codegua, had similar caries prevalence and children in both regions had dental care in the same regional capital. No baseline demographic data shown and no adjustments appear to have been made in the analysis. In previous study authors note similar water fluoride levels in both regions and that nearly all children in Chile use fluoridated toothpaste. Baseline fluorosis (measured by mean community fluorosis index) higher in control community (0.15 vs 0.06). Outcome assessment not blinded. Inter-examiner and intra-examiner assessments carried out on sample of 24 children with inter-examiner kappa 0.65 to 0.93. Baseline survey in test group carried out at same time as introduction of milk fluoridation. Follow-up survey conducted after 8 years in test group (including 3 years after milk fluoridation ceased), but only 2 years in control group. **Quality rating:** Poor
Comments: This study was considered to be of poor methodological quality due to the lack of assessment of baseline characteristics of children in the two regions and lack of blinding of outcome assessment. Any fluorosis increased from 12% to 24% in Codegua over the study period (OR 1.12; 1.04, 1.20). Fluorosis remained stable in the control town (24% to 26%).					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

A.2.3 FLUORIDATED SALT

Level IV (Intervention) Mariño et al (2003)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=108	8th Grade children who were lifetime residents of three villages with salt fluoridation and one control village without salt fluoridation	Salt fluoridation 350 ppm/kg Note: children received fluoride supplements after salt discontinued.	No salt fluoridation	Fluorosis measured using TF and TSIF scales	Survey conducted in areas with or without salt fluoridation Examinations conducted prospectively. Children were lifetime residents of the fluoridated or non-fluoridated regions. No adjustment made for potential confounders. Outcome assessment not blind. **Quality rating:** Poor
Comments: This study was considered to be of poor methodological quality due to the lack of assessment of baseline characteristics and extent of other fluoride exposures of children in the test and control groups regions and lack of blinding of outcome assessment. Any fluorosis was 6% in test group and 3% in control group. Fluorosis of aesthetic concern was 0.05% in test group (using one scale) and 0% in the control group.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

A.2.4 TOPICAL FLUORIDES

Level II (Intervention) Tavener et al (2004)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
RCT N=703/7422 initially randomised Part of Davies et al (2002) caries study	Initially recruited children aged 12 months from regions of northwest England with high prevalence of dental caries. Children included in present analysis were those who were now aged 5-6, in regions chosen for this study, attended schools with 6 or more participants and were available on day photographs for examination were taken.	Toothpaste 1450 ppm F and 440 ppm F	No toothpaste	Fluorosis measured wet and dry using TF index.	A. Yes. In original study treatment group allocated centrally. B. No. Families were aware of treatment allocation but caries examinations were blinded. C. Data not provided D. No, analysis includes only 10% of originally randomised subjects who met certain criteria. E. No adjustments made for potential confounders. F. No. **Quality rating:** Poor
Comments: This study was considered to be of poor methodological quality due to the small proportion of randomised subjects included in the analysis, the lack of presentation of baseline characteristics between groups and the lack of adjustment for any potentially confounding factors. The results showed that 'any fluorosis' and 'fluorosis of aesthetic concern' were slightly higher in the 1450 ppm F group compared with the 440 ppm F group, higher again than that seen in the control group.					

The quality of randomised controlled trials was assessed using the following questions: (A) Was allocation to treatment groups concealed from those responsible for recruiting subjects? (B) Was the study double-blinded? (C) Were patient characteristics and demographics similar between treatment arms at baseline? (D) Were all randomised participants included in the analysis? (E) Were the statistical methods appropriate? (F) Were any subgroup analyses carried out?

Level IV (Intervention) Riordan et al (2002)					
Study type/patient no.	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study (before-and-after) N=582	12 year olds (in 1989/1990) and 10 year olds (in 2000) enrolled in the School Dental Service in Perth and Bunbury	Educational programme to discourage supplement and toothpaste ingestion and promote the use of low-fluoride toothpaste in children.	No comparator	Fluorosis measured using TF scale	Survey conducted in areas pre- and post the implementation of a programme to reduce supplement and fluoride use in children. Examinations conducted prospectively. Measurement of exposure relied on answers to questionnaire of supplement and toothpaste use. Factors measured included residence in fluoridated area, other fluoride exposures and use of fluoride supplements; adjusted for in the analysis. Outcome assessment not blinded. **Quality rating:** Poor
Comments: This study was considered to be of poor methodological quality due to the lack of assessment of baseline characteristics of subjects included in surveys at two timepoints, lack of blinding of outcome assessment and lack of adjustment for multiple confounding factors. Fluorosis was reduced in 200 compared with 1989/90 in both regions. Univariate analyses showed that residence in a fluoridated region was the only variable significantly associated with fluorosis.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

A.3 FRACTURE

A.3.1 FLUORIDATED WATER

Level III/IV evidence (Aetiology/harms) *McDonagh et al (2000a)*					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
29 studies 4 prospective cohorts; 6 retrospective cohort studies; 15 ecological studies; 1 case-control; 1 that was both case-control and ecological. 2 others were not included in analyses for reasons explained. Jacqmin-Gadda 1995; Kroger, 1994; Li 1999; McClure 1944; Avorn 1986; Sowers 1991; Karagas 1996; Arnala 1986; Cauley 1995; Danielson 1992; Hillier 2000; Jacobsen 1992; Jacqmin-Gadda 1998; Korns 1969; Kurttio 1999; Lehmann 1998; Madans 1983; Phipps 1999; Simonen 1985; Suarez-Almazor 1993; Cooper 1990; Korns 1969; Bernstein 1966.	Not specifically defined	Water fluoridation (natural or artificial) (level nearest to 1 ppm)	Another level of water fluoridation (or lowest water fluoride level)	Fracture (hip and other) Slipped epiphysis and otosclerosis (not reported here)	A. Yes. A specific objective was stated as "does water fluoridation have negative effects?" with the specific effect being examined in this section being bone fracture and bone developmental problems. B. Yes. Included electronic and manual searching up to Feb 2000. C. Yes. Assessed by three reviewers. D. Yes. Assessed using a NHS CRD checklist. E. Yes. Detailed summary provided in data extraction tables. F. Yes, but significant heterogeneity present. Sub-group data were treated as independent and assumed to come from separate studies. Some concern re pooling different exposures reflecting both intervention and control. G. Yes. Heterogeneity investigated using the Q statistic found to be significant. Meta-regression was used to investigate sources of heterogeneity between studies. **Quality rating:** Good.
Comments: The authors conclude that there is no clear association between fluoridation and hip fracture. The evidence relating to other fractures is similar. Overall the findings showed small variations around the 'no effect' mark. Evidence of other bone outcomes is extremely limited.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level III/IV evidence (Aetiology/harms) Demos et al (2001)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
33 studies 27 human studies (6 ecological, 4 cross-sectional, 1 ecological & cross-sectional, 3 cohort, 12 clinical trials, 1 case-control) Jacobsen 1992; Danielson 1992; Suarez-Almazor 1993; Jacobsen 1993; Fabiani 1995; Karagas 1996; Lehmann 1998; Kroger 1994; Lan 1995; Arnold 1997; Phipps 1998; Cauley 1995; Jacqmin-Gadda 1998; Sowers 1991; Feskanich 1998 (Note: only studies assessing effect of water fluoridation included here).	Not specifically defined	Water fluoridation (also looked at fluoride as a treatment for osteoporosis but not included here)	Non-fluoridated or low concentration	Fracture, BMD or bone strength	A. No specific question, aim or objective is stated. B. Unclear. Only Medline search was carried out. C. Specific exclusion criteria were stated. D. No. E. Yes. F. Data were not pooled. G. Not applicable. Quality rating: Poor.
Comments: The authors conclude that these studies provide a substantial body of evidence that fluoride at up to 1 ppm does not have an adverse effect on bone strength, bone mineral density or fracture incidence.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level III/IV evidence (Aetiology/harms) Jones et al (1999)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
21 studies Observational studies (10 ecological studies, 11 cross-sectional studies and 3 cohort studies) Goggin 1965; Korns 1969; Madans 1983; Simonen 1985; Avorn 1986; Arnala 1986; Jacobsen 1992; Danielson 1992; Jacobsen 1993; Suarez-Almazor 1993; McClure 1944; Bernstein 1966; Sowers 1986; Kroger 1994; Lan 1995; Jacqmin-Gadda 1995; Sowers 1991; Cauley 1995; Ansell 1968; Phipps 1990	Not specifically defined	Water fluoridation	Lower level of water fluoridation (generally but not always no fluoridation)	RR of fracture, difference in bone mass, OR of a diagnosis of osteoporosis	A. Yes. Two questions were defined: (i) is water fluoridation associated with altered fracture risk (particularly of the hip) at a population level; and (ii) are the differences between studies consistent with confounding or chance variation between studies? B. Unclear. Medline search and manual checking of bibliographies only. C. Inclusion criteria included observational study, assessed fracture or bone mass and in English. D. Yes. Rated using specific criteria and performed by two reviewers. E. Yes. F. Yes. G. Yes. Influence of a number of variables on results was examined **Quality rating:** Good
Comments: The authors conclude that fluoridation appears to have little effect on fracture risk, either protective or deleterious, at the population level.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level IV evidence (Aetiology/harm levels) Li et al (2001)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N=8266 in total from six Chinese populations	Six groups of subjects >50 years. Subjects 'recruited randomly' from the communities. 25 years of confirmed continuous residence in community required to be eligible.	No active water fluoridation intervention, however different rural communities were exposed to different natural water fluoride concentrations, including levels well beyond those occurring in Australia. Water fluoride concentration was confirmed by chemical analysis. Groups: Gp 1: 0.25–0.34 ppm Gp 2: 0.58–0.73 ppm Gp 4: 1.45–2.19 ppm Gp 5: 2.62–3.56 ppm Gp 6: 4.32–7.97 ppm	Control group considered to be: Gp 3: 1.00–1.06 ppm	Self-reported fracture that were then verified by medical records or x-ray. Prevalence of overall fractures since age 20 years Information on number of fractures per person was collected but not used in analyses. Analyses limited to 'occurrence' vs 'no occurrence' of fracture for each person (ie, only counted one fracture per person)	A. No. B. Subjects 'recruited randomly' from communities. No detail of how this was done, and if method was the same in all groups. Minimum of 25 years residence required. Residence was confirmed. Fractures are self-reported in the first instance, therefore may have been under-reported. Osteoporotic fractures more likely to be under-reported than traumatic fractures. Minimal exposure to other sources of fluoride in these communities. Data was collected regarding other fracture risk factors (eg. physical activity, alcohol, smoking). Regression analyses adjusted for age and gender, but not alcohol (as strongly correlated with gender) or physical activity. **Quality rating:** Fair
Comments: Prevalence of overall fractures was lowest in those in the 1.00–1.06 ppm group, however it was not significantly different from those in the 0.58–0.73 ppm group or the 1.45–2.19 ppm group. However those in the more extreme groups of 0.25–0.34 ppm (low) and 4.32–7.97 (high), had a significantly higher overall fracture rate (both $p<0.05$). ie, U-shaped relationship). The prevalence of hip fracture was significantly higher in the high fluoride group (4.32–7.97) than in the control group. However, there was no difference in hip fracture between the control and the low fluoride groups (ie, J-shaped relationship).					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Aetiology/harm levels) Sowers et al (2005)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Predominantly cross-sectional study (although fractures recorded longitudinally for a 4 year window) N=1300 in total from three Iowa populations (but only two relevant to the current review)	Two groups of subjects >18 years, originally selected from community census. No criteria regarding duration of residence within community, but this was included as a variable.	No active water fluoridation intervention, but naturally high fluoride in community water supply. 210.4 µmol/l ≈ 4 ppm. therefore beyond levels occurring in Australia. Water fluoride concentration was confirmed by chemical analysis.	Control group (achieved by water fluoridation): 52.6 µmol/l ≈ 1 ppm.	Participants asked to self-report fracture every 6 months for 4 years. 87% were able to be confirmed by medical records.	All eligible women in community identified by census. No additional selection criteria. Participation 70% in high fluoride community and 81% in control community. Analyses of association between fluoride and fracture is adjusted for BMD, when all three are likely to be co-linear (BMD as a surrogate marker for fracture). Possible that effect of fluoride upon fracture has been masked by BMD adjustment. Quality rating: Fair
Comments: The frequency of osteoporotic fractures was higher in the high fluoride community (2.9%) than in the control fluoride community (1.4%). However, the authors conclude that this was no longer significant after adjustment for covariates. However, one of these covariates was BMD - the effect of which may have masked the effect of the fluoride exposure if not independent of fluoride exposure.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Aetiology/harm levels) Alarcon-Herrera et al (2001)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study N= 1437 individuals from five different areas in the Guadiana Valley in Mexico. N=902 adults and 333 children included in the fracture analyses.	Five zones based on fluoride concentration of wells. Combination of city and rural dwellers (although zone II predominantly city dwellers) Only individuals with permanent residence in a zone were included in the fracture analyses.	No active water fluoridation intervention, however different communities were exposed to different natural water fluoride concentrations, the majority being well beyond those occurring in Australia. Water fluoride concentration was confirmed by sampling wells. Groups: Zone 2: 1.51–4.99 mg/l Zone 3: 5.00–8.49 mg/l Zone 4: 8.50–11.99 mg/l Zone 5: 12.00–16.00 mg/l	Control group (zone with lowest concentration) <1.5 mg/l (≈ <1.5 ppm)	Participants asked to self-report any previous fractures in a survey. Survey was administered by interviewers. Only fractures 'that had ever occurred without apparent cause, where a bone fracture would not normally be expected to occur" were included in the fracture analyses. (ie, not the result of trauma). Fractures not confirmed by medical records.	"Population surveys were conducted according to a descriptive transverse correlated design Families were then selected using a polystage conglomerate random sampling". The reviewer is not familiar with this design or sampling, and no further detail is provided. Participation amongst selected individuals is not reported. Validation of 'unexpected' fractures was dependent upon the subjectivity of the interviewer and interviewee. There is no adjustment for potentially confounding factors, and little description of differences in demographic and risk factors between groups. Quality rating: Poor
Comments: Amongst adults, there was a significantly lower fracture frequency in the control zone (3.1%) when compared to both the zone II (7.9%) and zone III (8.9%)(both $p<0.05$). The rates in zone IV (7.2%) and zone V (6.3%) were not significantly different from control, but these zones had a smaller sample size. The authors suggest that these later two points reflect a paradoxical effect at high fluoride concentrations (ie, a decrease in fracture frequency) however that reviewer does not agree that the data strongly supports this assertion.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

A.4 CANCER

A.4.1 FLUORIDATED WATER

Level III/IV evidence (Aetiology/harms) *McDonagh et al (2000a)*					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
24 studies 10 before-after; 11 ecological studies; 3 case-control Smith 1980; Lynch 1985; Chilvers 1983; Hoover 1976; Chilvers 1985; Goodall 1980; Raman 1977; Cook-Mozaffari 1981; Richards 1979; Schlesinger 1956; Kinlen 1975; Hoover 1991; Mahoney 1991; Moss 1995; Gelberg 1995; Hrudey 1990; McGuire 1991; Cohn 1992. 2 others were not included in analyses for reasons explained.	Not specifically defined	Water fluoridation (natural or artificial) (level nearest to 1 ppm)	Another level of water fluoridation (or lowest water fluoride level)	Cancer incidence and mortality Osteosarcoma, bone and joint cancer incidence and mortality Thyroid cancer incidence and mortality	A. Yes. A specific objective was stated as "does water fluoridation have negative effects?" with the specific effect being examined in this section being cancer incidence and mortality. B. Yes. Included electronic and manual searching up to Feb 2000. C. Yes. Assessed by three reviewers. D. Yes. Assessed using a NHS CRD checklist. E. Yes. Detailed summary provided in data extraction tables. F. N/A, pooling not undertaken as cancer types and measures too heterogeneous G. N/A **Quality rating:** Fair/Good
Comments: The authors conclude that the evidence relating fluoridatin to cancer incidence or mortality is mixed, with small variations on either side of the effect.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level III-3 evidence (Aetiology/harm levels) Bassin et al (2006)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Hospital-based case-control N=318 (103 cases, 215 controls) 11 hospitals in USA Part of Harvard Fluoride Osteosarcoma study. The larger study also included prospective cases (incident 1993–2000) that allowed more thorough investigation, including bone biopsies. (not yet published but see Letter to Editor, Douglass & Joshipura, Cancer Causes Control 17:481–82.	Males and females less than 20 years old Cases: Identified through orthopaedic departments at 11 teaching hospitals across USA. Cases had histologically confirmed osteosarcoma diagnosed between Nov 1989 and Nov 1992. Exclusion criteria >40 years old, any history of radiation therapy or renal dialysis. Controls: Patients from the same hospital's orthopaedics department seen ±6 months of the case's diagnosis and matched on age (±5 yrs), gender, distance from hospital, with the same exclusion criteria. NB. Analysis presented in the current paper was limited to those <20 yrs old.	Telephone interview of parent or patient determined residential history, use of fluoride supplements and mouth rinses, source of water (municipal, bottled, private well), and age at each address. Interviews conducted Jan 1992 to Jan 1995. CDC information used for municipal fluoride levels, a sample used for well water. As brand of bottled water was not asked, an average fluoride level was assumed (0.1 ppm). These data used to assign a fluoride exposure at each age for each subject. Fluoride exposure was standardised based on climate targets of the CDC. Study fluoride exposure is per year, not cumulative.	Primary analyses used climate-standardised exposure categorised into three categories (<30%, 30–99%, >99% of target fluoride content). Secondary analyses used non-climate standardised categories (<0.3, 0.3–0.69, and ≥0.7 ppm).	Histologically confirmed osteosarcoma diagnosed between Nov 1989 and Nov 1992 at the 11 hospitals in question.	Cases and controls theoretically part of same broader population, although not clear to what extent additional cases could have been present in other hospitals (eg, non-teaching, and to what extent these cases may have differed from those included. Importantly, cases had a statistically significantly lower socioeconomic status than controls (p<0.01), and fewer of them used bottled water (p=0.002). Residential history (and therefore fluoride exposure level) determined for each patient, from patient, parent or proxy. Individual exposure assumed to be that indicated by the CDC fluoridation data (ie, individual residence fluoride concentration and consumption of water not accounted for). Biological confirmation of fluoride not available (eg. bone marker). Adjustments were made in the logistic regression for socioeconomic status, (using a crude measure of median family income for their residential postcode, categorised into quartiles), age, county population, use of well or bottled water, fluoride supplements or mouthrinses. Not reported if interviewer was aware of case/control status. Only 103/157 (65%) eligible cases provided complete data for analyses. Inclusion rate for potential controls not reported. Model does not allow for cumulative exposure, or lag effects from exposure in previous years. **Quality rating:** Fair/good

Level III-3 evidence (Aetiology/harm levels) Bassin et al (2006)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Comments: For males, the unadjusted odds ratios for higher exposures were greater than 1.0 at each exposure age, reaching a peak of 4.07 (95%CI, 1.43–11.56) at exposure age 7 years (statistically significant for at exposure ages 6–8 inclusive). Adjusting for potential confounders produced similar results with an adjusted odds ratio peaking at 5.46 (95%CI 1.5–19.9) at exposure age 7 years. The association was not apparent for females. (SEE ALSO: Letter to Editor in same issue (Douglass & Joshipura, Cancer Causes Control 17:481–82).					

Case-control studies were assessed using the following questions: (A) How were the cases defined and selected?; (B) How were the controls defined and selected?; (C) Does the study adequately control for demographic characteristics and important potential confounders in the study design or analysis?; (D) Was measurement of exposure to the factor of interest (eg, the new intervention) adequate and kept blinded to case/control status?; (E) Were all selected subjects included in the analysis?

Level IV evidence (Aetiology/harm levels) Takahashi et al (2001)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Ecological study N=21.8 million inhabitants from nine US populations	Cancer data from the IACR/IARC (WHO) database (1978–1992), reporting the age-specific cancer rates for three states and six cities distributed widely throughout the USA. Data for three 5-year periods (1978–82, 1983–87 and 1988–92). Males and females analysed separately. No requirement for long-term residence in an area to be included.	Extent of water fluoridation based on the 'Fluoridation Census 1985; giving the number of citizens receiving fluroide (artificial ~1 ppm or natural >0.7 ppm) as a percentage of total population - the fluoridation index (FD). Actual fluoride concentration neither measured nor considered. Exposure level purely determined by percentage receiving fluoride. Fluoridation index ranged from 2% to 84%.	No discrete control group - authors performed a regression analyses based on Fluoridation Index.	Age-specific rates of registered cancer for three 5-year periods (also age-standardised to world populations). Cancer incidence was investigated for 36 bodily sites.	As an ecological study, no individual level data available. Nine communities were included. Five were excluded with reasons. Not clear if others were also available. Included states included Iowa, where very high levels of natural fluoride do occur. No specification of fluoride levels in each area - only percentage exposed. No requirement for residence, so not clear if cancer rates relate to the fluoride exposure data. Fluoride census data only relates to one point in time, and only to water fluoridation. Regression assumes fluoride exposure present over time (including some time prior) in order to influence the three time period cancer rates in question. No adjustment for potential confounders (other than sunshine - only applied to lip cancer and melanoma) **Quality rating:** Poor
Comments: Of the 36 sites, 23 were positively significantly associated (more cancers), 9 not significant and 4 negatively significantly associated (less cancers).					

Note: No guidance regarding the quality assessment of ecological studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Aetiology/harm levels) Yang et al (2000)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Ecological study N=673,806 for 10 naturally fluoridations municipalities and N=500,467 unfluoridated municipalities in Taiwan.	Two groups of 10 municipalities matched for urbanisation levels and sociodemographic characteristics. No criteria regarding duration of residence within community.	10 municipalities with no active water fluoridation intervention, but low level naturally fluoridation water (NFMs) (0.24–0.28 mg/l) Water fluoride concentration was confirmed by chemical analysis by Taiwan Water Supply Company.	10 municipalities with unfluoridated water (UFMs) (<0.01 mg/l).	Age-adjusted cancer mortality rates for males and females separately (as standardised rate ratios), by cancer bodily site	10 highest NFMs were chosen - to give the highest end of naturally fluoridated spectrum (NB. still low compared to artificial fluoridation) UFM were matched to NFMs on basis of urbanisation index and socio-demographic factors. Smoking not adjusted for. Migration between cancer diagnosis and mortality (eg, to larger urban centre) can not be ruled out. **Quality rating:** Fair
Comments: The results of the study do not support an association between fluoridation and cancer mortality in Taiwan. NB. Levels of natural fluoridation in this study are lower than those of most artificial fluoridation.					

Note: No guidance regarding the quality assessment of ecological studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Aetiology/harm levels) Steiner (2002)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Ecological study N=N/A (international comparison based on published national statistics, all data expressed as incidence)	Countries/ states with different cancer incidences. Authors categorise as 'very low' and 'very high' cancer incidence groups	Countries/states had varying natural fluoride concentrations and intentional fluoridation NB. Latitude and temperature also investigated.	Countries/states had varying natural fluoride concentrations and intentional fluoridation	Age-standardised total cancer incidence per 100,000 (excluding NMSC)	All countries/states from "Cancer Incidence in Five Countries, vol VII" that had pre-specified very high or very low incidence rates were included. Some were reported by race, others for total population. Data for high cancer incidence areas was overwhelming from developed countries, whilst data for very low cancer incidence was from developing countries. Fluoride concentrations reliant upon published levels, not actually measured. Extremely high likelihood of confounding factors. Other factors different between populations not measured. No adjustments performed. Appears correlation only included data from areas with very high and very low cancer level - not areas with intermediate cancer incidences (not clear from methodology). **Quality rating:** Poor
Comments: Authors report an inverse correlation between cancer incidence and fluoride concentration (r=-0.75), ie, low fluoride concentration, higher cancer incidence. Result likely to be heavily confounded (eg, socioeconomic status, diet, smoking etc).					

Note: No guidance regarding the quality assessment of ecological studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

A.5 OTHER ADVERSE EFFECTS

LEVEL III/IV EVIDENCE (AETIOLOGY/HARMS) *McDonagh et al (2000a)*					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
25 studies 6 before-after; 5 cross-sectional; 12 ecological; 1 retrospective cohort; and 1 case-control Forbes 1997; Still 1980; Jacqmin-Gadda 1994; Griffith 1963; Farkas 1983; Erickson 1976; Erickson 1980; Berry 1958; Needleman 1974; Rapaport 1957; Rapaport 1963; Dick 1999; Overton 1954; Erickson 1978; Hagan 1954; Rogot 1978; Schatz 1976; Weaver 1944; Zhao 1996; Lin 1991; Jolly 1971; Gedalia 1963; Jooste 1999. 8 others were not included in analyses for reasons explained.	Not specifically defined	Water fluoridation (natural or artificial) (level nearest to 1 ppm)	Another level of water fluoridation (or lowest water fluoride level)	Various outcomes eg. Down's syndrome, Goitre, mortality or infant mortality, IQ, mental retardation, dementia, cognitive impairment, anaemia during prgnancy and age at menarche.	A. Yes. A specific objective was stated as "does water fluoridation have negative effects?" other than those reported elsewhere within the systematic review B. Yes. Included electronic and manual searching up to Feb 2000. C. Yes. Assessed by three reviewers. D. Yes. Assessed using a NHS CRD checklist. E. Yes. Detailed summary provided in data extraction tables. F. N/A, pooling not undertaken as heterogeneous outcomes included here. G. N/A **Quality rating:** Fair/Good
Comments: The authors conclude that the studies provide insufficient evidence on any particular outcome to reach a conclusion.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level III/IV evidence (Aetiology/harms) Whiting et al (2001)					
Study/patient number Study type Included studies	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Review quality**
6 studies Ecological studies Berry 1958; Erickson 1976; Erickson 1980; Needleman 1974; Rapaport 1963; Rapaport 1957	Populations with differing levels of fluoride	Fluoride	Fluoride at differing levels	Down's syndrome	A. Yes. The objective was to investigate the association of water fluoride level with Down's syndrome. B. Yes. Electronic searches were conducted and additional references were sought via a website and advisory panel. C. Yes. Inclusion status checked by two reviewers. D. Yes. Study validity formally assessed using specific criteria by two reviewers. E. Yes. F. Results not pooled. G. Not applicable. Quality rating: Good.
Comments: The authors note that the evidence of an association between water fluoride level and Down's syndrome is inconclusive.					

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined? (B) Was an adequate search strategy used? (C) Were the inclusion criteria appropriate and applied in an unbiased way? (D) Was a quality assessment of included studies undertaken? (E) Were the characteristics and results of the individual studies appropriately summarised? (F) Were the methods for pooling the data appropriate? (G) Were sources of heterogeneity explored?

Level IV evidence (Aetiology/harm levels) Singh et al (2001)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Cross-sectional study Endemic area: N=8,270 Non-endemic area: N=10,436 India	Tribal people in Udaipur region of India. No requirement reported for long-term residence in the area.	Endemic area: 3.5–4.9 ppm Fluoride concentration measured by ion electrode method.	Non-endemic area: 0.5 ppm (reference)	Urolithiasis (Urinary stone disease) determined by personal interview with tribesmen and tribeswomen. Authors state "only patients with a proven history were marked as 'stone formers'", but no further details are provided. Prevalence/100,000 Also reported recurrence	Non-participation rate of communities or individuals not reported. Fluoride measurements made at each location. No requirement for proof of residence or particular duration of residence, so contamination is possible (may be unlikely if populations not very mobile or transient). Accuracy and confirmation of self-reporting of urinary stones not clear. Male:female ratio different in endemic and non-endemic areas No adjustment for potential confounders that differed between endemic and non-endemic areas. **Quality rating:** Poor
Comments: Urinary stone prevalence 750/100,000 in endemic area compared to 163/100,000 in non-endemic areas. No adjustment for possible confounders.					

Note: No guidance regarding the quality assessment of cross-sectional studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Aetiology/harm levels) Lowry et al (2003)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Ecological study (NB. Short report only) N=3 million population North East England	Residents of former Northern health region with population of 3 million and ~35,000 deliveries per year Fluoridated and non-fluoridated areas with similar populations, socio-demographic characteristics, terminations rates and fluoride supplementation regimens.	Areas with full fluoridation: >0.9 ppm Source and confirmation of fluoride concentrations not reported	Areas with no fluoridation: <0.3 ppm (reference)	Still births from Perinatal Mortality Survey and congenital abnormalities from Congenital Abnormality Survey (all trisomies ICD-9 codes 758.0, 758.1, 758.2, Downs syndrome, Neural tube defects ICD-9 codes 740.0, 740.1, 740.2, 741.0, 741.9, 742.0, and facial clefts ICD-9 codes 749.0, 749.1, 749.2, 756.03). Miscarriages were excluded. Denominator birth data were obtained from the Office of National Statistics.	Not clear if all areas <0.3 ppm and >0.9 ppm were included as states that matching areas were chosen (with respect to similar populations, socio-demographic characteristics, terminations rates and fluoride supplementation regimens - no reported how this was done. No difference in material deprivation or mean maternal age between fluoridated and non-fluoridated areas. Not reported if adjusted for alcohol or smoking status. Methodology and results are minimally reported in this short report. **Quality rating:** Poor (quality may improve when reported as a full paper)
Comments: The authors conclude that the analyses indicate there is no evidence that fluoridation has had any influence on the rate of congenital abnormalities or stillbirths in the north east of England.					

Note: No guidance regarding the quality assessment of ecological studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.

Level IV evidence (Aetiology/harm levels) Kaipio et al (2004)					
Study design Patient number	**Population**	**Intervention**	**Comparator**	**Outcomes**	**Study quality**
Ecological study N=2,117,000 population in 1961 to 1,971,000 population in 1995 in 365 rural communes Finland	Rural communes in Finland (therefore assumed to be consuming well water)	Rural communes had varying natural fluoride concentrations Inhabitants assumed to be consuming well water. Measurement of well water fluoride was made in 1958, with one primary school child per 1000 inhabitants required to bring a sample of their well water to school for assessment by the National Board of Agriculture. (76 of these wells were re-examined in 1989, but not necessarily in 76 different communes) Fluoride exposure categorised within quintiles: V: 0.3–2.15 ppm IV: 0.15–0.30 ppm III: 0.10–0.15 ppm II: 0.064–0.10 ppm I: 0.00–0.064 ppm (reference)	Rural communes had varying natural fluoride concentrations	CHD deaths (underlying cause of death on death certificate ICD-9 codes 410–414 (different ICD versions and codes used for earlier years. Deaths for persons 35 years or older that occurred between 1961 and 1995 were included. Age-specific mortality rates were first standardised for age by the direct method and expressed as indices of a national average of 1.0.	Data is limited to rural communes, and excludes active fluoridation. Measurement of exposure likely to be inaccurate. Based on measures in 1958, with very limited sampling. Assumes inhabitants are not receiving fluoride from other sources (eg. bottled water, fluoride supplements). Assumes inhabitants drinking well water rather than rain water. Quintiles I-IV not very different in fluoride exposure. Quintile V has much broader range (0.3–2.5 ppm). Does not allow for migration between areas or into towns and cities. High likelihood of confounding factors. Other factors different between populations not measured. Some adjustments performed for age, period, drinking water magnesium and calcium, and average income (but not smoking, physical activity and other CVD risk factors). Mortality amongst migrants from Eastern Europe may confound results. **Quality rating:** Poor
Comments: Authors report a geographical pattern of CHD that is consistent with concentration of fluoride (more fluoride, less CHD), however do not assert causality. Adjusted risk ratio amongst 34–64 year olds was 0.80 (95%CI 0.77–0.83) in the highest fluoride quintile compared to the lowest quintile while adjusted risk ratio amongst over 64 year olds was 0.93 (95%CI 0.90–0.95). The magnitude of the effect was less in more recent years.					

Note: No guidance regarding the quality assessment of ecological studies is provided by the NHMRC. Therefore, a summary of various relating to potential biases is provided.