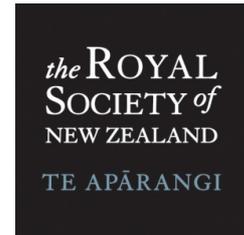




Office of the Prime Minister's
Chief Science Advisor



Health effects of water fluoridation: A review of the scientific evidence

A report on behalf of the Royal Society of New Zealand
and the Office of the Prime Minister's Chief Science Advisor

August 2014

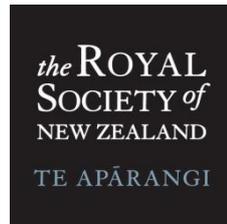
Office of the Prime Minister's Chief Science Advisor
PO Box 108-117, Symonds Street, Auckland 1150, New Zealand
Telephone: +64 9 923 6318
Website: www.pmcsa.org.nz
Email: csa@pmcsa.org.nz

Royal Society of New Zealand
11 Turnbull Street, Thorndon, PO Box 598, Wellington 6140, New Zealand
Website: www.royalsociety.org.nz
Telephone: +64 4 472 7421
Fax: +64 4 473 1841

ISBN- 978-1-877317-08-8



Office of the Prime Minister's
Chief Science Advisor



20 August 2014

Dr Roger Blakeley
Chief Planning Officer
Auckland Council

Dear Dr Blakeley

In February this year, on behalf of several Councils, you made similar requests to the Prime Minister's Chief Science Advisor (PMCSA), the Royal Society of New Zealand (RSNZ), and the Ministry of Health, to review the scientific evidence for and against the efficacy and safety of fluoridation of public water supplies. After discussion between the parties, it was agreed that the Office of the PMCSA and the RSNZ would establish a panel to undertake a review. This review would adhere strictly to the scientific issues of safety and efficacy (or otherwise), but take into account the various concerns that have been raised in the public domain about the science and safety of fluoride. It would not consider the ethical and philosophical issues that have surrounded fluoridation and influenced legal proceedings lately. The Prime Minister gave his consent for the Office of the PMCSA to be involved and funding was provided by Councils through your office and by the Ministry of Health.

We are pleased to advise the report is being delivered on the timetable agreed.

Process

Given this is inevitably an issue that arouses passions and argument, we summarise in some detail the process used.

As this was the first formal scientific review conducted jointly between the Office of PMCSA and the Royal Society a memorandum of understanding for the process was developed and has been followed.

The essence of the process was that the PMCSA appointed an experienced literature researcher to undertake the primary research and literature reviews. Following an initial scoping that included an extensive reading of the literature (informal, grey and peer reviewed) on the subject, a draft table of contents was agreed between the PMCSA and the President of the RSNZ. The RSNZ then appointed a panel of appropriate experts across the relevant disciplines that was approved by the PMCSA.

A member of civil society with expertise in local body issues, Ms Kerry Prendergast, was invited to be an observer to the panel and to be included in the discussions and drafting to be sure that it met local body needs. The scientific writer then produced an early partial draft of the report that was presented to a meeting of the expert panel, and their input was sought both as to framing and interpretation of the literature. The panel paid particular attention to the claims that fluoride had adverse effects on brain development, on the risks of cancer, musculoskeletal and hormonal disorders – being the major areas where claims about potential harms have been made.

Over the following weeks, the panel members joined in an iterative process with the scientific writer to develop the report. In its advanced form all the members of the panel, together with the PMCSA and the President of the RSNZ, agreed via email exchange on the final wording of the report and its executive summary. In this form it was sent out for international peer review by appropriate scientific experts in Australia, UK and Ireland. Following their suggestions (which were minor and did not affect the panel's conclusions), the report and executive summary were returned to the panel for comment.

Findings and recommendations

The report and its executive summary are very clear in their conclusions.

There is compelling evidence that fluoridation of water at the established and recommended levels produces broad benefits for the dental health of New Zealanders. In this context it is worth noting that dental health remains a major issue for much of the New Zealand population, and that economically and from the equity perspective fluoridation remains the safest and most appropriate approach for promoting dental public health.

The only side effect of fluoridation at levels used in NZ is minimal fluorosis, and this is not of major cosmetic significance. There are no reported cases of disfiguring fluorosis associated with levels used for fluoridating water supplies in New Zealand.

The use of fluoridated toothpastes does not change these conclusions or obviate the recommendations.

Given the caveat that science can never be absolute, the panel is unanimous in its conclusion that there are no adverse effects of fluoride of any significance arising from fluoridation at the levels used in New Zealand. In particular, no effects on brain development, cancer risk or cardiovascular or metabolic risk have been substantiated, and the safety margins are such that no subset of the population is at risk because of fluoridation.

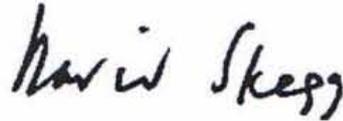
All of the panel members and ourselves conclude that the efficacy and safety of fluoridation of public water supplies, within the range of concentrations currently recommended by the Ministry of Health, is assured. We conclude that the scientific issues raised by those opposed to fluoridation are not supported by the evidence.

Our assessment suggests that it is appropriate, from the scientific perspective, that fluoridation be expanded to assist those New Zealand communities that currently do not benefit from this public health measure – particularly those with a high prevalence of dental caries.

Yours sincerely



Sir Peter Gluckman
Prime Minister's Chief Science Advisor



Sir David Skegg
President, Royal Society of New Zealand

Acknowledgements

This report was commissioned by Sir Peter Gluckman, the New Zealand Prime Minister's Chief Science Advisor (PMCSA), and Sir David Skegg, the President of the Royal Society of New Zealand (RSNZ), at the request of Auckland Council on behalf of several local Councils to review the scientific evidence for and against the efficacy and safety of fluoridation of public water supplies. Funding was provided by local bodies and the Ministry of Health. An Expert Panel (including a Panel Lay Observer) was appointed by the RSNZ to undertake the review, and international peer reviewers were selected. The report was prepared by Dr. Anne Bardsley, PhD, a researcher/writer in the PMCSA office working in close collaboration with the Expert Panel. The report was peer reviewed by international experts and the Director of the New Zealand National Poisons Centre before its release. Advisors from the New Zealand Ministry of Health (Departments of Oral Health, and Environmental & Border Health) provided comments on the final draft. In addition to the panel members and invited reviewers, we thank members of PMCSA staff for their contributions.

Expert Panel Members

Charles Eason, PhD, MIBiol

CEO Cawthron Institute; Professor, Faculty of Agriculture and Life Sciences, Lincoln University, Christchurch, NZ

J. Mark Elwood, DSc, MD, MBA, SM, MB, BSc; FRCPC, FAFPHM

Professor, Epidemiology & Biostatistics, School of Population Health, University of Auckland, Auckland, NZ

Gregory Seymour, BDS, MDSc, PhD, FRCPath, FFOP(RCPA), FRACDS, FICD, FADI, FRSNZ

Professor, Faculty of Medicine and Biomedical Sciences, University of Queensland, Brisbane, QLD, Australia; Former Dean, Faculty of Dentistry, University of Otago, Dunedin, NZ

W. Murray Thomson, BSc, BDS, MA, MComDent, PhD

Professor, Dental Epidemiology and Public Health, Faculty of Dentistry, University of Otago, Dunedin, NZ

Nick Wilson, MB ChB, DIH, MPH

Associate Professor, Department of Public Health; Co-Director, Burden of Disease Epidemiology, Equity and Cost Effectiveness (BODE³) Programme, University of Otago, Wellington, NZ

Panel Lay Observer

Kerry L. Prendergast, CNZM

Chair, Environmental Protection Authority, and former Mayor, Wellington, NZ

New Zealand reviewer

Wayne Temple, BSc(Hons), PhD, FNZIC, CChem, FRSC, MAACT

Director, National Poisons Centre, University of Otago, Dunedin, NZ

International reviewers

Professor David Coggon, OBE, MA, PhD, DM, FRCP, FFOM, FFPH, FMedSci

Professor Occupational and Environmental Medicine, University of Southampton; Southampton, UK

Professor Mark W.J. Ferguson, CBE, BDS, BSc, PhD, DMedSc, FFD, FDS, FMedSci,

Director General, Science Foundation Ireland; Chief Scientific Advisor to the Government of Ireland, Dublin, Ireland

Laureate Professor Eric Reynolds, AO, BSc, PhD

Head, Melbourne Dental School; Associate Dean, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne; CEO, Oral Health Centre of Research Cooperation; Melbourne, VIC, Australia

Health effects of water fluoridation: A review of the scientific evidence

Executive Summary

Oral health and tooth decay in New Zealand

Despite notable overall improvements in oral health over the last half century, tooth decay (dental caries) remains the single most common chronic disease among New Zealanders of all ages, with consequences including pain, infection, impaired chewing ability, tooth loss, compromised appearance, and absence from work or school. Tooth decay is an irreversible disease; if untreated it is cumulative through the lifespan, such that individuals who are adversely affected early in life tend to have pervasive decay by adulthood, and are likely to suffer extensive tooth loss later in life. Prevention of tooth decay is essential from very early childhood through to old age.

The role of fluoride

Fluoride is known to have a protective effect against tooth decay by preventing demineralization of tooth enamel during attack by acid-producing plaque bacteria. In infants and young children with pre-erupted teeth, ingested fluoride is incorporated into the developing enamel, making the teeth more resistant to decay. Drinking fluoridated water or brushing teeth with fluoride toothpaste raises the concentration of fluoride in saliva and plaque fluid, which reduces the rate of enamel demineralisation during the caries process and promotes the remineralisation of early caries lesions. When ingested in water, fluoride is absorbed and secreted back into saliva, where it can again act to inhibit enamel demineralisation. A constant, low-level of fluoride in the mouth has been shown to combat the effects of plaque bacteria, which are fuelled by dietary sugars. Drinking fluoridated water accomplishes this through both topical and systemic actions.

Community water fluoridation as a public health measure

New Zealand water supplies generally have naturally low concentrations of fluoride. Fluoridation of public drinking-water supplies involves the deliberate adjustment of fluoride concentrations in drinking water from their naturally low levels (~0.1-0.2 mg/L* in most parts of New Zealand), upwards to between 0.7 and 1.0 mg/L. Public health authorities worldwide agree that community water fluoridation (CWF) is the most effective public health measure to reduce the burden of dental caries, reducing both its prevalence within a population and its severity in individuals who are affected. With a history dating back to the 1940s in the US, CWF is now practised in over 30 countries around the world, providing over 370 million people with optimally fluoridated water. Epidemiological evidence of its efficacy and safety has been accumulating for over six decades. The fluoride concentrations

* Fluoride concentrations in water are expressed as either mg/L or parts per million [ppm]; these units are effectively interchangeable. Fluoride concentrations in toothpaste are typically expressed as ppm.

recommended for CWF have been set based on data from both animal toxicology studies and human epidemiological studies to provide a daily oral exposure that confers maximum benefit without appreciable risk of adverse effects.

Naturally occurring concentrations of fluoride in water in some parts of the world (e.g. parts of China, Africa, and India) are much higher than those found in fluoridated water, and in some of these regions high fluoride intakes are known to cause problems in teeth and bones (dental and skeletal fluorosis). It is important to distinguish between effects of apparent fluoride toxicity at very high intakes, and effects that may occur at the much lower intakes from CWF. Some studies have failed to do so, giving rise to potentially misleading statements and confusion.

There remains ongoing debate about the long-term safety of adding fluoride to drinking water. It is important to separate concerns that are evaluable by science and those concerns that arise from philosophical/ideological considerations. With respect to the former it is important to note that the inherent nature of science is such that it is never possible to prove there is absolutely no risk of a very rare negative effect – science can only draw conclusions that are highly probable, but not absolute.

Most recently, the concerns for potential side effects have revolved around (a) whether consuming fluoridated water increases the risk of cancer (in particular osteosarcoma), and (b) the effects of fluoride on the cognitive development of children. The potential for increased bone fracture risk has also been extensively examined. While the scientific consensus confirmed in this review is that these are not significant or realistic risks, as a matter of public health surveillance, such claims continue to be studied and monitored in populations receiving fluoridated water.

'Artificial' vs 'natural' fluoride

The fluoride-containing compounds used for adjusting fluoride levels in drinking water have been shown to dissolve fully in water to release fluoride ions. These ions are identical to those found naturally in the water. The reagents used for water fluoridation in New Zealand are regularly tested for purity and to ensure that any trace metals (or other impurities) that they may contain, when added to drinking water, are well below the maximum safe limits described in the Drinking Water Standards for New Zealand. The water supply itself is then regularly monitored to ensure fluoride levels and any impurities (including from the source water) are within the maximum safe limits set in the Drinking Water Standards.

Evidence for benefits of water fluoridation

Analysis of evidence from a large number of epidemiological studies and thorough systematic reviews has confirmed a beneficial effect of CWF on oral health throughout the lifespan. This includes relatively recent studies in the context of the overall reduced burden of caries that has resulted from the widespread use of topical fluoride products (e.g. toothpastes, mouth rinses, and fluoride varnishes). In New Zealand, significant differences in decay rates between fluoridated and non-fluoridated communities continue to exist, despite the fact that the majority of people use fluoride toothpastes. These data come from multiple studies across different regions of the country conducted over the last 15 years, as well as from a national survey of the oral health status of New Zealanders conducted in

2009. Various studies indicate that CWF has an additive effect over and above that of fluoride toothpaste and other sources of fluoride that are now in common use. The burden of tooth decay is highest among the most deprived socioeconomic groups, and this is the segment of the population for which the benefits of CWF appear to be greatest.

Known effects of fluoride exposure – dental fluorosis

Dental fluorosis is a tooth enamel defect characterised by opaque white areas in the enamel, caused by excess exposure to fluoride while the teeth are forming in the jaw and before they erupt into the mouth. Tooth development occurs during the first 8 years of life; beyond this age children are no longer susceptible to fluorosis. In the common, mild forms it is of minor or no cosmetic significance, but severe forms result in pitted and discoloured teeth that are prone to fracture and wear. Dental fluorosis reflects overall fluoride absorption from all sources at a young age, and is a known effect of drinking water containing naturally very high concentrations of fluoride. The amount of fluoride added to water in CWF programmes is set to minimise the risk of this condition while still providing maximum protective benefit against tooth decay. No severe form of fluorosis has ever been reported in New Zealand.

The prevalence of mild dental fluorosis has increased somewhat since the initiation of CWF in communities around the world, but further increases have coincided with the widespread use of fluoridated dental products, particularly toothpaste and fluoride supplements. There is a substantial evidence base to indicate that inappropriate use of such dental products (e.g. young children swallowing large amounts of toothpaste; inappropriate prescribing of supplements) is the main factor in increasing fluorosis risk, as the prevalence of fluorosis has increased more in non-fluoridated areas than in fluoridated ones. Most of the dental fluorosis that occurs in this country is very mild, having effects that are only identified by professional dental examination. The levels of fluoride used for CWF in New Zealand are relatively low in the range that is known to cause minimal risk for cosmetically problematic fluorosis, as reflected in data from the 2009 New Zealand Oral Health Survey, which showed the overall prevalence of moderate fluorosis to be very low. The survey indicated that fluorosis prevalence is not increasing, and that levels of fluorosis are similar between fluoridated and non-fluoridated areas.

The risk for mild fluorosis that is associated with fluoride exposure is highest for formula-fed infants, and young children who are likely to swallow toothpaste. In some cases the fluoride intake by these groups can approach or exceed the currently recommended conservative upper intake level, but the rarity of cosmetically concerning dental fluorosis in New Zealand indicates that such excess intake is not generally a safety concern.

Analysis of evidence for adverse effects

A number of potential adverse effects of the consumption of fluoride have been suggested, though many have only been reported in areas where the natural level of fluoride in water is very high.

Most recently, the main issues in question are whether fluoride in drinking water has an impact on cancer rates (particularly the bone cancer osteosarcoma) or on the intellectual development (IQ) of children. Because fluoride accumulates in bones, the risk of bone

defects or fractures has also been extensively analysed. While there are published studies suggesting that such associations exist, they are mostly of very poor design (and thus of low scientific validity) or do not pertain to CWF because the fluoride levels in question are substantially higher than would be encountered by individuals drinking intentionally fluoridated water.

Cancer

The large majority of epidemiological studies have found no association between fluoride and cancer, even after decades of exposure in some populations. This includes populations with lifetime exposure to very high natural fluoride levels in water, as well as high-level industrial exposures. The few studies that have suggested a cancer link with CWF suffer from poor methodology and/or errors in analysis. Multiple thorough systematic reviews conducted between 2000 and 2011 all concluded that based on the best available evidence, fluoride (at any level) could *not* be classified as carcinogenic in humans. More recent studies, including a large and detailed study in the UK in 2014, have not changed this conclusion.

Bone cancers have received specific attention because of fluoride's deposition in bone. Although a small study published in 2006 claimed an increased risk for osteosarcoma in young males, extensive reviews of these and other data conclude that there is no association between exposure to fluoridated water and risk of osteosarcoma. Likewise, in the New Zealand context, data from the New Zealand Cancer Registry from 2000-2008 show no evidence of association between osteosarcoma incidence and residence in CWF areas.

We conclude that on the available evidence there is no appreciable risk of cancer arising from CWF.

Effects on IQ

Recently there have been a number of reports from China and other areas where fluoride levels in groundwater are naturally very high, that have claimed an association between high water fluoride levels and minimally reduced intelligence (measured as IQ) in children. In addition to the fact that the fluoride exposures in these studies were many (up to 20) times higher than any that are experienced in New Zealand or other CWF communities, the studies also mostly failed to consider other factors that might influence IQ, including exposures to arsenic, iodine deficiency, socioeconomic status, or the nutritional status of the children. Further, the claimed shift of less than one IQ point suggests that this is likely to be a measurement or statistical artefact of no functional significance. A recently published study in New Zealand followed a group of people born in the early 1970s and measured childhood IQ at the ages of 7, 9, 11 and 13 years, and adult IQ at the age of 38 years. Early-life exposure to fluoride from a variety of sources was recorded, and adjustments were made for factors potentially influencing IQ. This extensive study revealed no evidence that exposure to water fluoridation in New Zealand affects neurological development or IQ.

We conclude that on the available evidence there is no appreciable effect on cognition arising from CWF.

Bone fractures

Fluoride is incorporated into bone during bone development and remodeling. Evidence from both animal and human studies suggests that water fluoride levels of 1 mg/L – a level considered optimal for prevention of tooth decay – may lead to increased bone strength, while levels of 4 mg/L may cause a decrease in bone strength.

Prolonged exposure to fluoride at five times the levels used in CWF (~5 mg/L) can result in denser bones that may be more brittle than normal bone, and may increase the risk of fracture in older individuals. However, despite a large number of studies over many years, no evidence has been found that fluoride at optimal concentrations in water is associated with any elevated risk of bone fracture. In children, intake of fluoridated water does not appear to affect bone density through adolescence.

We conclude that on the available evidence there is no appreciable risk of bone fractures arising from CWF.

Other effects

A number of other alleged effects of CWF on health outcomes have been reviewed, including effects on reproduction, endocrine function, cardiovascular and renal effects, and effects on the immune system. The most reliable and valid evidence to date for all of these effects indicates that fluoride in levels used for CWF does not pose appreciable risks of harm to human health.

Fluoride exposure in specific population groups

A number of public health agencies around the world, including the US Institute of Medicine, Health Canada, the European Food Safety Authority, the Australian National Health and Medical Research Council, and the New Zealand Ministry of Health provide recommendations on adequate intakes (AIs) for nutrients considered necessary for optimal health, as well as safe upper levels of intake (ULs). Fluoride is included among the nutrients assigned AI and UL recommendations.

Infants

Infants who are exclusively breastfed to 6 months of age have very low fluoride intake, and the low recommended intake level for this age group (0.01 mg/day) reflects this. Infants 0-6 months of age who are exclusively fed formula reconstituted with fluoridated water will have intakes at or exceeding the upper end of the recommended range (UL; 0.7 mg/day). The higher intakes may help strengthen the developing teeth against future decay, but are also associated with a slightly increased risk of very mild or mild dental fluorosis. This risk is considered to be very low, and recommendations from several authoritative groups support the safety of reconstituting infant formula with fluoridated water.

Young children (1-4 years)

Typical intakes of fluoride from water, food, and beverages in young children in New Zealand are within or below the recommended levels (0.7-2.0 mg/day depending on age and weight). However, intake of fluoride from toothpaste contributes a significant proportion of total ingested fluoride in this group. In combination with dietary intake this can raise the total daily intake above the recommended adequate intake level.

Consumption of fluoridated water is highly recommended for young children, as is the use of fluoride toothpaste (regular strength – at least 1000ppm), but only a smear of toothpaste should be used, and children should be supervised during toothbrushing to ensure that toothpaste is not swallowed/eaten.

Children (5+years) and adolescents

Fluoride exposure estimates for children and adolescents in New Zealand indicate that the average total dietary intake for this age group (including fluoride ingested from toothpaste) is below the recommended adequate intake level even in fluoridated areas. This group is not considered at high risk of exposure to excess fluoride, and consumption of fluoridated water and use of fluoride toothpaste (≥ 1000 ppm) are both recommended.

Pregnant or breastfeeding women

Pregnant women are not themselves any more vulnerable to the effects of fluoride than their non-pregnant counterparts, but they may have concerns about fluoride ingestion and its possible effects on their unborn fetus. However, no studies to date have found any evidence of reproductive toxicity attributable to fluoride at or around levels used for CWF. The recommendations for fluoride intake for pregnant women therefore do not differ from those for non-pregnant women – i.e. they are encouraged to drink fluoridated water and to use full-strength fluoride toothpaste throughout their pregnancy. This is considered beneficial to their own oral health (which is often compromised by physiological changes in pregnancy) and safe for their offspring.

The same recommendations apply during breastfeeding. Fluoride does not transfer readily into breast milk, so the fluoride intake of the mother does not affect the amount received by her breastfeeding infant.

Adults and the elderly

Although most studies of the effects of CWF have focused on benefits in children, caries experience continues to accumulate with age, and CWF has also been found to help reduce the extent and severity of dental decay in adults, particularly with prolonged exposure. Elderly individuals may have decreased ability to undertake personal oral healthcare, and therefore are vulnerable to tooth decay, particularly in exposed root surfaces. As with other groups who are at high risk of tooth decay, consumption of fluoridated water can have important preventive impact against this disease in the elderly. Epidemiological studies have shown that elderly individuals indeed benefit from drinking fluoridated water, experiencing lower levels of root decay and better tooth retention. It should be noted that the increasing retention of natural teeth in the elderly brings with it an increased need for long-term maintenance of tooth function, and a continuing benefit of CWF exposure in this group.

Individuals with kidney disease

Chronic kidney disease is relatively common in New Zealand, with a higher prevalence amongst Māori, and numbers are increasing due to the increasing prevalence of hypertension and diabetes. Because the kidney is the major route of fluoride excretion, blood fluoride concentrations are typically elevated in patients with end-stage kidney disease, and this group may be considered to be at increased risk of excess fluoride

exposure. However, to date no adverse effects of CWF exposure in people with impaired kidney function have been documented.

Cost-effectiveness of water fluoridation

Tooth decay is responsible for significant health loss (lost years of healthy life) in New Zealand. The 'burden' of the disease – its 'cost' in terms of lost years of healthy life – is equivalent to 3/4 that of prostate cancer, and 2/5 that of breast cancer in New Zealand. Tooth decay thus has substantial direct and indirect costs to society.

There is strong evidence that CWF is a cost-effective use of ratepayer funds – with it being likely to save more in dental costs than it costs to run fluoridation programmes (at least in communities of 1000+ people). There is New Zealand evidence for this, along with evidence from Australia, the US, Canada, Chile and South Africa. CWF appears to be most cost-effective in those communities that are most in need of improved oral health. In New Zealand these include communities of low socioeconomic status, and those with a high proportion of children or Māori

Conclusions

The World Health Organization (WHO), along with many other international health authorities, recommends fluoridation of water supplies, where possible, as the most effective public health measure for the prevention of dental decay.

A large number of studies and systematic reviews have concluded that water fluoridation is an effective preventive measure against tooth decay that reaches all segments of the population, and is particularly beneficial to those most in need of improved oral health. Extensive analyses of potential adverse effects have not found evidence that the levels of fluoride used for community water fluoridation schemes contribute *any* increased risk to public health, though there is a narrow range between optimal dental health effectiveness and a risk of mild dental fluorosis. The prevalence of fluorosis of aesthetic concern is minimal in New Zealand, and is not different between fluoridated and non-fluoridated communities, confirming that a substantial proportion of the risk is attributable to the intake of fluoride from sources other than water (most notably, the swallowing of high-fluoride toothpaste by young children). The current fluoridation levels therefore appear to be appropriate.

This analysis concludes that from a medical and public health perspective, water fluoridation at the levels used in New Zealand poses no significant health risks and is effective at reducing the prevalence and severity of tooth decay in communities where it is used. Communities currently without CWF can be confident that this is a safe option that is cost saving and of significant public health benefit – particularly in those communities with high prevalence of dental caries.

Review methodology

This report aimed to evaluate the current state of scientific knowledge on the health effects of water fluoridation, in order to inform decision-making on continuing or implementing community water fluoridation, particularly within the New Zealand context. Several previous rigorous systematic reviews were used as the basis for this analysis, and literature searches in Medline, EMBASE, the Cochrane library database, Scopus, and Web of Science were undertaken to identify subsequent studies in the peer-reviewed scientific literature. Alleged health effects from both the scientific and non-scientific literature were considered, and many original studies relating to these claims were re-analysed. The main review sources are presented in the Appendix.

Aside from animal toxicity studies, articles considered for this review were those that had a primary focus on community water fluoridation or human exposure to fluoride at levels around those used for CWF. Studies were assessed for robust design, including adequate sample size, appropriate data collection and analysis, adjustment for possible confounding factors, and conclusions appropriate to the data analysis.

The report does not consider in depth the broader philosophical issues that lead some people to have objections to CWF.

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Health effects of water fluoridation:

A review of the scientific evidence

1. Background to water fluoridation issues

Fluoridation of public water supplies began as a public health measure in the United States in the 1940s, following results of epidemiological studies showing a link between elevated levels of fluoride in drinking water and reduced prevalence and severity of tooth decay (dental caries) in local populations. Community water fluoridation (CWF) entails an upward adjustment of the fluoride concentration in fluoride-poor water sources to a level that is considered optimal for dental health, yet broadly safe for the population that drinks the water.

Geological factors cause a significant variation in the natural concentration of fluoride in water around the globe. Much of the early work on fluoride was concerned with the effects of naturally occurring excessive fluoride concentrations in water and the associated prevalence of varying degrees of dental fluorosis, a tooth enamel mineralization defect that causes changes to the appearance of the enamel.^[1] Investigations into the causes of such enamel changes led to the discovery of the dental health benefits – specifically a protective effect against tooth decay – of an appropriate concentration of fluoride in drinking water. The link between moderately elevated levels of fluoride in water and reduced prevalence and severity of tooth decay led to trials of the addition of fluoride to drinking water supplies in some areas where the natural level of fluoride in the water was low.

Fluoridation of water supplies in New Zealand began in 1954. Currently more than half the population receives fluoridated water. Some of the larger centres without fluoridated water supplies currently are Whangarei, Tauranga, Whanganui, Napier, Nelson, Blenheim, and Christchurch and Rotorua. The most recent decision to fluoridate a low-fluoride community occurred in South Taranaki in 2014. New Plymouth and Hamilton have recently stopped their fluoridation programmes, though a decision has been made to restart fluoridation in Hamilton. A map of fluoridated water supplies in New Zealand can be viewed at: <http://www.drinkingwater.esr.cri.nz/supplies/fluoridation.asp>.

Despite its long history and a wealth of data showing marked improvements in oral health in communities following the introduction of fluoridated drinking water, and in general a broad social license for its use, this public health measure remains controversial. There is a perception that some questions of the potential for adverse health effects of water fluoridation remain incompletely resolved, and its usefulness has been debated given the significantly lower overall prevalence of caries (attributed to the widespread use of topical fluoride dental products), and in light of its known side effect of mild dental fluorosis. Recent years have seen some reevaluation of recommended fluoride levels in water, based on current research into fluoride availability in the broader environment, including intake from processed foods and beverages, and the introduction of new and/or improved fluoride dental products into the marketplace.

This report aims to evaluate the current state of scientific knowledge on the health effects of water fluoridation, in order to inform decision-making on continuing or implementing CWF, particularly within the New Zealand context.

1.1 Why is there societal concern?

At the core of opposition to water fluoridation is the viewpoint that it conveys an unacceptable risk to public health. It is also argued that adding fluoride to public water supplies is an infringement on individual rights. Silicofluorides used in CWF have been labelled by some opponents as 'unlicensed medical substances' that pose unknown dangers to human health. Such views have been put forth in essay format by Connett, [2] on anti-fluoride websites, [3] and in books such as *'The Fluoride Deception'*, [4] the forward of which describes fluoride as "another therapeutic agent...that had not been thoroughly studied before it was foisted on the public as a panacea to protect or improve health."[†]

The public perception of risk can differ from that of scientists and experts, and involves not only the perception of the potential 'hazard', but also 'outrage factors' that include voluntariness and control. Outrage factors, as initially defined by Sandman,[5] modify the emotions associated with a risk and thereby inflate the perception of the risk. When exposure to a hazard is voluntary, it is perceived as being less risky. Disagreement between apparent 'experts' indicates to the public that the risks are unknown or unknowable, in which case they tend to take the 'worst case scenario' and judge the risk as more serious. In debates about water fluoridation, the public is confronted with wildly conflicting claims (largely via the internet and news media), and most citizens are not able to easily distinguish differences in authority of the 'experts'. Such confusion leads many to choose what they view as the 'safe' course – to vote against water fluoridation.

A recent survey in Australia indicated that Sandman's[5] outrage factors were indeed linked to opposition to water fluoridation.[6] However, the survey also found that the majority of respondents expressed support for water fluoridation, and overall, little outrage. To the opponents in the minority, fluoridation remains a high-outrage issue, despite scientific evidence that is strongly suggestive of its very low risk. The objection to CWF as a violation of rights is a philosophical argument that may vary with ease of access to non-fluoridated water. Such an objection would not necessarily diminish with increasing availability of evidence-based scientific information on fluoridation effects.

[†] The foreword to *'The Fluoride Deception'* also declares that fluorine is "an essential element in the production of the atom bomb, and there is good reason to believe that fluoridated drinking water and toothpaste – and the development of the atom bomb – are closely related."

□

Examples of issues that have caused some to express concern

- Dental fluorosis of any degree (although typically very mild) is fairly common. Fluorosis of some aesthetic concern may occur in around 8% of children consuming water containing fluoride at 1.0 mg /L from birth.
- Intake of fluoride by infants exclusively fed formula reconstituted with water fluoridated at 1.0 mg/L can reach or exceed the currently recommended daily upper level of intake, potentially increasing their risk of dental fluorosis.
- There are claims of health risks including cancer and reduced IQ in children. This is against the background that science cannot ever give absolute proof of the certainty of no risk – only state that risk is imperceptibly small.
- Some people are concerned about the lack of choice when their water supply is fluoridated and therefore the inconvenience of obtaining non-fluoridated water.

1.2 Consensus and Debate

Analysis of the peer-reviewed scientific literature reveals a clear consensus on the effectiveness of CWF: a large number of epidemiological studies and thorough systematic reviews concur that CWF has a beneficial effect on oral health throughout the lifespan. This includes relatively recent studies in the context of the overall reduced burden of caries that has resulted from the widespread use of topical fluorides. Yet the effectiveness of CWF continues to be questioned by a small but vocal minority. The avenues used to present opposing views tend to be those most easily accessed by the public, giving the impression that there is an even debate among 'experts.' In reality, the weight of peer-reviewed evidence supporting the benefits of water fluoridation at the levels used in New Zealand is substantial, and is not considered to be in dispute in the scientific literature.

There is, however, considerable ongoing debate about the long-term safety of adding fluoride to drinking water, because it is difficult to determine cause and effect and to definitively rule out all potential risks. The nature of science is such that no conclusion can be absolute, and while something can be readily proved to be unsafe, conceptually it is never possible to say that something has absolutely no risk associated with it. In other words, epidemiological methods cannot prove beyond a shadow of a doubt that there is no negative effect – it can make a conclusion highly probable, but not 100% certain. Absolute certainty is therefore an impossible claim. Demanding it can lead to the inappropriate use of the precautionary principle, causing unnecessary public alarm when the weight of evidence indicates that significant harm is extremely unlikely. Most recently, the CWF debate has revolved around (a) whether consuming fluoridated water increases the risk of cancer (in particular osteosarcoma), and (b) the effects of fluoride on the cognitive development of children. It is important to review the quality of evidence for such claims. While there are published studies suggesting that such associations exist, they are mostly of low validity (being poorly conducted or improperly analysed) or do not pertain to CWF because the fluoride levels in question are substantially higher than would be encountered by individuals drinking intentionally fluoridated water. Nonetheless, while the scientific consensus is that these are not significant risks, the nature of public health surveillance is such that such claims will continue to be studied and monitored in populations receiving

fluoridated water. The evidence for and against these and other claimed adverse effects of water fluoridation is presented in section 4.

There is a consensus that chronic consumption of high levels of fluoride in water increases the risk of dental fluorosis, and, at very high levels, skeletal fluorosis (changes in bone structure resulting from excess fluoride accumulation) can occur. Naturally occurring fluoride concentrations in water can range from very low (<0.1 mg/L,[‡] as is common in New Zealand) to in excess of 20 mg/L in parts of China and Africa. Risk/benefit analyses of fluoride concentrations associated with reducing the burden of caries and varying risks of dental fluorosis has established a range between 0.7 and 1.2 mg/L as a level of fluoride in water at which caries prevention is optimal and dental fluorosis risk is minimised (but not absent). Skeletal fluorosis does not occur with fluoride concentrations in this range.

The range of 0.7-1.2 mg/L was recommended for fluoridation of water supplies in the US to account for possible differences in fluid intake based on ambient air temperature (i.e. the lower bound was used in hotter climates where water consumption was assumed to be higher). However, more recent data have shown that tap water intake does not differ substantially based on ambient temperature, indicating that there is no need for different recommendations in different temperature zones, at least in the US. In 2011 the Department of Health and Human Services proposed that 0.7 mg/L fluoride should be the target level throughout the country.[7] This updated recommendation assumes that significant caries preventive benefits can be achieved, and the risk of fluorosis reduced, at the lowest concentration of the original recommended range. Health Canada also recommends 0.7 mg/L as the fluoride target level for CWF.[8] These lowered targets reflect concerns about increasing risks of dental fluorosis because of increasing fluoride exposure from additional sources, including toothpastes and food and beverages made with fluoridated water (see section 3.3). The revised fluoridation target level has not yet been widely adopted in the US, so the effects of this change are as yet unclear.

Knowns	Unknowns
<ul style="list-style-type: none"> • Tooth decay remains a major health problem in New Zealand, especially among low socioeconomic groups • Water fluoridation at levels used in New Zealand reduces the prevalence and severity of tooth decay without causing significant health effects • High intakes of fluoride can cause dental and skeletal fluorosis • High intakes of fluoride do not regularly occur in New Zealand 	<ul style="list-style-type: none"> • The absolute level of risk for potential, very rare health effects other than fluorosis • While benefit is certain there is less clarity as to the magnitude of the beneficial effect against the background of additional fluoride sources

[‡] Fluoride concentrations in water are expressed as either mg/L or parts per million [ppm]; these units are effectively interchangeable. Fluoride concentrations in toothpaste are typically expressed as ppm.

1.3 Weighing the evidence

1.3.1 Beneficial vs toxic doses

Like many elements that affect human health, fluoride is beneficial in small amounts and toxic in excess. More than 500 years ago, the physician and alchemist Paracelsus first stated the basic principle that governs toxicology: “All things are poisons, for there is nothing without poisonous qualities. It is only the dose which makes a thing poison.” In other words, for substances that have beneficial effects on health, “the dose differentiates a poison from a remedy.” Fluoride clearly benefits dental health when used topically or ingested in small doses, but in very high doses it is poisonous, and has been used as a component of pesticides. Similar examples can be found among beneficial health-promoting vitamins, including vitamin D, which in high doses is an effective rodenticide used to eradicate rats and possums, and in humans can cause musculoskeletal and renal disease.[9]

A principle of toxicology is that the individual response of an organism to a chemical increases proportionally to the exposure (dose). For most chemicals, there is a threshold dose below which there is no apparent adverse effect; however, this may depend on the sensitivity of the measurement technique and the size of the study. The larger a study is, the smaller the effect that can be detected. Further, a biological effect might be detected but have no functional (or health) significance. Threshold concentrations causing acute toxicity are determined through dose-response experiments in laboratory animals. The progression and reproducibility of an effect over multiple doses (known as a dose-response curve) can allow extrapolation of the potential for, or lack of, effects at other doses. Animal studies can sometimes provide evidence of potential impacts of long-term exposure to a range of different doses; in humans this requires epidemiological studies. From such studies, a ‘no observed adverse effect level (NOAEL)’ is derived, from which a tolerable daily intake (TDI) reference dose is determined by applying a safety margin of several orders of magnitude. The TDI indicates a daily oral exposure to the human population (including sensitive groups) that is estimated to be without an appreciable risk of deleterious effects during a lifetime.

Water fluoridation is a measure to regulate the fluoride concentrations in community water supplies to a level that is beneficial to health and not harmful for human ingestion. Because fluoride exhibits both beneficial and harmful effects, the World Health Organization (WHO) recognises an adequate lower level of intake and sets an upper limit on levels of fluoride in water (range 0.5-1.5 mg/L).[10] The recommendations are devised to ensure protection against adverse effects over the course of a lifetime, including in the most sensitive segments of the population. Likewise, the US Institute of Medicine (IOM), the Australian National Health and Medical Research Council (NHMRC), the New Zealand Ministry of Health (NZMoH), and other health authorities similarly recommend optimal intake levels for fluoride in their dietary guidelines for nutrients, but also set upper levels of intake to protect against potential adverse effects (see section 2.4).

1.3.2 Risk assessment

In public health and risk management terms, a distinction is made between a hazard, or an intrinsic propensity to cause harm, and a risk, which is the likelihood that a hazard will result in harm. Fluoride in high doses (beyond those used in CWF) does indeed pose a hazard, but in low doses the risk is considered minimal. Public health policy is based on the best estimate of true human risk.

<p>Hazard = an intrinsic propensity to cause harm Risk = likelihood that a hazard will result in harm</p>

Estimates of risk from epidemiological studies, combined with toxicokinetic and mechanistic data, provide a starting point for risk analysis. Randomised, controlled clinical trials are not generally possible with an intervention such as CWF, so human data must come from epidemiological studies that compare exposed populations to non-exposed ones and make a statistical evaluation to determine whether there is an association between the exposure and a human health effect. A causal relationship is inferred based on the strength and consistency of the association in a sufficient number of different circumstances, and the presence of a graded relationship (for example, a progressive increase or decrease in adverse effect rates over a range of fluoride levels), as well the existence of a plausible biological mechanism by which fluoride could cause the effect. A common error is to accept an hypothesis on the basis of isolated supportive findings without looking at the evidence as a whole. A further error is to confuse observed associations between two factors with evidence for causation – i.e. that one factor causes the other.[§] Epidemiology has a number of ways of trying to resolve between association and causation.

Human risk estimates should be based on reproducible results, preferably in studies of human populations that have similar characteristics and exposures. Findings from studies of populations chronically exposed to high levels of fluoride – for example, those found naturally in groundwater and/or from industrial pollution or coal burning, as in China (where levels are often >4 mg/L) – cannot be easily extrapolated to populations receiving fluoride primarily from intentionally fluoridated drinking water over the range of 0.5-1.5 mg/L recommended by WHO.

In the case of CWF, epidemiological data have been gathered and scrutinised for over six decades, and vast amounts of research into its positive and negative effects have been published. Suggestions of harmful effects are put forth regularly, and the scientific and health communities regularly assess the risks with the best available laboratory and epidemiological tools. But science cannot prove a negative – it is not possible to design an experiment that proves without doubt that no harm will ever come from ingesting fluoride. Instead, results must be tested against the 'null hypothesis,' which posits that there will be no difference in health impact between a group that ingests fluoridated water and a control group that does not.

[§] To use a trite example, ice cream consumption and burglaries might be correlated in an epidemiological study. This does not mean that eating ice cream causes bad behavior (burglaries); rather the association could be explained by the increased likelihood that in hot weather people eat more ice cream, and are also more likely to leave their windows open.

The most reliable and valid evidence indicates that fluoride in levels used for CWF does not pose appreciable risks of harm to human health, and that the benefits significantly outweigh the risks.

1.4 Fluoridation around the world

The WHO recommends fluoridation of drinking water as the single most important intervention to reduce dental caries in communities.[10] Around 30 countries worldwide have intentionally fluoridated water supplies, serving an estimated 370 million people. An additional >50 million people drink water that is naturally fluoridated at or near the optimal level, including those supplied from some water sources in Canada, the UK, Spain, Japan, Finland, Chile, Argentina and Australia that have natural fluoride levels of around 1.0 mg/L. Some of the countries where CWF is practised are shown in table 1, along with the percent of the population reached by the CWF schemes and also the number of people in these countries who have access to naturally-fluoridated water that is around the CWF optimum level (~1.0 mg/L).

It is sometimes claimed that European nations have abandoned the practice of fluoridation; this, in fact, is not the case. As of 2014, the UK, Ireland, and Spain fluoridate their water, while other nations put fluoride in table salt or acquire it naturally from higher levels present in drinking water, as in Sweden and Italy. Most experiences gained through water fluoridation, accumulated over decades of epidemiological research, also apply to salt fluoridation. As with water fluoridation, salt delivers fluoride both systemically and topically, and is used in some areas where water fluoridation is not feasible. Approximately 70 million Europeans consume fluoridated salt, including most of the population of Germany and Switzerland. The use of salt for fluoridation in Europe is based on the precedent of iodisation of salt to prevent endemic goitre, where, in Austria and Switzerland, a universally implemented salt iodisation programme totally prevented iodine-deficiency diseases. Salt fluoridation has been used in Switzerland since 1955.[11] For many European communities, salt is used because their complex water systems make water fluoridation impractical.

Water fluoridation ceased in Germany after reunification of the country in 1990. A continued decrease in caries after cessation of CWF was observed, and has been put forth by some as proof that water fluoridation is both ineffective and unnecessary. However, the caries decline coincided with several other trends, including the introduction of fluoridated salt in 1992, a decrease in national sugar consumption in 1993 (down to 1967 levels of intake), and complete restructuring of the dental care system after reunification.[12] A further study of other former East German cities suggested that the caries decline was unlikely to be caused by any one single factor, but that the availability of topical fluorides probably had the greatest impact. The authors concluded that for Germany "from our point of view, water fluoridation would still seem to be reasonable in all heavily-populated industrial areas with high or increasing caries prevalence." [13]

Fluoridation practices in Asia were reviewed in 2012 by Petersen et al.[14] Several countries that are currently unable to implement CWF programmes have used fluoridation of salt (e.g. Cambodia, Laos) or milk (Thailand) as a community public health measure. Costa Rica, Jamaica, and Colombia have salt fluoridation programmes that reach virtually 100% of their populations.[11] In 2007, the 60th World Health Assembly called on countries that have not yet established fluoridation schemes (water, where feasible, or alternatively salt or milk) to consider doing so.[15]

Table 1 – Countries/regions with fluoridated water (including community water fluoridation (CWF) and naturally fluoridated)

Country/region	Total population with CWF (number)	Population with naturally fluoridated water (number)	% of the population with optimally fluoridated water
Pacific			
New Zealand	2,330,000	--	56
Australia	17,600,000	144,000	80
Fiji	300,000	NA	36
Papua New Guinea	102,000	70,000	6
North America			
USA	194,206,000	10,078,000	74**
Canada	14,260,000	300,000	44
Central and South America			
Argentina	3,100,000	4,500,000	19
Brazil	73,200,000	NA	41
Chile	11,000,000	800,000	70
Guatemala*	1,800,000	NA	13
Guyana	45,000	200,000	32
Panama*	510,000	NA	15
Peru	500,000	80,000	2
Asia/Middle East			
Brunei	375,000	NA	95
Hong Kong	6,968,000		100
Libya	400,000	1,000,000	22
Malaysia	20,700,000	NA	75.5
Singapore	5,080,000	--	100
South Korea	2,820,000	NA	6
Vietnam	3,500,000	NA	4
UK/Europe			
Republic of Ireland	3,250,000	200,000	73
Serbia	300,000	NA	3
Spain	4,250,000	200,000	11
UK	5,797,000	330,000	10

Data from the British Fluoridation Society. *One in a million: the facts about fluoridation* (3rd edition March 2012)[16]

*pre-2003 data; **as % of population connected to public water supplies.

2. Fluoride sources, fluoridation, intakes & exposure

2.1 Naturally occurring fluoride levels

Fluoride is the naturally occurring reduced form of the electronegative element fluorine, which is found in all water sources in small but traceable amounts. High fluoride concentrations are found in groundwater in areas where fluoride-bearing minerals are common. Thermal waters of high pH are generally rich in fluoride. Seawater typically contains around 1.3 mg fluoride/L; surface waters such as rivers and lakes usually contain well below 0.5 mg/L. High natural groundwater fluoride concentrations have been reported from India, Pakistan, Africa, Thailand, Sri Lanka, Southern Asia, the Eastern Mediterranean countries, and many areas of China, where levels as high as 20 mg/L are reported. Both shallow and deeper groundwaters are affected; in general, the deeper groundwaters have higher concentrations. These areas are affected by endemic fluorosis (see section 4.3.2). [10]

Many groundwater resources in Central Europe exceed the WHO guideline value of 1.5 mg/L.[17] Concentrations in natural waters span more than four orders of magnitude (most 0.1-10.0 mg/L but some higher and lower).[18] It is not possible to predict the fluoride content of water on the basis of geology alone, other than in general terms.

In New Zealand, the highest natural levels of fluoride in groundwater are around 0.56 mg/L; rivers and lakes typically have fluoride levels around 0.05 mg/L. In most areas the fluoride levels are around 0.1-0.2 mg/L, though some areas (e.g. Northland) have natural fluoride levels of around 0.02-0.03 mg/L.[19] Geothermal or hydrothermal waters are the most likely to contain elevated fluoride levels, but these sources are not used for drinking-water supplies.[20]

2.2 Water fluoridation levels and monitoring in NZ

The NZMoH recommends that, for oral health reasons, the level of fluoride in drinking water in New Zealand should be between 0.7 and 1.0 mg/L. Based on WHO advice, the maximum acceptable value for fluoride in drinking water is 1.5 mg/L to prevent any known adverse health effects (dental or skeletal fluorosis).[21]

Actual fluoride levels in areas where fluoride is added to drinking water in New Zealand vary slightly, but are generally in the range of 0.7-0.9 mg/L. Samples from Dunedin ranged between 0.7 and 0.8 mg/L, with no evidence of attenuation with distance from the dosing point.[22] Other treatment plants show similar consistency in maintaining fluoride concentrations within a narrow range. The majority of samples were below 0.75 mg/L from most treatment plants in 2012-2013, with an average *maximum* level of 0.89 mg/L.[23]

Fluoride levels in fluoridated supplies around the Auckland region average ~0.8 mg/L.[24]

2.2.1 Fluoride forms used for fluoridation

The fluorine-containing compounds used for fluoridation include sodium fluoride (NaF), sodium fluorosilicate (Na_2SiF_6), and hydrofluorosilicic acid (H_2SiF_6 ; also known as hexafluorosilicic acid [HFA]). The latter is most commonly used in New Zealand.[25] HFA is a liquid and is therefore easier to handle and to measure accurately into bulk water. This fluoride source is comparatively dilute; 15% acid contains just under 12% fluorine by mass (NaF contains 46% and Na_2SiF_6 contains 60% F).

To produce HFA, phosphate rock containing fluoride and silica is treated with sulphuric acid to produce two gases: silicon tetrafluoride and hydrogen fluoride. These gases are passed through scrubbers where they react with water to form hydrofluorosilicic acid.[26]

'Artificial' vs 'natural' fluoride in water

There have been assertions that 'artificial' fluorosilicates differ from 'natural' fluorides in their dissolution in water and their bioavailability following ingestion in humans. Jackson et al.[27] addressed these issues, and determined that HFA used to fluoridate water is effectively 100% dissociated to form fluoride ion under water treatment conditions, with bioavailability comparable to natural fluoride. Testing a range of water pH values and HFA concentrations, Finney et al.[28] also reported that at around pH7.0 and typical drinking water fluoride concentration, HFA dissociation to produce free fluoride ions was essentially complete.

In terms of chemistry and bioavailability there is no difference between added and "natural" fluoride. The laws of chemistry dictate that fluoride ions in solution in water are identical regardless of their source. The pharmacokinetics of exposure to natural vs artificial fluorides in water is discussed below in section 2.4.2.

Fluoridation compounds and interactions

The analysis by Jackson et al.[27] also concluded that fluoride at a concentration of 1 mg/L has essentially no interaction with other chemical species in water and no appreciable effect on the chemical speciation of iron, copper, or lead, and therefore would not influence their bioavailability and potential toxicity. The quantities of trace metal impurities occurring as a result of fluoridation were also determined to be very small, having no discernible impact on drinking water quality. The Irish Forum on Fluoridation (2002)[29] examined this issue with specific regard to HFA, which is also used for fluoridation in New Zealand. The assessment showed that the resulting concentrations of heavy metals in the HFA additive (including arsenic, mercury, chromium, cadmium, lead, nickel, selenium and antimony) after dilution in drinking water would be a minute fraction of the guideline values recommended by the WHO, and would have no appreciable toxic effects. The reagents used for water fluoridation in New Zealand are regularly tested for purity and to ensure that any trace metals (or other impurities) that they may contain, when added to drinking water, are well below the maximum safe limits described in the Drinking Water Standards for New Zealand.[30] The water supply itself is then regularly monitored to ensure fluoride levels and any impurities (including from the source water) are within the maximum safe limits set in the Drinking Water Standards.

There has been concern that fluoride in drinking water may increase human exposure to lead because it would cause the release of lead from pipes. This concern appears to be based on a single case study suggesting a relationship between fluoridation levels and blood lead concentrations,[31] and a study testing the release of lead from pipes with water containing fluoride at 2 mg/L in combination with chlorine, chloramine and/or ammonia.[32] The impact of fluoridation on lead bioavailability was carefully analysed by Urbansky and Schock,[33] who found no evidence for adverse health impacts of fluoridation via effects on lead. They concluded that reports linking fluoridating agents with human lead exposure were “inconsistent with accepted scientific knowledge” and that the chemical assumptions were “scientifically unjustified.” An evaluation by the European Commission’s Scientific Committee on Health and Environmental Risks (SCHER) in 2011[34] concurred with this conclusion.

2.2.2 Monitoring systems

There are 46 treatment plants for water fluoridation in New Zealand, supplying over two million people with drinking water in 116 ‘zones’. To comply with the Drinking Water Standards for New Zealand[30], fluoridated drinking water supplies must be sampled at least weekly to monitor levels at the point where the water leaves the treatment plant. Fluoride added to drinking water is not considered a contaminant or a health risk at the usual level of application, but is listed as a ‘Priority 2’ determinand** for monitoring in drinking water in New Zealand, based on the known effects of high concentrations of fluoride on human health.[30]

NZMoH publishes an annual report detailing the levels of monitored substances in drinking water.[35] In 2012-2013, no fluoride exceedances were found in water leaving any fluoridating treatment plant. Monitoring of fluoride was adequate for water supplied to 92 zones (2,059,000 people), but inadequate (low) at seven treatment plants supplying 12 zones (64,000 people). The previous year (2011-2012) the maximum acceptable value (MAV; 1.5 mg/L) was exceeded in one fluoridated zone (744 people), in 1 out of 52 samples. The fluoride concentration in this sample exceeded the MAV by 0.1 mg/L, and “action was taken to reduce the dose when the test result was obtained.”[35]

In general, it is concluded that fluoride levels in public water supplies are well controlled. Most of the test results fall within the required range according to the Drinking Water Standards for New Zealand[30], and are predominantly towards the lower end of the range (~0.7-0.8 mg/L).

** Priority 2 determinands are substances known to have some adverse effects on human health, but do not have to be measured in every water supply. They are distinguished from Priority 1 determinands - substances or organisms of public health significance with the highest priority for monitoring

2.3 Other sources of fluoride in NZ

2.3.1 Dental products

Aside from drinking water, toothpaste is the most common source of ingested fluoride in New Zealand. Young children have relatively poor control over swallowing reflexes, and are likely to swallow toothpaste during toothbrushing.[36, 37] This has led to concern that it could result in excessive intakes of fluoride.

Regular fluoridated toothpastes contain 1000 ppm fluoride, though higher strength varieties (1450 mg/L) have recently become available; those marketed for children 0-6 years contain 400-500 ppm fluoride. However, currently available data suggest that low fluoride toothpastes are not very effective in preventing tooth decay in children, and the NZMoH, as well as other health bodies such as Public Health England (PHE), recommends the use of toothpaste containing at least 1000 ppm fluoride in children 0-6 years of age (using a smear of toothpaste only), beginning as soon as the first primary tooth erupts. PHE recommends higher concentrations for children >6 years of age, and for adolescents and adults. A 2014 PHE report on oral health in England concluded that the risk of fluorosis from ingesting too much fluoride is linked more to the amount of toothpaste that is used, rather than to the fluoride concentration in the toothpaste.[38]

Data on actual toothpaste use in New Zealand children are not available, but, based on other studies, it is assumed that infants under the age of 12 months ingest 80% of the toothpaste dispensed on the brush, while children between 12 months and 3 years of age swallow ~68-72% of the toothpaste on the brush.[39]

2.3.2 Food and beverages

Most foods, aside from tea and marine fish, are relatively low in fluoride (<0.05 mg/100g[40]), although foods and beverages prepared with fluoridated water can contain appreciable amounts, depending on the fluoride concentration in the water. Tea leaves have high concentrations of fluoride (up to 400 mg/kg dry weight), and individual exposure due to the consumption of tea can range from 0.04 to 2.7 mg/day. High consumption of some types of tea (e.g. 'brick tea' made from older tea leaves) over long periods has been associated with the development of skeletal fluorosis in some developing countries, particularly if the water used for brewing is high in fluoride.[41] This has not been observed in New Zealand.

Infant formula

There has been some legitimate concern about the systemic intake of fluoride by infants and young children, and in particular, the level of fluoride present in infant formulas. The average intake by infants exclusively fed formula made up with fluoride-free water was estimated as 0.056 mg/day, or approximately 0.01 mg fluoride per kilogram body weight per day (mg/kg/day), which is at the lower end of the recommended range (see below – section 2.4.1). This is because infant formulas currently available in New Zealand are low in fluoride, but if they are reconstituted with water fluoridated at 0.7-1 mg/L, they can provide infants with fluoride at levels approaching or exceeding the recommended upper level for daily intake (particularly at the upper end of the fluoridation range, and for exclusively formula-fed infants drinking the maximum amount).[39]

The Australia New Zealand Food Standards Code specifies that powdered or concentrated infant formulas containing >17µg of fluoride per 100 kilojoules (prior to reconstitution), or 'ready to drink' formulas containing >0.15mg fluoride per 100mL must indicate on the label that consumption of the formula may cause dental fluorosis.[42]

2.4 Fluoride intakes and pharmacokinetics of exposure

In 2009, the Institute of Environmental Science & Research (ESR) estimated the total intake of fluoride from dietary sources (including water) and dental products by New Zealanders of all age groups using dietary modeling and analysis of total diet studies in the scientific literature.[39] The overall conclusion of the ESR report is that, aside from infants and young children, most New Zealanders have fluoride intakes that are below levels considered adequate for the prevention of dental caries, whether or not they consume fluoridated water.

2.4.1 Nutrient Reference Values and typical intakes

Nutrient Reference Values (NRVs) for Australia and New Zealand are provided by the NHMRC and NZMoH,[43] and include recommendations for fluoride intake. Dietary Reference Values (DRVs) used in Europe, which are similar to the NRVs, have recently been reviewed by the European Food Safety Authority (EFSA).[44] The US IOM also provides recommended dietary intakes for fluoride.[45]

The NRVs include recommendation on adequate intakes (AIs) for nutrients considered necessary for optimal health, as well as safe upper levels of intake (ULs). The AI level is estimated to be adequate for about 50% of the population (i.e. some will need more, and some less), and the UL is the highest intake level that is likely to cause no adverse effects in most of the population. In the case of fluoride, however, the UL for children up to 8 years of age (0.7-2.2 mg/day depending on age – see table 2) is based on the 'lowest observed adverse effect level' (LOAEL) for the occurrence of moderate dental fluorosis (see table 3 in section 3.3 for explanation of fluorosis levels), which is considered a cosmetic rather than functional adverse effect. For older children and adults, the UL is 10 mg/day, which is considered a 'no observed adverse effect level' (NOAEL) for the occurrence of skeletal fluorosis (i.e. there are no signs of skeletal fluorosis at this level of intake).[43, 45]

The ESR report suggests that the UL values should be reviewed, given the rarity of moderate dental fluorosis in Australia and New Zealand populations. Current data indicate that fluoride intake exceedances that occur occasionally in New Zealand do not constitute a safety concern.[39] As is the case with many environmental exposures, very young children are the group at greatest risk of exceeding the UL. This is because some infant diets rely heavily on foods/formula made up with the addition of water that may be fluoridated, and because young children tend to ingest fluoride from toothpaste[39] (see below).

Table 2 Nutrient reference values for fluoride as recommended by the US IOM[45] and the Australian NHMRC/New Zealand MOH[43]

Age group (reference weight)	Adequate Intake (AI)		Upper Level of intake (UL) ^c	
	mg/kg/day	mg/day	mg/kg/day	mg/day
<i>Infants</i>				
0-6 months		0.01		0.7
7-12 months (9kg)	0.05	0.5	0.1	0.9
<i>Children</i>				
1-3 years (13kg)	0.05	0.7	0.1	1.3
4-8 years (22kg)	0.05	1.0	0.1	2.2
9-13 years (40kg)	0.05	2.0	0.1	10
<i>Adolescents</i>				
14-18 years boys (64kg)	0.05	3.0	0.1	10
14-18 years girls (57kg)	0.05	3.0	0.1	10
<i>Adult males</i>				
19+ years (76kg)	0.05	4.0	0.1	10
<i>Adult females</i>				
19+ years (61kg)	0.05	3.0	0.1	10
Pregnant (61kg)	0.05	3.0	0.1	10
Lactating (61kg)	0.05	3.0	0.1	10

The Agency for Toxic Substances and Disease Registry (ATSDR) in the USA derived a chronic-duration, oral Minimal Risk Level (MRL) for fluoride of 0.05 mg/kg/day.[37] This represents an estimate of daily human exposure that is unlikely to pose any appreciable risk of adverse health effects. The MRL equates to a daily fluoride intake of 3.5 mg/day for a 70 kg adult or 0.65 mg/day for a 13kg toddler. These values are lower than the NHMRC ULs (0.9-1.3 mg/day for toddlers and 10 mg/day for adults).

In assessing the US Environmental Protection Agency (EPA) standards for maximum allowable levels of fluoride in drinking water (set at 4 mg/L – substantially higher than the MAV recommended by the WHO and used in New Zealand), the US National Research Council (NRC) determined that intakes in the 0.03-0.1 mg/kg/day range would be reached by persons with average exposures at fluoride concentrations of 1-4 mg/L in drinking water, especially the children.[46] These concentrations exceed those encountered in New Zealand, where drinking water supplies are normally below 0.9 mg/L (see section 2.2). The highest intakes (>0.1 mg/kg/day) would be reached by some individuals with very high intakes of water containing fluoride at 1 mg/L (e.g. 7L for a 70kg adult).

Infants

The adequate intake (AI) recommendation for fluoride for infants up to 6 months of age is 0.01 mg/day, which is based on the average concentration of fluoride in breast milk. It is estimated that breastfed infants (up to 6 months of age) have an average daily fluoride intake of 0.003-0.01 mg/day, reflecting ingestion of ~780 ml breast milk (less for newborns) at a fluoride concentration of 0.013 mg/L.[45] The AI of 0.5 mg/day for infants 7-12 months old is based on the well-documented relationship between water fluoride concentrations and caries.[43, 45] This corresponds to an intake of ~0.05 mg fluoride/kg bodyweight/day. The recommended upper intake level (UL) is 0.7 mg/day and 0.9 mg/day for infants 0-6 months and 7-12 months, respectively.

The average intake of fluoride for breastfed infants is low compared with that of formula-fed infants, regardless of whether the formula is reconstituted with fluoridated or non-fluoridated water. The fluoride content of prepared infant and toddler formula products available in New Zealand range from 0.069 to 0.081 mg/L.[39] Infants consuming formula made with non-fluoridated water will have fluoride intakes of around 0.059 mg/day – well below the UL of 0.7 mg/day (note – intake of 0.7 mg fluoride/day in formula equates to ~0.11 mg/kg/day for a 6kg infant[39]). However, if formula is reconstituted with water containing 0.7 or 1.0 mg/L fluoride, the mean estimated intakes are 0.66 and 0.93 mg/day, respectively.[39] A further modelling of fluoride intake by formula-fed infants in New Zealand calculated similar intake estimates,[47] and concluded that infants who are exclusively fed formula made with water fluoridated at 1.0 mg/L will thus regularly exceed the current UL for fluoride. However, it was also noted that the elevated risk associated with such exposure was almost exclusively for ‘very mild’ or ‘mild’ forms of fluorosis.(see section 3.3.4)

For infants aged 6-12 months whose teeth are brushed with a fluoride toothpaste, the estimated intake of fluoride is 0.14 mg/day for toothpaste with 400 mg/L fluoride, and 0.35 mg/day if the toothpaste contains 1000 mg/L fluoride. Based on modeling and diet studies, the ESR report concluded that fluoride ingestion from toothpaste combined with intake from food and drink would raise the total daily fluoride intake to just above the UL of 0.9 mg/day in fluoridated areas.[39] It is recommended that a minimal amount (a smear) of toothpaste should be placed on the brush when brushing an infants teeth.

Children and adolescents

The AI for children is based on the same mg/kg body weight requirement as infants (0.05 mg/kg/day), adjusted for standard body weights for the different age groups (see table 2). For older children who are no longer at risk of dental fluorosis, the maximum level for fluoride was set at 10 mg/day regardless of weight.

For a 4-year-old of average body weight (18 kg) and average water consumption (0.65 L/day;[48]), a fluoride concentration of 1.5 mg/L equals a daily dose of approximately 0.05 mg/kg/day. This average fluoride exposure is roughly equivalent to the US EPA reference dose (TDI) value of 0.06 mg/kg/day.[49] The TDI indicates a daily oral exposure that is estimated to be without an appreciable risk of adverse effects.

In young children, intake of fluoride from toothpaste contributes a significant proportion of total ingested fluoride, particularly in low-fluoride areas. The estimated mean intake of fluoride from toothpaste in toddlers aged 1-3 years is 0.3 mg/day for the recommended 1000 mg/L toothpaste (or 0.12 mg/day for 400 mg/L toothpaste). In combination with dietary intake this can raise the total daily intake above the AI.[39]

For children aged 5 and above, the estimated total dietary intake (including fluoride ingested from toothpaste) is below the AI even in fluoridated areas.[39] A study conducted in 6-7 year old children in the UK in 2007 found that total fluoride intake, urinary excretion and fluoride retention no longer reflect the fluoridation status of the community in which they reside, in part because of intakes from fluoridated dental products.[50]

Adults

The recommendation for fluoride intake in adults in Australia and New Zealand is 3 mg/day for women and 4 mg/day for men.[43] This is the same recommendation given by the US IOM.[45]

The average fluoride intake for adults living in fluoridated communities in the US ranges from 1.4 to 3.4 mg/day, while it is 0.3 to 1 mg/day in non-fluoridated areas.[45] The highest tolerable fluoride intake (10 mg/day) is only exceeded in areas with exceptionally high levels of natural fluoride in drinking water. This assumes that over three litres of water per day, containing ≥ 3 mg/L fluoride is consumed daily. [34] The estimated mean fluoride intakes for New Zealand adults, based on total diet and dietary modeling approaches, range from ~1.4 to 2.5 mg/day with fluoridated water, and ~0.8-1.3 mg/day with non-fluoridated water.[39] Only very high fluoride diets (0.1% of diets that include fluoridated water) would exceed the UL of 10 mg/day.

The US EPA recently reviewed and updated exposure estimates for fluoride, which account for dietary intake, changes in fluoridation practices and current use of consumer dental products,[51] and clarified the relationships between fluoride exposure and dental fluorosis. The agency identified a reference dose (TDI) of 0.08 mg/kg/day (5.6 mg/day for a 70 kg person) for protection of 99.5% of the vulnerable population against severe fluorosis.

In Germany, Austria, and Switzerland, reference values for nutrient intake are in agreement with the 0.05 mg/kg/day (3.5 mg/day for a 70 kg person) recommendations of the IOM, EFSA, and Australian NHMRC/NZMoH. If the fluoride content of drinking water is below 0.7 mg/L, the use of fluoridated table salt and/or fluoride supplements is recommended in these countries.[52]

Pregnant or breastfeeding women

The recommendations for fluoride intake for pregnant and breastfeeding women do not differ from those for non-pregnant women (AI 3 mg/day; UL 10 mg/day). Fluoride supplements are not required, as studies have not found a significant benefit to the offspring's dentition from enhancing maternal fluoride intake. Typical intake levels for women in New Zealand are considered safe for pregnant women. There are no data that show an increased susceptibility to fluoride that would warrant establishing a different intake recommendation for pregnant or breastfeeding women.[43, 45]

During pregnancy, fluoride is transferred from maternal blood through the placenta to the fetus. However, there are also data to suggest that the placenta sequesters some fluoride, resulting in lower concentrations in umbilical cord blood than in maternal blood.[53] Fluoride levels in cord blood reach, on average, 87% (~60-90%) of those in maternal blood.[54] The differences in concentrations suggest that the placenta acts as a partial filter.[55] Fluoride accumulation in the peripheral regions of the placenta has been observed, possibly correlating with foci of calcification.[56] This may limit passage of fluoride to the fetal circulation to some degree, such that the fetal blood fluoride concentration is not increased to the same extent as maternal plasma fluoride when maternal fluoride intake is increased. The effect of maternal intake on fluoride concentration in the amniotic fluid and fetal blood does not vary between intakes of 0.25 and 1.0 mg/day.

Only a small percentage of the fluoride from 1 mg/L drinking water reaches the fetal teeth. [57]

The transfer of fluoride from maternal plasma into breast milk is minimal (average concentrations are <0.02 mg/L), [42] and is virtually unaffected by the mother's fluoride intake unless intake is very high. Even at high daily intakes (e.g double the UL of 10 mg/day), breast milk fluoride levels were only found to be around 0.03 mg/L. [58]

2.4.2 Fluoride pharmacokinetics

Absorption, distribution and clearance

Most fluoride in food or water enters the bloodstream rapidly via the digestive tract, and about half leaves the body quickly in urine, usually within 24h unless large amounts (>20mg) are ingested. The majority of the fluoride that remains in the body is deposited in teeth and bones. [37, 46] There is substantial inter-individual variation in the metabolism of fluoride, which can be affected by dietary factors, age, and health status. The ingestion of fluoride with food delays its absorption and reduces its bioavailability. [59] In particular, intake of milk or other calcium-rich foods significantly lowers the peak plasma concentration of fluoride after ingestion. The plasma fluoride concentration is also modulated by the rate of urinary excretion. There are no apparent age-related differences in renal clearance rates between children and adults, [60] but renal insufficiency delays fluoride clearance. [61] Individuals with reduced glomerular filtration are likely to have increased plasma fluoride levels, and consequently, increased levels of fluoride in tissues, making them more susceptible to fluorosis (see section 4.6.5).

The amount of fluoride taken up by bone and retained in the body is inversely related to age. More fluoride is retained in young, growing bones than in the bones of older adults. Whereas adults retain about 50% of ingested fluoride, young children may retain as much as 80%, because it is incorporated into the rapidly developing skeleton and teeth. [61]

Once absorbed, fluoride is rapidly distributed throughout the body via the circulation. Ingested fluoride is taken up from the bloodstream into bone, and can be released back into blood as bone is remodelled. No homeostatic mechanism maintains blood fluoride concentrations – levels are determined by intake and exchange with fluoride accumulated in remodelling bone. [62] Fluoride also moves from blood into the salivary glands and back into the oral cavity in saliva. With regular intake, salivary fluoride concentration is maintained at a higher level, reflecting fluoride concentrations in the blood. [63] This is relevant to understanding the mechanisms of fluoride action in preventing dental caries (see section 3.2.2).

Exposure to 'natural' vs 'added' fluoride

The absorption, distribution, and excretion of fluoride that has been added to drinking water is similar to that of naturally occurring fluoride. Maguire et al. [64] analysed the pharmacokinetics and bioavailability of fluoride from naturally and artificially fluoridated tap waters with different degrees of water hardness (which is due to minerals in the water supply). The study concluded that any possible differences in bioavailability of fluoride between drinking waters in which fluoride was present naturally or added artificially (or hard

vs soft waters) are insignificant compared with the large within- and between-individual variation in fluoride absorption following ingestion of water with fluoride concentrations close to 1.0 mg/L. No differences in fluoride absorption, distribution, or excretion in humans have been found for water fluoridated with any of the three commonly used fluoride sources.[65]

3. Water fluoridation and dental health

3.1 Oral health in New Zealand

Oral health is integral to general health and well-being. The 2009 New Zealand Oral Health Survey[66] has provided a detailed snapshot of the status of the nation's oral health, including data on the effect of CWF at a national level. The report concluded that, although oral health in New Zealand is generally good (and despite notable overall improvements in oral health in the last half century), dental caries remains the single most common chronic disease among New Zealanders of all ages, with consequences including pain, infection, impaired chewing ability, tooth loss, compromised appearance, and absence from work or school.[66] Caries is both cumulative and irreversible, continuing through the lifespan at an average rate of around one tooth surface per person per year. This has large direct and indirect costs to society. A 2013 report on health loss in New Zealand[67] found that dental caries was the cause of a loss of 7536 disability-adjusted life years (DALYs) in 2006, taking a greater toll on health than lower respiratory tract infections and chronic kidney disease. This is equivalent to 77% of the health loss from prostate cancer (9786 DALYs), and 42% of the health loss from breast cancer (17,870 DALYs).

A recent cohort study of 430 adolescents examined in 2003 at age 13 and again at age 16 showed that caries is still an important health problem in this age group in New Zealand adolescents, particularly among low-socioeconomic groups.[68] Although the study provides further evidence of the overall decline in caries prevalence and severity since the 1980s, it also suggests that there have been no improvements in recent years. Nearly 80% of the adolescents studied had experienced caries in their permanent teeth. There was a high proportion of Māori and people of low-socioeconomic status with untreated decay, confirming substantial ethnic and socioeconomic inequalities in dental health.

Significant disparities still exist in oral health status and access to services for children and adolescents, particularly for those of Māori and/or Pacific ethnicity. Cost remains an important factor in accessing dental care, and most adults receive care only when there is a problem, rather than attending for routine check-ups.[66]

3.2 Fluoride and caries prevention

3.2.1 Causes of dental caries

Dental caries is one of the most prevalent diseases in children, and remains a significant public health issue throughout the lifespan. Carious lesions are brought about by the metabolism of fermentable carbohydrates (dietary sugars) by oral bacteria, producing acid that diffuses into the tooth and dissolves the mineral of the enamel and dentine. The disease is initiated within the bacterial biofilm (dental plaque) that covers the tooth surface. It is initially reversible by removal of plaque, but otherwise progresses into chronic decay of the tooth surfaces.[69]

Caries is a disease process that ideally needs to be prevented and managed over a person's lifetime. In addition to the removal of plaque by tooth brushing and professional dental services, the most obvious approach to primary prevention of caries is to reduce sugar intake. These measures, however, require individual compliance and political will (e.g., only a few countries have adopted taxes on sugar-sweetened beverages or other high sugar products, and the impact of such fiscal approaches remains uncertain). Fluoride is an important complementary approach and is recognised as the main factor responsible for the considerable worldwide decline in caries prevalence that has occurred over the past half-century. Fluoride toothpaste has well-proven clinical effectiveness for caries prevention[70] and is the leading intervention for self-administered care, but as with brushing alone, is dependent on individual oral hygiene practices. In contrast, protection from caries by fluoride in the water supply appears to be independent of oral hygiene. The effects of fluoride toothpaste and fluoridated water are independent and additive.[71]

3.2.2 Mechanisms of fluoride action

The protective effect of fluoride in tooth enamel is due to its strong, spontaneous reaction with mineral ions such as calcium. Upon systemic exposure during tooth formation, fluoride is incorporated into fluorapatite [$\text{Ca}_5(\text{PO}_4)_3\text{F}$] in tooth enamel, replacing hydroxyapatite [$\text{Ca}_5(\text{PO}_4)_3\text{OH}$]. The fluorapatite crystals are more symmetric and stack better than hydroxyapatite, resulting in the formation of stronger teeth with shallower fissures, and enamel that is more resistant to decay.[72, 73] After topical exposure to fluoride in dental products (e.g. toothpaste) or water, fluoride can be found in several compartments in the oral cavity: ionized in saliva and plaque fluid, bound as calcium fluoride, bound to enamel, and bound to soft tissues.[74] A constant low level of fluoride ion in saliva and plaque fluid reduces the rate of enamel demineralisation during the caries process and promotes the remineralisation of early caries lesions[72, 73] The usual levels in saliva are 0.03 mg/L fluoride or less, dependent on the use of fluoride products and fluoride in the drinking water. Models have predicted that a concentration of 0.1 mg/L fluoride in saliva would be almost completely protective against caries progression.[75, 76] In a review of studies of dental enamel chemistry and the mechanism of fluoride action on caries lesions, Robinson[77] determined that fluoride must continuously enter caries lesions to combat the effects of demineralisation by plaque.

These various studies suggest that the predominant effect of fluoride is mainly local (interfering with the caries process) rather than systemic (pre-eruptively changing enamel

structure), though the latter effect should not be dismissed (see below). To affect the caries process, fluoride must be present in plaque fluid and saliva during or shortly after sugar exposure in order to interfere with demineralization events.[63] This can be achieved either by topically-applied or water-borne fluoride.

A 2005 study by Ingram et al.[78] established that fluoride at the low levels found in fluoridated drinking water was capable of interacting with enamel apatite mineral in the presence of other salivary components. This research showed that a range of fluoride concentrations up to those in fluoridated water areas produced discernible differences in salivary fluoride levels, favourably influencing remineralisation.

Contribution of pre-eruptive fluoride exposure to preventive effects

Despite a substantial body of evidence suggesting that the predominant effect of fluoride in mitigating the caries process occurs post-eruptively and topically, some recent studies provide additional evidence of a systemic effect of fluoride on pre-erupted teeth. Singh et al.[79] found that fluoride is acquired in enamel during crown completion in the first permanent molars, during the time that the matrix is formed and calcified in the first 26-27 months of life. The same group had previously evaluated the pre- and posteruptive effects of fluoride exposure at the individual level, controlling for multiple fluoride sources and potential confounders, and showed a significant effect of pre-eruptive fluoride exposure on caries in permanent teeth.[80] However, they determined that maximum benefit was gained by having both pre- and post-eruptive fluoride exposure. Other groups have also found that a higher percentage of total lifetime exposure to fluoride was associated with lower caries burden,[81-83] indicating that fluoride is effective throughout the lifespan, including pre-eruptively.

3.2.3 Epidemiological evidence of CWF effects

Most of the studies and systematic reviews discussed below evaluated the efficacy of water fluoridation on dental caries prevention in children and adolescents. Studies that specifically looked at effectiveness of fluoridation in adults and the elderly are presented separately in section 3.2.4.

Evidence from international reviews and recent studies

Acknowledging that the prevalence of dental caries has declined markedly since the 1980s, a number of thorough systematic reviews have been carried out since 2000 to assess the ongoing public health effects and effectiveness of water fluoridation in the modern context. Some of the criteria used in these reviews to assess the quality of evidence, and a summary table of the main reviews and studies, are provided in the Appendix (tables A2 and A3). A number of additional comprehensive reviews provide support for the conclusions discussed below, including those published by the US Public Health Service in 1991,[84] the New Zealand Public Health Commission in 1994[85] the US Centers for Disease Control and Prevention (CDC) in 2001,[86] the UK Medical Research Council in 2002,[87] the Institut National de Sante Publique du Quebec in 2007,[88] and SCHER in 2011,[34] among others. These are summarised in the table A2 and are not described in detail here.

There are two common outcome measures reported in studies of the effect of fluoridation on dental caries. The percentage of caries-free children measures the proportion of children

in the population who have no past or current experience of caries in their teeth, and the number of decayed, missing, or filled teeth (designated 'dmft' for primary teeth, and 'DMFT' for permanent teeth) measures the severity of dental decay in an individual.

The UK [NHS/York Review](#)[\[89, 90\]](#) used stringent inclusion criteria of studies of the beneficial effect of CWF on caries. That is, it included only before/after studies (CWF was initiated after a baseline survey and caries prevalence/severity assessed later in the same age group – i.e. different group of children) or prospective cohort studies (following the same group of children from prior to initiation of fluoridation for a number of years, compared with a control group in a non-fluoridated area). Studies with a cross-sectional design were excluded, as these were not considered to be of sufficient epidemiological quality to draw conclusions (see Appendix table A2 for quality of evidence criteria used in the York review). This limited the number of included studies to 26, which were of 'moderate' quality, as most were not blinded (i.e. the examiners were aware of subject exposure status), and multivariate analysis was not used to control for potential confounding factors.

The review concluded that the best evidence available at the time (2000) supported fluoridation of drinking water for reducing caries prevalence, "both as measured by the proportion of children who are caries free and by the mean change in dmft/DMFT score." The report calculated the 'number needed to treat' as 6 (i.e. a median of six people need to receive fluoridated water for one extra person to be caries free). It also concluded that caries prevalence increases in communities that were fluoridated after withdrawal of fluoride from the water.[\[89, 90\]](#) Evidence from a subset of these studies conducted after 1974 (n = 10) also suggested that CWF has an additive effect over and above that of fluoride toothpaste and other sources of fluoride that are now in common use.

The second major systematic review of CWF was conducted by the [Australian National Health and Medical Research Council](#) in 2007.[\[91\]](#) This review included comparative cross-sectional studies that had been excluded in the York review, and additional studies that had been carried out in the intervening years. Only one additional relevant study was identified,[\[92\]](#) and this did not alter the conclusion of the York review. This new study was carried out by the [US Community Preventive Services Task Force](#), which has recently released a statement recommending CWF "based on strong evidence of effectiveness in reducing dental caries across populations. Evidence shows the prevalence of caries is substantially lower in communities with CWF. In addition, there is no evidence that CWF results in severe dental fluorosis."[\[93\]](#) The NHMRC review pooled and reanalysed data from the York review and, after multivariate meta-regression analysis to adjust for confounding variables, found a 14.3% mean difference in the percentage of caries-free children following the introduction of CWF. In answer to the posed question 'Is intentional water fluoridation more efficacious than no water fluoridation in the prevention of dental caries?', the review concluded that 'the existing evidence strongly suggests that water fluoridation is beneficial at reducing dental caries'.[\[91\]](#)

The [North South survey of children's oral health in 2002](#)[\[94\]](#) found that decay rates among children in the Republic of Ireland, where water fluoridation reaches >70% of the population, were significantly lower than among children from non-fluoridated Northern Ireland. For example, among 5-year-old children, the average dmft (decayed, missing, or

filled primary teeth) was 1.3 in the Republic of Ireland vs 2.2 in Northern Ireland. This difference existed in spite of children in the Republic of Ireland having less favorable dental habits, including higher sugar intake, less frequent tooth-brushing, and lower usage of fluoride toothpaste. Caries levels among 15-year-olds with water fluoridation in the Republic of Ireland were 39.5% lower than those for the same age group with no water fluoridation in Northern Ireland.

[Public Health England's 2014 Water Fluoridation Health Monitoring Report\[95\]](#) on the effects of England's water fluoridation schemes on dental health indicators (including tooth decay and related hospital admissions and dental health inequalities) found that five-year-olds living in CWF areas were (on average) 15% less likely to have tooth decay than those in non-CWF areas (this was adjusted to 28% when deprivation and ethnicity were taken into account). Likewise, 12-year-olds were 11% less likely (21% accounting for deprivation and ethnicity) to have tooth decay than children of the same age in non-CWF areas. The lower caries experience associated with CWF was most apparent in the most deprived areas. In CWF areas, there were 45% fewer hospital admissions of children aged one to four for dental caries (mostly for extraction of decayed teeth under a general anaesthetic) than in non-CWF areas.

A recent (2014) [Australian study of early-life fluoride exposure\[96\]](#) used a cross-sectional population-based design that included 2,611 children aged 8-12-years from New South Wales, where >60% were exposed to fluoridated water almost continuously during their first 3 years of life, and just under 15% had no early exposure. Exposure to fluoridated water during the first 3 years of life was associated with better oral health of school-age children. The association between exposure to fluoridated water and dental caries in the primary dentition was confirmed in multivariate models for both the prevalence (prevalence ratio 0.83 for 100% exposure in first 3 years vs no exposure) and extent of dental caries (risk ratio 0.65). Exposure during the first 3 years was also associated with significantly lower caries experience in permanent teeth (RR 0.76 for 100% exposure vs 0% exposure). Another recent Australian study found that the introduction of CWF in 2005 to five remote indigenous communities with very poor oral health resulted in a significant reduction in the prevalence and severity of dental caries by 2012, particularly in children who had lifetime exposure to fluoridated water (4-8 year-olds in 2012 vs 4-8 year-olds in 2004).[97]

The [US IOM Committee on Examination of the Evolving Science for Dietary Supplements](#) analysed the evolution of evidence for relationships between nutrient intake and disease status in 2002[98] and found that the evidence for fluoride in reducing dental caries had strengthened since the previous report in 1997.[45] Fluoride was one of the few nutrients for which there was increased confidence in the relationship between the nutrient and a health effect (the others being calcium and vitamin D in relation to bone status). The additional evidence reviewed was considered to support and strengthen previous conclusions that exposure to fluoride at all ages (from fluoridated water, supplements, and topical application) prevents dental caries, and that both pre- and post-eruptive exposure has cariostatic (decay-stopping) effects.

The [WHO](#) considers fluoride a micronutrient with a beneficial effect on oral health. Following reviews of the evidence for health effects of fluoride in drinking water,[10, 99] the WHO continues to recommend fluoridation of water supplies, where possible, as the most

effective public health measure for the prevention of dental decay, as stated in their 2010 document for decision makers[100] and reiterated on the current (2014) WHO website, which states: “Public health actions are needed to provide sufficient fluoride intake in areas where this is lacking, so as to minimise tooth decay. This can be done through drinking water fluoridation, or, when this is not possible, through salt or milk fluoridation.”[101]

Recent data from New Zealand

A number of studies have been carried out in New Zealand over the last decade that provide epidemiological data on oral health in relation to community access to optimally fluoridated drinking water.

The [New Zealand Oral Health Survey 2009](#)[66] found that overall, the NZ population had relatively good oral health, showing substantial improvements since the 1980s. The survey found that significant differences in decay rates between fluoridated and non-fluoridated communities continue to exist, despite the fact that the majority of people use fluoride toothpastes. The prevalence and severity of dental decay in five-year-old children was higher in non-fluoridated areas (55% caries-free; dmft = 2.2) than in fluoridated areas (58% caries-free; dmft = 1.8), a pattern that has been consistent over time. Similarly, 12-13-year-olds from non-fluoridated areas were less likely to be caries-free than their counterparts in fluoridated areas (45.1% vs 56.2%) and more likely to have higher DMFT scores (1.7 vs 1.2; i.e. more decayed, missing or filled permanent teeth), indicating more severe decay.

Importantly, levels of fluorosis were similar between fluoridated and nonfluoridated areas, and the overall prevalence of moderate fluorosis was very low. The findings support international evidence that water fluoridation has oral health benefits for both adults and children, and minimal risk of increasing fluorosis.

Auckland

In 2009, Kanagaratnam et al.[102] collected data on a cohort of 9-year-old children in the Auckland region in relation to their length of residence in fluoridated versus non-fluoridated areas, and observed a dose-response relationship between fluoride exposure and the prevalence of both dental caries and enamel defects (specifically diffuse opacities). The prevalence of decay in primary (deciduous) teeth was lowest in continuous residents of fluoridated areas (51%), highest in continuous residents of non-fluoridated areas (67%), and intermediate for those with intermittent fluoridation residency status. The severity of deciduous caries (dmft scores) also followed this pattern.

Northland

A cross-sectional epidemiological survey was conducted in 2007 that provided baseline data prior to initiation of fluoridation in two Northland communities (Kaitaia and Kaikohe); two other towns (Dargaville and Kawakawa/Moerewa) served as non-fluoridated control areas. The prevalence and severity of caries in Northland was very high compared with the rest of New Zealand (e.g. mean dmft of 5.6 vs a national mean of 2.3).[103] A second cross-sectional survey constituted the final report.[19] This study found that the water treatment plants serving the fluoridated communities did not consistently achieve fluoride concentrations at the desired level (levels ranged from 0.20-0.78 mg/L in Kaikohe and from 0.24-0.84 mg/L in Kaitaia, while they were 0.02-0.03 mg/L in the non-fluoridated areas).

Fluoridation for 2 years was associated with some improvement in caries levels, particularly among 12-13-year-olds. Of note was that the caries prevalence and severity in this age group was 2.5x the national average at baseline. This study has some weaknesses but suggests that fluoridation at optimal levels would be effective in reducing caries prevalence and severity in this region of very high caries burden.

Southland

A 2005 cross-sectional survey in which 436 children (mean age 9.8 years) were examined for enamel defects and dental caries found that children who were continuous residents of fluoridated communities had about half the caries experience (50% lower DMFS scores) of residents of non-fluoridated communities, but also a greater risk for diffuse enamel opacities (which were seen in just over half of all the study participants).[104] Children who had lived all of their lives (to age 4) in a fluoridated area had over twice the odds of having mild enamel fluorosis (diffuse opacity). Children who were reported as having eaten toothpaste before the age of 4 had 4-fold higher odds of having a hypoplastic defect (moderate fluorosis).

Canterbury and Wellington

A large cross-sectional analysis in 2004 of routinely collected data from school dental services examined differences in dental caries rates between children (8375 5-year-olds and 7158 12-year-olds) living in fluoridated and non-fluoridated areas of Canterbury and Wellington.[105] This study also looked at differences between ethnic and socio-economic groups. Overall, the study determined that the benefits of CWF continue to be significant in New Zealand. The prevalence and severity of caries was >30% lower in fluoridated areas, than in non-fluoridated areas. The advantage of fluoridation was greatest for Māori and Pacific children, and those in low socioeconomic groups.

Otago

A recent (2013) retrospective analysis of the need for treatment under general anaesthesia for children in fluoridated and non-fluoridated areas of Otago found that children from non-fluoridated areas underwent treatment at younger ages and had more teeth affected by caries than those from areas with CWF.[106] This suggests that CWF may have a positive impact on early childhood caries at the severe end of the spectrum, where the disease has the greatest cumulative negative consequences over the lifespan.

3.2.4 Studies in adult and elderly populations

With the exception of water fluoridation, virtually all primary caries-preventive programmes target children and youth, yet caries experience continues to increase with age. For example, among military recruits in Australia, those aged 31-35 had mean DMFT scores that were more than double that of the 17-20 year old group. Recruits who had lived more than half of their life with access to fluoridated drinking water had approximately 25% less caries experience than those with no lifetime exposure.[107] Young military recruits with long-term exposure to CWF had 38% less caries experience in approximal tooth surfaces (between teeth), and 26% reduction in caries in occlusal (chewing) surfaces than those with no or limited exposure.[108]

Griffin et al.[109] performed a systematic review that included 9 studies of the effect of CWF in adult populations, and concluded that CWF was beneficial in adults of all ages. Overall, the caries-prevented fraction was 34.6% in populations with lifetime exposure (vs no exposure). For the five studies conducted after 1979 (i.e. since the introduction of fluoridated dental products), the prevented fraction was 27.2% for water fluoridation.

A thorough review of adult oral health in Ireland in 2007[110] revealed that adults exposed to water fluoridation had lower DMFT scores, less caries on the aesthetically important teeth in the front of the mouth, and an average of 2.8 more healthy teeth than those in the non-fluoridated group. The New Zealand Oral Health Survey 2009[66] also found a statistically significant difference in DMFT scores for adults living in fluoridated vs non-fluoridated areas.

Slade et al. 2013[111] reported that Australian adults with prolonged exposure to fluoridated water had significantly lower age-adjusted DMFT and fewer decayed or filled tooth surfaces than those with negligible exposure. This included adults born before 1960, who were not exposed to CWF during early childhood, indicating that later but prolonged exposure was still effective in reducing the prevalence and severity of tooth decay in adults.

Elderly

The long history of CWF around the world now means that many adults in late life have experienced a lifetime of fluoridation. The benefits for adult dental health include lower levels of root caries, and better tooth retention into old age. A 2010 study in the US,[112] using data from the Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System annual survey data (1995-1999), estimated the association between adult tooth loss and current CWF, CWF 20 years ago, and CWF at time of birth in a cohort of adults born between 1950 and 1969. They reported that CWF levels in an individual's county of residence at the time of birth were significantly associated with tooth loss – consistent with a lasting effect of early fluoride exposure throughout the lifespan. Similarly, elderly individuals in Ireland whose water supplies were fluoridated were found to be more likely to retain their natural teeth than those in non-fluoridated areas.[110]

It should be noted that the increasing retention of natural teeth in the elderly brings with it an increased need for long-term maintenance of tooth function. Elderly individuals may have decreased ability to undertake personal healthcare due to frailty, sarcopenia (loss of muscle strength), poor vision, and/or dementia. As with other groups who may have inadequate oral healthcare habits, the consumption of fluoridated water can have important preventive impact against caries in the elderly.

3.2.5 Health inequalities and cost effectiveness

A number of studies have suggested that the benefits of CWF are greatest among the most deprived socioeconomic groups, although the magnitude of the difference is uncertain.

The York Review[89] assessed 15 UK studies of the effect of CWF on social equity in dental health and concluded that the caries reduction benefit for disadvantaged social classes was greater than for higher social classes (the difference in mean DMFT score between fluoridated and non-fluoridated areas was 52.6% among low socioeconomic groups and

38.9% among high socioeconomic groups). However, the methodology used in the studies varied, and statistical analysis was not possible, so the reviewers suggested caution in interpreting the results. Other studies demonstrating a greater difference in caries reduction from CWF for low vs high socioeconomic groups include communities from New Zealand,[105, 113] Australia,[114] Ireland[115], and a recent blinded study from the UK.[116]

Cost-effectiveness

The cost-effectiveness of CWF in New Zealand was last evaluated in 1999; the findings were published in 2001.[117] CWF was found to be “cost-saving (dental cost savings exceeded fluoridation costs) for communities above about a thousand people”. The authors noted that for smaller communities, CWF may be considered cost-effective, depending on how a prevented decayed tooth surface is valued. They also reported that CWF was particularly cost-effective for “communities with high proportions of children, Māori, or people of low socio-economic status”. These conclusions may indeed underestimate the value of CWF in that this study did not include benefits of CWF after age 34 years and cost savings after age 45 years. It also used a relatively high discount rate (of 5%) compared to contemporary health economic practice in New Zealand (typically 3%).

In 2012 a cost-effectiveness study was performed in Australia,[118] a country that shares many characteristics with New Zealand. This study reported that extending CWF to all communities of at least 1000 people would lead to improved population health (3700 disability-adjusted life-years (DALYs), 95% uncertainty interval: 2200–5700 DALYs), and that there would be a 100% probability of this being cost saving. Furthermore, it found that by “averting 760,000 (430,000–1,300,000) child and adolescent caries lesions, the intervention can reduce the total cost of caries treatment by \$95 million (\$45 million–\$170 million)” (Australian dollars).

These New Zealand and Australian studies detailed above are compatible with other studies which indicate cost savings from CWF in the US,[119, 120] Australia,[121, 122] and Quebec, Canada.[123] A modelling study on CWF in South Africa also reported that benefits of CWF would exceed costs.[124] At least since the year 2000, there appear to be no published studies in the peer-reviewed literature that show that CWF is not cost-effective (i.e., in communities over 1000 people and where the water is not naturally fluoridated).

3.3 Dental fluorosis

Dental fluorosis is a type of hypomineralisation of tooth enamel that manifests as visually detectable differences in enamel opacity. Fluorosis develops from pre-eruptive exposure to excess fluoride in susceptible children; its effects occur only while the teeth are forming in the jaw and before they erupt into the mouth (age <8 years). In the mildest forms, the tooth is fully functional but has cosmetic alterations – almost invisible opaque white spots. In more severely fluorosed teeth, the enamel is pitted and discoloured and is prone to fracture and wear. An explanation of the different levels of fluorosis is provided in table 3. There is a dose-response relationship between fluoride intake and fluorosis, even when intake level is

relatively low.[34, 96] A higher prevalence of dental fluorosis has been observed concomitantly with overall lower caries experience.[125]

Table 3. Explanation of levels of fluorosis (scores according to the WHO Oral Health Surveys Manual)[126]

0 = Normal.	Enamel surface is smooth, glossy and usually a pale creamy- white colour
1 = Questionable	The enamel shows slight aberrations in the translucent normal enamel and which may range from a few white flecks to occasional spots
2 = Very mild	Small opaque, paper-white areas scattered irregularly over the tooth but involving less than 25% of the labial tooth surface
3 = Mild	White opacities of the enamel involving more than 25% but less than 50% of the tooth surface
4 = Moderate	The enamel surfaces show marked wear, and brown staining
5 = Severe	The enamel surfaces are severely affected and the hypoplasia is so marked that the general form of the tooth may be affected. There are pitted or worn areas and brown stains are widespread; the teeth often have a corroded appearance

There are other conditions that appear similar to very mild fluorosis, most notably the white spotting of teeth caused by use of antibiotics such as amoxycillin during childhood.[127] Enamel hypomineralisation can also occur as a result of illness (e.g. measles) or other major upset during tooth formation. The common misdiagnosis of these conditions may contribute to an over-estimation of the overall prevalence of fluorosis.

Dental fluorosis reflects overall fluoride absorption from all sources at a young age. The development and severity of fluorosis is highly dependent on the dose, duration, and timing of fluoride exposure.[34] The timing of fluoride exposure relative to developmental events for dentition is shown in table 4. The exposures listed therein do not imply that fluorosis can occur as a result of each exposure; for example, maternal fluoride intake during pregnancy and breastfeeding are unlikely to have a significant impact on the dentition of the fetus or nursing infant, unless intakes are extremely high (i.e. doses that would be toxic to the mother). From an aesthetic point of view, the only fluorosis that is of concern is that affecting the permanent incisors and canines, and the timing is restricted to a few years when the crowns of these teeth are forming.

Table 4. Timing of fluoride exposure relative to developmental events for dentition

Developmental event	Timing	Means of fluoride exposure
Early ossification of jaw and development/ amelogenesis of deciduous teeth	4-8 months <i>in utero</i>	Maternal intake crossing placenta
Eruption of deciduous teeth	6-24 months	Systemic ingestion – breast milk or formula
Amelogenesis of unerupted permanent teeth	3 months to 5 years	ingested milk (breast/formula/dairy), water, dental products
Eruption of permanent teeth enamel surface	5-16 years	food, water, soft drinks, tea, dental products

3.3.1 Mechanisms of fluorosis

The presence of excess amounts of fluoride during tooth formation can temporarily disturb the function of cells (ameloblasts) that secrete enamel-forming proteins during tooth development. Such disruption can cause hypomineralisation defects in the enamel of unerupted teeth,[75] and may represent a perturbation of fluoride's cariostatic effects on stabilisation of calcium apatite crystals and proteins in enamel. Excess fluoride alters the activities of calcium-dependent proteases, resulting in a delay in protein removal and disrupted mineralisation at the maturation stage of enamel formation. Continuous intake of excess fluoride during and after the secretory phase increases the risk of these defects occurring.[128]

There is some evidence for a genetic predisposition to fluorosis, possibly relating to differences in fluoride metabolism, which may explain some of the variability in fluorosis severity among individuals with similar fluoride intakes.[129]

3.3.2 Infant formula and fluorosis risk

Human breast milk is very low in fluoride, and it is clear that infants who are exclusively formula-fed have higher fluoride intakes than breastfed infants, and are thus at higher risk of dental fluorosis. However, the magnitude and significance of this increased risk is not clear. Levy et al.[130] suggested that the six- to nine-month-old period is most important for development of dental fluorosis in the primary teeth. An increase in fluorosis risk was found with greater intakes of reconstituted infant formula (with fluoridated water) between the ages of 3 and 9 months.[131] A review of changing trends in fluoride intake and fluorosis in infants[132] concurred that the higher risk of fluorosis in formula-fed infants related mainly to the reconstitution of powdered formula with fluoridated water (and not the formula itself), and suggested that, when feasible, low-fluoride water should be used. Erdal and Buchanan[133] used a health risk assessment approach to quantify fluoride intakes from infant formula and other sources associated with fluorosis in children. Their report supported concerns that a segment of the infant population in the US may be exposed to amounts of fluoride that elevate the risk of mild fluorosis, but the specific contribution of infant formula to this risk was not determined. It was again suggested that infant formula could be made up with low-fluoride water in order to reduce the potential risk.

A 1977 study in Sweden had reported that intakes of 0.1 mg fluoride/kg bodyweight/day caused some fluorosis in formula-fed infants. At the time, it was assumed that this level could be consumed by low-weight infants fed formula in low fluoride areas, by normal-weight infants in 0.8 mg/L fluoride areas, and by high-weight infants in 1.2-1.5 mg/L fluoride areas.[134] More recently, a systematic review found some data supporting the association between infant formula consumption and a higher prevalence of enamel fluorosis in permanent dentition, but considered the evidence for this effect to be weak.[135] The 2013 EFSA review determined that an intake of less than 0.1 mg F/kg bodyweight/day in children up to 8 years old corresponds to no significant occurrence of "moderate" forms of fluorosis in permanent teeth.[44]

Recommendations in the US previously suggested that powdered infant formula should be reconstituted with low-fluoride water to reduce the risk of dental fluorosis, but updated

recommendations are to use water fluoridated at around 0.7 mg/L.[136] Advice from Australia indicates that infant formula is safe for consumption whether reconstituted with fluoridated or non-fluoridated water.[137] Fluoridated water supplies in New Zealand are also considered safe for use in infant formula, though as with recommendations elsewhere, if parents are concerned with the risk of mild fluorosis, low-fluoride bottled water can be used for reconstitution in order to reduce fluoride exposure in this age group.

3.3.3 Topical fluorides and fluorosis risk

Intake of fluoride from fluoridated water in infants and young children is clearly not the only risk factor for dental fluorosis. Higher intake of fluoridated toothpaste between 16 and 36 months was also found to increase the risk of mild fluorosis.[131] A Cochrane review of topical fluoride and fluorosis in children found a statistically significant reduction in fluorosis if brushing of a child's teeth with fluoride toothpaste commenced after the age of 12 months, based on observational studies (odds ratio 0.70).[138] Randomised controlled trials showed use of toothpaste with 1000 mg/L fluoride was associated with an increased risk of mild fluorosis. The review concluded that if fluorosis is of concern, the fluoride level of toothpaste for children under 6 should be <1000mg/L. For children considered at high risk for dental caries (by a dentist), the benefits of higher fluoride toothpaste may outweigh risks of fluorosis – but careful parental monitoring is recommended.[138] Young children should use only a smear of toothpaste and should be supervised during toothbrushing to ensure that toothpaste is not swallowed/eaten.

3.3.4 Water fluoride levels associated with fluorosis

The increased prevalence of fluorosis that has been observed since the 1970s has been primarily attributed to the widespread availability of discretionary fluorides such as fluoridated toothpaste, fluoride supplements, and professionally applied fluoride varnishes, because the increase has occurred in both fluoridated and nonfluoridated areas. An examination of fluorosis trends in the US from the 1930s to the 1980s showed that the largest increase in fluorosis prevalence occurred in areas with suboptimal water fluoride levels.[139] The NHS/York review[89, 90] estimated that the overall prevalence of any fluorosis is 48% in areas fluoridated at 1.0 mg/L, and predicted that fluorosis of aesthetic concern would affect 12.5% of the population drinking water at this level of fluoride. The report acknowledged, however, that there is some debate about the significance of the lowest fluorosis scores of each of the various indices for defining an individual as 'fluorosed'.

In the US, some water supplies have natural fluoride levels around 4 mg/L, which is the concentration corresponding to the 'maximum contaminant level goal' (MCLG) – set by EPA. Severe enamel fluorosis occurs at an appreciable frequency, approximately 10% on average, among children in US communities with water fluoride concentrations at or near the current MCLG of 4 mg/L.[46] The prevalence of severe enamel fluorosis is very low (near zero) at fluoride concentrations below 2 mg/L.

The high levels of fluoride approaching the MCLG in the US are not found in drinking water in New Zealand, where most water supplies are below 1.0 mg/L fluoride (and closer to 0.7-

0.8 mg/L) most of the time. The NZ Oral Health Survey 2009[66] reported that 44.5% of 8–30-year-olds in New Zealand had some dental fluorosis, with the majority of fluorosis being 'questionable' or very mild; i.e. effects that are only identified by dental examination. Moderate dental fluorosis was rare (2.0%), and severe fluorosis was not observed (0.0%). In 9-year-old children living continuously throughout their lives in fluoridated areas of Southland, 'questionable' mild to moderate fluorosis could be detected by a dental professional in around 29%. Very mild, mild or moderate fluorosis was equally prevalent between fluoridated and nonfluoridated areas.[66]

A 2011 analysis by the US Department of Health and Human Service of fluorosis trends and fluoride concentrations showed that a plateau in the caries-preventive effects of fluoride occurred as levels in water increased between 0.7 and 1.2 mg/L, but that the percentage of children with at least very mild dental fluorosis continued to increase with increasing fluoride concentrations. This led to a proposal that the fluoride concentration for fluoridated water supplies should be adjusted to 0.7 mg/L rather than a range between 0.7 and 1.2 mg/L.[7] An evaluation of fluorosis prevalence in children before and after a minor downward adjustment in target fluoride levels (from 1.0 to 0.7 mg/L) in Hong Kong drinking water showed that fluorosis was less prevalent in children who were born after the reduction than in cohorts born before. Older cohorts with longer exposure to the higher fluoride concentration had correspondingly higher, but generally mild fluorosis prevalence.[140] Although it was not assessed directly in this study, a previous survey suggested that this reduction in fluorosis did not occur at the expense of increased dental caries, as the prevalence of caries continued to decline in Hong Kong during the period of the study.[141]

A 2010 report by the US EPA,[49] using studies that analysed caries scores in relation to fluorosis scores, found a U-shaped fluoride-caries relationship (i.e. high caries with both low [<0.5 mg/L] and high [>4 mg/L] fluoride) but a linear fluoride-fluorosis relationship (low fluorosis with low fluoride, high with high). Optimum fluoride between 0.7 and 1.0 was protective against caries and had minimal impact on fluorosis incidence.

3.3.5 Fluorosis of aesthetic concern

It is important to note that the seemingly high prevalence of fluorosis reported in some studies and systematic reviews includes mainly mild and very mild (and sometimes questionable) degrees of fluorosis, with only a small proportion that would be considered to be of aesthetic concern.

Surveys have shown that very mild to mild dental fluorosis is not associated with negative impact on perception of oral health,[142] and that adolescents actually preferred the whiteness associated with mild fluorosis.[143] In a recent study, adolescents answered a questionnaire regarding the impact of enamel fluorosis on dental aesthetics, older adolescents rated photographs of mild fluorosis more favorably than younger ones. A fluorosis score indicative of moderate fluorosis was the level considered to have aesthetic significance. Carious teeth were rated significantly lower than fluorosed teeth.[144]

Findings from a longitudinal cohort study of 314 South Australian children (aged 8-13 years) analysing the natural history of dental fluorosis were presented at the 2013 conference of

the International Association for Dental Research (IADR). The data showed that the diffuse mottling of enamel indicative of fluorosis fades during the adolescent years, with over 60% of teeth with mild fluorosis at baseline in 2003-4 showing no fluorosis at follow-up in 2010-11.[145] These changes are most likely the result of ongoing mineralisation by saliva.

4. Water fluoridation and potential health risks

A number of potential adverse effects of the consumption of fluoride have been suggested, though many have only been reported in areas where the natural level of fluoride in water is very high. Reports of possible adverse effects have been systematically reviewed in both the York review[89] and the more recent Australian NHMRC review.[91] Although the York review excluded a large number of cross-sectional studies when assessing CWF benefits, it included all studies for evaluation of potential adverse effects. The NHMRC used similar inclusion criteria. Evidence from these reviews as well as subsequent studies supporting or refuting these claims is evaluated below.

4.1 General toxicity

Over the years, fluoride has been tested in many of the same assays and test systems that are applied in the safety evaluation of new drugs and pesticides, including *in vitro/in vivo* genotoxicity assays, acute and chronic dose toxicity assays, and 2-year carcinogenicity studies in rats and mice.[59]

Acute toxic doses in animals are several hundred times higher than human intake levels in CWF areas (typically 0.05-0.1 mg/kg/day). Multiple-dose animal experiments show potential adverse effects on bone, liver, kidney, heart and testes, but only at doses greater than 4.5 mg/kg/day – again, far exceeding typical human exposures.[59] With regard to genotoxicity, various assays have shown inconsistent results. Fluoride does not show mutagenic potential in standard bacterial systems, but at high doses can produce chromosome aberrations in mammalian cells.[146] The 2002 WHO/IPCS[59] and 2006 NRC reviews[46] considered the evidence for genotoxic effects of fluoride, including assays using blood from people exposed to high levels of fluoride, to be inconclusive, and not relevant to exposures to humans from intentionally fluoridated water.

The York review[89] did not include analysis of *in vitro* or animal studies because the reviewers considered the available human data to be the most relevant in assessing the potential effect of doses used in CWF schemes, outweighing the potential effects of very high doses administered to animals or applied to cells in *in vitro* toxicity studies.

Nonetheless, animal and *in vitro* studies can generate mechanistic and toxicological data that provide biological plausibility for claims of cause and effect. Where appropriate, results of these toxicity studies will be described as background to the review of each type of potential human adverse effect in the following sections.

4.2 Cancer

A number of studies have investigated hypothetical mechanisms by which fluoride could act as a potential carcinogen, either directly via genotoxic or mitogenic effects, or indirectly via effects on thyroid and immune function. These studies were reviewed in a recent analysis by the California EPA,[147] which considered that an effect of fluoride on the development of osteosarcoma was mechanistically plausible, but concurred with previous analyses that human epidemiological evidence for fluoride carcinogenicity has not been demonstrated.

4.2.1 Animal data

A large number of animal carcinogenicity studies have been reported, and to date no effects have been observed at concentrations relevant to intentionally fluoridated drinking water. In most studies in which fluoride was administered orally to rodents, no mutagenic effects were observed. The most comprehensive carcinogenicity studies were conducted as part of the US National Toxicology Program (NTP) in the early 1990s. The first study showed a small number of bone cancers in male rats (but not in mice or female rats) exposed to fluoride in drinking water at concentrations up to 175 mg/L (intakes of 2.5-4.1 mg/kg body weight/day – 50 times the typical human exposure).[148] A follow-up NTP study found no increase in risk when fluoride concentrations were increased to 250 mg/L.[149]

Animal data have not shown a positive link to other forms of cancer. A two-year diet study in male and female rats (4-25 mg/kg/day in food) found no treatment-related tumors of any type despite clear signs of fluoride toxicity in teeth, bones, and stomach[150] A further study which showed an increased incidence of non-malignant osteomas in mice was confounded by possible effects of retroviral infection; thus the osteomas cannot be interpreted as an effect of fluoride.[151] In the more than 20 years since these studies were published, no experimental evidence of an association between cancer and fluoride has been reported.

4.2.2 Human data

Most studies have not found any association between fluoride and cancer in humans, even after decades of exposure in some populations. This includes industrial exposures as recorded and analysed by the US ATSDR.[37] A 1985 review of epidemiological evidence gathered since the introduction of CWF (~70 studies using data from 12 different countries), which included a commissioned reevaluation of some of the data,[152] found an absence of demonstrable effects on cancer rates following long-term exposures to either naturally elevated levels of fluoridated water or artificially fluoridated water supplies. The review found that studies suggesting an association between CWF and cancer had failed to consider the effects of social and environmental differences between the comparator groups, had applied and/or selected data inappropriately, and/or made errors in analyses. More rigorously conducted studies in the UK, Canada, Australia, and New Zealand did not reveal any association between CWF and cancer. The large human populations observed, and the consistency of the findings from many different sources of data in multiple countries, allowed the reviewers to conclude that CWF was not linked to cancer.

An ecological study of nine communities in the US examined cancer incidence rates in 36 body sites in relation to the proportion of residents supplied with CWF. Rates were positively correlated with the proportion of residents with CWF for 23 cancer types, negatively for four types, and for nine types no significant relationship was seen.[153] This study is considered to be flawed because actual fluoride concentrations were neither measured nor considered, and no adjustments for other causes of cancer were made.

Two additional ecological studies reported either no association[154] or an inverse relationship between water fluoride levels and cancer incidence (i.e. low cancer incidence in areas with high fluoride concentrations in the drinking water),[155] but these studies are also of low validity and should be interpreted with caution.

4.2.3 Osteosarcoma

Bone cancers have received attention because of fluoride's deposition in bone. A number of studies have been conducted in human populations to evaluate the potential association of CWF with osteosarcoma (a rare cancer, but the most common type of bone cancer). A 1993 review by the US NRC Committee on Health Effects of Ingested Fluoride[36] concluded that the weight of evidence available at that time did not support an association between fluoridation and osteosarcoma. A 1995 case-control study in osteosarcoma patients under the age of 25[156] found an inverse relationship between total fluoride exposures and osteosarcoma in males, (that is, high concentrations of fluoride were associated with less cancer), but no association in females. The study concluded that CWF exposure does not increase the risk of osteosarcoma, and may be protective. Other case-control studies also failed to find a link between CWF and osteosarcoma.[157, 158] The York review in 2000 concluded that there was no clear association between exposure to fluoridated water and risks of osteosarcoma or other cancers.[89]

A study published since the York review by Bassin et al.[159] has been the source of many claims linking fluoridated water with osteosarcoma. The study used a hospital-based case-control design with fluoride exposure assessment based on retrospectively collected data. A statistically significant increased risk was observed for males who were exposed to CWF at the upper end of the CDC target level (1.2 mg/L F) between 6 and 8 years of age, a time that coincides with the mid-childhood growth spurt in boys. No increased risk was observed in females. A subsequent correspondence submitted by some of the study's co-investigators warned that the findings of this preliminary study were not replicated in the larger study.[160] Patients recruited later than those in the preliminary subset agreed to provide bone samples in which the levels of fluoride could be tested, as fluoride levels in bone serve as an objective biomarker of chronic fluoride exposure. It has since been reported that bone fluoride levels in these samples did not correlate with the occurrence of osteosarcoma.[161]

Systematic reviews including the 2006 NRC review,[46] the 2007 NHMRC review,[91] and the 2011 SCHER report[34] all concluded that based on the best available evidence, fluoride could *not* be classified as carcinogenic in humans.

More recent studies have not changed this conclusion (see Appendix table A4 for a summary of cancer epidemiology data/conclusions and key animal studies):

- Analysis of data from the Northern Ireland Cancer Registry (NICR) and the National Cancer Registry of Ireland (NCRI) in 2011 on osteosarcoma incidence found no difference in incidence rates between fluoridated Republic of Ireland and non-fluoridated Northern Ireland (though no statistics were presented for specific age groups under 25 years).[162]
- An ecological analysis in 2012 of CDC Wonder database data on osteosarcoma incidence and fluoride in drinking water concluded that water fluoride status has no influence on osteosarcoma incidence rates.[163]
- A large and detailed study in England, Scotland and Wales, published in 2014, included 2566 cases of osteosarcoma and 1650 cases of Ewing sarcoma (a rare bone cancer) diagnosed in 1980-2005 and data on fluoride levels in small areas of residence. The analysis, which is more informative than those of previous ecological studies, found no correlation between fluoridated water consumption and these cancers.[164]
- A recent Water Fluoridation Health Monitoring report published by Public Health England[95] found no evidence of a positive association between fluoridation and osteosarcoma or other forms of cancer.
- Finally, in the New Zealand context, National Fluoridation Information Service (NFIS) data from New Zealand cancer registries from 2000-2008 shows no evidence of association between osteosarcoma incidence and residence in water fluoridated areas.[165]

4.3 Skeletal effects

4.3.1 Animal studies

Fluoride naturally accumulates in bone, but its prolonged maintenance there requires a rate of uptake equal to or exceeding the rate of clearance.[166] Thus, from a mechanistic viewpoint, fluoride may be expected to have effects on bone following high and prolonged exposure. Chronic, high-dose fluoride exposure studies in rats (22-50 mg/L in drinking water for up to 18 months) have shown inhibition of bone mineralization and reduced femoral bone strength, and bone remodelling alterations were observed in pigs given fluoride at 2 mg/kg/day.[59] These exposures are 20-50 times those experienced by people drinking optimally fluoridated water, but are relevant to areas of endemic fluorosis where natural fluoride levels are very high.

When considering exposures closer to those associated with CWF, evidence from animal studies suggests that a water fluoride level of 1 mg/L may lead to increased bone strength, while levels ≥ 4 mg/L may cause a decrease in bone strength.[167]

4.3.2 Skeletal fluorosis

Skeletal fluorosis is the result of very high fluoride intake over long periods of time – e.g. intakes of 20 mg/day over periods of 20 years or more cause crippling fluorosis

characterised by osteomalacia, osteoporosis, and/or osteosclerosis. Areas of the world where this is prevalent include parts of India, China, South Africa, and Tanzania.

The NRC 2006 report used modelling to test whether the EPA MCLG (4 mg/L) was protective against skeletal fluorosis.[46] The model estimated that bone fluoride concentrations resulting from lifetime exposure to fluoride in drinking water at 2 mg/L or 4 mg/L fall within or exceed the ranges historically associated with stage II and stage III skeletal fluorosis. However bone fluoride concentrations at which skeletal fluorosis occur can vary widely. The potential for fluoride accumulation in the skeleton is increased in patients with reduced renal function, who therefore have a higher risk for skeletal fluorosis. Nonetheless, evidence indicates that high fluoride intakes are still required (e.g. consumption of 4-8 L/day of water containing fluoride at 2-3 mg/L, or 2-4 L/day at 8.5 mg/L) to become symptomatic.[46] According to the ATSDR, skeletal fluorosis is extremely rare in the United States; it has occurred in some people consuming greater than 30 times the amount of fluoride typically found in fluoridated water.[37] Skeletal fluorosis has not been known to occur in New Zealand.

4.3.3 Fractures

The effects of fluoride intake on fracture risk and bone strength have been studied in animal models and in a large number of epidemiological studies, which have been extensively reviewed in the NRC report.[46], and more recently in a dose-response analysis by the US EPA.[49] The weight of evidence indicates that increasing amounts of fluoride might increase bone volume, but there is less strength per unit volume. The ATSDR found that fluoride at five times the level found in fluoridated water can result in denser bones that may be more brittle than normal bone and may increase the risk of fracture in older individuals.[37]

When study results were combined, a dose-response relationship indicated a gradient of exposure and increasing fracture risk at fluoride concentrations between 1.0 and 4.0 mg/L.[46, 49] The EPA review council concluded that lifetime exposure to fluoride at drinking-water concentrations of 4 mg/L or higher is likely to increase fracture rates in the population, compared with exposure to 1 mg/L, particularly in some demographic subgroups that are prone to accumulate fluoride into their bones (e.g., people with renal disease).

It should be noted that in many of the studies, the reference group was exposed to 1.0 mg/L fluoride in drinking water, and fracture rates were compared with groups having higher exposures. This makes these studies somewhat irrelevant to studying the effect of CWF. A study in Chinese populations with water fluoride levels ranging from 0.25 to 7.97 mg/L found a U-shaped pattern for prevalence of bone fracture and fluoride level; i.e. both high and low fluoride levels were associated with increased risk.[168] The lowest fracture rate was observed in populations where the fluoride concentration in water was 1-1.06 mg/L – near optimal levels used in CWF.

The York report[89] reviewed 29 studies (all of low validity) that assessed whether there was an association between water fluoridation and bone fractures or bone development problems. No evidence of an elevated risk of fractures could be attributed to water

fluoridation at optimal levels. In children, intake of fluoridated water does not appear to affect bone density parameters through adolescence.[169]

4.4 Neurotoxicity/IQ effects

4.4.1 Animal studies

Animal studies using extremely high doses of fluoride have revealed various deficits in learning and behaviour following prolonged exposure. For example, Pereira et al.[170] studied rats fed 100 mg/L fluoride in drinking water for 30 days – 100 times the level in optimally fluoridated water – and noted memory deficits compared with rats who were not dosed with fluoride. Other studies fed rats sodium fluoride by gavage at a level of 5.0 mg/kg/day – again 100 times the recommended level for children (0.05 mg/kg/day). In one study, rats consuming fluoridated water (0, 2.9, 5.7, 11.5 mg/kg body weight/day) showed no evidence of learning deficits in any of the fluoride-exposed groups.[171] This represents chronic ingestion up to 230-fold higher than that experienced by humans whose main source of fluoride is fluoridated water. While these studies are informative from a high-dose, chronic toxicity standpoint, they have little relevance for typical exposures to humans from drinking water at levels used in CWF regimens.

4.4.2 Human studies

Recently there have been a number of reports from China and other areas where fluoride levels in groundwater are naturally very high (fluorosis endemic regions) claiming an association between high water fluoride levels and slightly reduced intelligence (measured as IQ) in children. These studies, which were almost all of very low validity (no adjustment for confounding variables, population level data), were reviewed and meta-analysed by Choi et al,[172] who concluded that the results supported a possibility of adverse neurodevelopmental effects of high fluoride intake. The definition of 'high' fluoride varied considerably in these studies, but most levels were higher than those considered acceptable in the US, and much higher than any level found in New Zealand. In many cases the fluoride level of the 'low' fluoride group was similar to that of artificially fluoridated regions of New Zealand. Setting aside the methodological failings of these studies, Choi et al. determined that the standardised weighted mean difference in IQ scores between "exposed" and reference populations was only -0.45. The authors themselves note that this difference is so small that it "may be within the measurement error of IQ testing".[172] The studies considered only fluoride exposure from drinking water at the population level, although it is likely that other significant environmental sources of fluoride exposure may have been overlooked. In China, for example, grains and other foods are often contaminated with fluoride from coal fires.[173] Most of the studies fail to consider the effects of lead, arsenic, iodine deficiency, socioeconomic status, or nutritional status of the children; thus the strength of evidence is questionable,[46] and not considered relevant to the situation in New Zealand.[174] The 2011 SCHER report also concluded that human studies do *not* support the conclusion that fluoride in drinking water impairs children's development at levels permitted in the EU.[34]

In including fluoride in a list of chemicals possibly causing human developmental toxicity, Grandjean and Landrigan[175] cite only the Choi et al.[172] review, of which Grandjean is a coauthor, as evidence. While no plausible biological mechanism explains the alleged association of fluoride with IQ, overall there is some evidence of possible, slight adverse effect on the developing brain at high fluoride concentrations. There is no convincing evidence of neurological effects at fluoride concentrations achieved by CWF.

A recently published prospective, longitudinal study in New Zealand compared data on IQ and reasoning abilities in a cohort of 1037 individuals born in 1972-73. IQ was assessed at ages 7, 9, 11 and 13 years and averaged into a measure of childhood IQ. Adult IQ was assessed at the age of 38 years. Early-life exposure to fluoride from a variety of sources was recorded using prospective data, and adjustment was made for potential confounding variables. This relatively high quality study revealed no evidence that water fluoridation affects neurological development or IQ.[176]

4.5 Other effects

4.5.1 Reproductive and related effects

No laboratory animal studies have reported reproductive toxicity at low fluoride doses.[37] Decreased fertility and sperm and testes damage have been observed in laboratory animals (rats) at extremely high doses (over 100 times higher than levels of fluoridated water). Other studies reviewed by the ATSDR found no effect.[37] The 2006 NRC review of EPA fluoride standards[46] concluded that adverse reproductive and developmental outcomes occur only at very high concentrations that are unlikely to be encountered by US populations. Although a single, small study on rats exposed to 2, 4, and 6 mg/L sodium fluoride for 6 months reported adverse effects on fertility and reproduction (reduced sperm motility),[177] other larger studies have shown no reproductive effects over multiple generations of rats exposed to fluoride in drinking water at doses up to 175 mg/L[178-180] and no effects on spermatogenesis in doses up to 100 mg/L.[181, 182] A study of Mexican men found that fluoride intakes up to 27 mg/day did not affect sperm motility or other sperm parameters. Some of the men had occupational exposure to fluoride in addition to exposure from drinking water at a concentration of ≥ 3 mg/L.[183]

Rats exposed to very high doses of sodium fluoride (100 or 200 mg/L) in drinking water for 6 months exhibit ovarian dysfunction, possibly as a result of increased oxidative stress in ovarian cells.[184] Female fertility also decreased following 12 weeks of exposure of rats to these same excessive concentrations of fluoride. The daily fluoride intake of these rats was 5.2 mg/kg/day.[185]

The York review in 2000[89] did not find any evidence of fluoride-attributable reproductive toxicity in humans, and the 2006 NRC review of EPA fluoride standards[46] concluded that adverse reproductive and developmental outcomes occur only at very high concentrations that are unlikely to be encountered by U.S. populations. Equally, these high concentrations of fluoride are unlikely to be found in New Zealand. The 2011 SCHER report[34] found no

new studies indicating that fluoride in drinking water influences human reproductive capacity. No additional studies have been identified since this review.

Birth defects

Animal studies have not found any increase in the incidence of birth defects at doses that do not cause maternal toxicity (i.e. the fetus is not more sensitive than the mother).[37] This, in combination with the lack of clear genotoxicity data, brings into question the plausibility of fluoride having a potential effect on the incidence of birth defects, particularly at the low exposure levels associated with CWF.

Nonetheless, several epidemiological studies have looked at the incidence of Down's Syndrome births in relation to fluoridation status. Early links between CWF and Down's syndrome were refuted by later studies.[186, 187] Takahashi[188] reworked the data of the later studies and claimed that fluoride exposure in optimally fluoridated areas was associated with increased risk of Down syndrome for younger mothers (<30-32y). However, a systematic review by Whiting et al.[189] judged all of the available evidence as being of low validity (see Appendix table 1 for criteria) as the studies did not properly assess or adjust for multiple confounding factors, and no conclusion of a link between fluoride exposure and Down's syndrome could be drawn.

The Water Fluoridation Health Monitoring Report for England 2014[95] analysed the distribution of Down's syndrome births in 324 local authorities by fluoridation status and also found no evidence of an association of CWF with Down's syndrome.

Sudden Unexplained Death of an Infant (SUDI)

Studies from New Zealand [190, 191] found no association between fluoride and SUDI (also known as 'sudden infant death syndrome' or 'cot death'). In one of those studies[191], a nationwide case-control database of SUDI was evaluated for fluoride exposure status and controlled for the method of infant feeding (breast or reconstituted formula) with the conclusion that exposure to fluoridated water prenatally or postnatally at the time of death did not affect the relative risk of SUDI.

4.5.2 Endocrine effects

Questions have been raised about potential thyroid impacts from fluoridated drinking water. Studies of animals with iodine deficiency showed effects on thyroid function at fluoride doses of 3-6 mg/kg/day,[192-194] and in one study, at doses in the range of 0.4-0.6 mg/kg/day.[192] The levels of thyroid hormones T3, T4, and TSH are altered in response to excess fluoride in rodents.[59]

The mechanisms of potential fluoride effects on endocrine organs and hormones have been extensively reviewed by the NRC.[46] Most of the reviewed animal studies were designed to ascertain whether certain effects occurred, and not to determine the lowest exposures at which they occurred. The report concluded that fluoride (at unspecified levels) can affect normal endocrine function or response, and that better characterisation of fluoride exposure in humans in epidemiological studies is needed to investigate the potential endocrine effects of fluoride. Two small studies in India that examined the relationship between dental fluorosis and thyroid hormone alterations yielded contradictory results.[195, 196]

Studies conducted in areas of endemic fluorosis suggest that excess fluoride may be associated with thyroid disturbances similar to those observed in iodine deficiency (e.g. goitre), and that high fluoride intake could exacerbate the effects of iodine deficiency. A review of the literature to 1984, including well-controlled studies in large populations exposed to fluoride over long periods, found no convincing evidence of a link between human goitre and fluoride intake.[197] Systematic analysis of studies by the NHS/York review[89] also yielded no significant association between fluoride levels in water and the prevalence of goitre. The York review included a study by Jooste et al.,[198] which examined the prevalence of childhood goitre in relation to water fluoride levels in six towns in the Northern Cape of South Africa where iodine deficiency was not noted. The study found that goitre prevalence did not correlate with fluoride levels: although goitre prevalence was highest in towns with high fluoride (where moderate to severe dental fluorosis was prevalent), it was also high in towns with low fluoride levels, and lowest in one town with optimal fluoride. The authors suggested that the high rates of stunting and undernutrition in the other towns predisposed the children to the risk of goitre development, which could be exacerbated in the presence of excess fluoride.

Both the NHS/York (2000)[89] and the SCHER (2011)[34] reviews concluded that neither animal or human studies to date support a role for fluoride-induced thyroid perturbations in humans in the absence of iodine deficiency.[34]

4.5.3 Cardiovascular and renal effects

Because fluoride accumulates in calcified tissues, there is a suggestion that exposure to fluoride will affect aortic calcification. In fact in animal studies, fluoride (50 mg/L in drinking water) did not affect the deposition of calcium in rat aorta – but blocked increase in phosphorus (in vivo and in vitro models). A number of studies indicate that fluoride may reduce aortic calcification in experimental animals and humans.[199] This preventive effect was recently confirmed by *in vitro* experiments, but *in vivo* findings from the same studies showed the opposite result – that phosphate-induced aortic calcification was accelerated following exposure of uremic rats to fluoride in water at around 1.5 mg/L.[200] The authors suggested that chronic kidney disease could be aggravated by relatively low concentrations of fluoride, which (in turn) accelerates vascular calcification. However, further studies are required to test this hypothesis.

Liu et al.[201] conducted a cross-sectional analysis of the possible relationship between excess fluoride intake from drinking water and carotid atherosclerosis development in adults in fluoride endemic areas of China. They reported a correlation between atherosclerosis prevalence and water fluoride concentration. However, no attempt was made to adjust for confounding variables or moving between regions. The 'normal' fluoride level group (considered low in this study) had mean fluoride water level of 0.85 mg/L (range 0.04-1.20 mg/L), which is similar to or higher than CWF levels in New Zealand. Epidemiological research suggests no link between water fluoride levels and heart attacks.[202-204]

A 1987 clinical case report suggested a possible link between long-term exposure to high-fluoride water (8.5 mg/L) and the development of renal disease,[205] but other studies and systematic reviews have found no evidence that consumption of optimally fluoridated drinking water increases the risk of developing kidney disease. However, individuals with impaired kidney function experience higher/more prolonged fluoride exposure after ingestion because of reduced urinary fluoride excretion, and those with end stage kidney disease may be at greater risk of fluorosis.[206]

The Water Fluoridation Health Monitoring Report for England 2014[95] analysed the incidence of kidney stones in relation to CWF and found evidence that the incidence was lower in fluoridated areas than in non-fluoridated areas.

4.5.4 Immunological effects

There are two types of potential effects of fluoride on the immune system – hypersensitivity reactions and immunotoxicity effects (weakening of the immune system). Information on both is limited. Earlier reviews concluded that the evidence did not support claims that fluoride was allergenic.[36, 87] The NRC committee, who analysed effects of fluoride in drinking water at the EPA's MCLG level of 4 mg/L, did not find any human studies where immune effects were carefully documented. The report suggested that immunosuppressed individuals could be at greater risk of potential immunological effects of fluoride.

An interesting case is presented by a study in Kuopio Finland, where a planned and publicised discontinuation of CWF was carried out one month early, without the public being told. Surveys were taken at three time points: 1) when the public was aware CWF was currently implemented, 2) when the public believed CWF was still implemented but it had been discontinued, and 3) when the public was aware the CWF had been discontinued. Symptoms of allergic skin reactions were reported for surveys 1 and 2 but the number of reports substantially diminished in survey 3, suggesting that some 'reactions' to fluoride were related to beliefs rather than actual exposure.[207]

4.6 Impact on specific demographic groups

4.6.1 Pregnant women

Pregnant women are not themselves any more vulnerable to the effects of fluoride than their non-pregnant counterparts, but they may have concerns about fluoride ingestion and its possible effects on their unborn fetuses. In humans, fluoride crosses the placenta and is transferred from mother to fetus,[208] but there is also evidence that the placenta may act as a partial barrier to accumulation of fluoride in the fetal circulation, since levels in amniotic fluid and cord blood are lower than in maternal blood. None of the major reviews of fluoride effects (2000 NHS/York,[89] NHMRC 2007,[91] SCHER 2011[34] found any evidence of reproductive toxicity attributable to fluoride at or around levels used for CWF. No new data have been published since these reviews.

In the past, fluoride supplements were recommended for pregnant women as fluoride was considered beneficial to fetal tooth development. The first enamel is formed in the

developing fetus around the third to fourth month of gestation. Although fluoride is not essential for tooth development, enamel containing fluoroapatite is more resistant to acids (dissolves at a lower pH) than enamel containing only hydroxyapatite.[73, 209] However, studies of fluoride supplementation in pregnancy have not shown them to be effective, and because of the possibility of increased risk of fluorosis, fluoride supplements are no longer recommended.

Physiological changes occurring in pregnancy can negatively affect maternal oral health. There is also evidence for *in utero* transmission of cariogenic bacteria from mother to child.[210] The American Academy of Pediatric Dentistry considers perinatal fluoride exposure a protective factor against the development of early childhood caries by helping to delay colonisation of the infant oral cavity by cariogenic bacteria.[211] Pregnant women are therefore encouraged to use fluoridated toothpaste and to consume fluoridated water.

4.6.2 Formula-fed infants

There is no evidence that typical fluoride intakes from formula feeding, using optimally fluoridated water for reconstitution, has any adverse effects on infant or child development aside from a possible greater risk of dental fluorosis. Feeding with formula reconstituted with fluoridated water may be associated with lower caries experience in permanent teeth.[212]

The American Dental Association have provided evidence-based recommendations[136] that suggest infant formula can be made up with 'optimally fluoridated' drinking water (now 0.7 mg/L in the US), but that parents should be aware of the potential risk for development of mild enamel fluorosis. If fluorosis is a concern, or in areas where local water supplies contain fluoride at higher levels, ready-to-feed formulas or powdered formulas reconstituted with low-fluoride water are recommended.

4.6.3 Young children

It is possible that some children in New Zealand could exceed the UL for fluoride intake when fluoridated water is consumed, although most evidence points to the effect of swallowing toothpaste in contributing to excess fluoride intake, and the development of mild to moderate fluorosis in young children.[39] Very young children should be supervised while toothbrushing, and should use only a smear of toothpaste with a fluoride concentration of 1000 ppm.

The UL for fluoride intake in children is based on the endpoint of increased risk of moderate dental fluorosis. Because moderate fluorosis is very rare in New Zealand, the level of exceedance of UL that may occur in New Zealand children is not considered to be a safety concern.[213]

4.6.4 Elderly

Fluoride plasma and bone concentrations tend to increase with age, partially due to accumulation over time, and also to decreased renal clearance. [46] The elderly are therefore likely to have relatively higher bone fluoride concentrations. However, epidemiological data to date do not suggest any increased risk of fracture due to fluoride exposure in this older population. Nevertheless, the NRC review[46] suggested that more

research is needed on bone concentrations in the elderly as a potentially sensitive population. A recent EPA study analysing exposure and risks [51] suggested that 0.08 mg/kg/day intake of fluoride was protective against fractures in all populations (including vulnerable groups).

4.6.5 Renal-impaired individuals

Chronic kidney disease affects a significant proportion of the New Zealand population, with a particularly high prevalence among Māori and Pacific people. Numbers of affected individuals are increasing due to the increasing prevalence of hypertension and diabetes. Because the kidney is the major route of excretion, blood fluoride concentrations are typically elevated in patients with kidney disease.[214, 215] Only a few studies have examined fluoride concentrations in bone in renal patients, but these have noted markedly elevated (possibly up to 2-fold) bone fluoride levels[46]. However, the potential effect of these higher bone fluoride levels is currently unknown. Adverse effects of fluoride exposure from CWF in renal-impaired individuals have not been documented. However, the scarcity of data indicates that further studies are required.

5. Summary

A large number of studies and systematic reviews have concluded that water fluoridation is an effective preventive measure against tooth decay that reaches all segments of the population, and is particularly beneficial to those most in need of improved oral health. Extensive analyses of potential adverse effects have not found evidence that the levels of fluoride used for community water fluoridation schemes contribute any increased risk to public health, though there is a narrow range between optimal dental health effectiveness and a risk of mild dental fluorosis.

In establishing guidelines for drinking-water quality, the WHO notes that fluoride is one of few chemicals for which the contribution from drinking water to overall intake is an important factor in preventing disease. Conversely, it is also noted as causing adverse health effects from exposure through drinking water when present in excessive quantity. WHO states that “it may not be possible to achieve effective fluoride-based caries prevention without some degree of dental fluorosis, regardless of which methods are chosen to maintain a low level of fluoride in the mouth”[216] A guideline value of 1.5 mg/L fluoride in drinking water has been recommended as a level at which dental fluorosis should be minimal.[10] A 2011 update of the WHO Guidelines for Drinking-Water Quality concluded that this guideline value should be maintained, as there is no new evidence to suggest a need for revision.[21] For optimal dental health, WHO suggests that the optimal range should be 0.8-1.0 mg/L, and that drinking water supplies should have fluoride levels raised or lowered to this range if possible.[100, 217]

Water fluoridation in New Zealand has been ongoing since the 1950s, with notable benefits to the oral health of its residents. The levels of fluoride found naturally in New Zealand water sources (typically 0.1-0.2 mg/L) are below those known to benefit oral health, but are

adjusted to between 0.7 and 1.0 mg/L (usually ~0.8 mg/L) in areas served by CWF schemes. The most recent New Zealand Oral Health Survey^[66] indicated that fluoridation continues to be of benefit to communities that receive it, despite overall reductions in tooth decay that have resulted from widespread use of fluoridated dental products since the mid-1970s. The prevalence of fluorosis of aesthetic concern is minimal in New Zealand, and is not different between fluoridated and non-fluoridated communities, confirming that a substantial proportion of the risk is attributable to the intake of fluoride from sources other than water (most notably, the swallowing of high-fluoride toothpaste by young children). The current fluoridation levels therefore appear to be appropriate. It is important, however, that the chosen limit continues to protect the majority of high-exposure individuals.

This analysis concludes that water fluoridation continues to provide dental health benefits to the population of New Zealand, with no evidence of serious adverse effects after many decades of exposure. Based on these findings, we conclude that CWF is a sound public health policy practice. Communities that currently do not provide CWF – particularly those with high dental caries prevalence – would benefit from its implementation. To be effective, a public health intervention must be meeting a public health need – the effectiveness of the intervention is highest where there is the highest need. There is strong evidence that CWF is a cost-effective use of tax payer funds – with it being likely to save more in dental costs than it costs to run fluoridation programmes (at least in communities of 1000+ people). There is New Zealand evidence for this, along with evidence from Australia (three studies), the US (two studies), Canada, Chile and South Africa. The New Zealand study reported that CWF was most cost-effective in “communities with high proportions of children, Māori, or people of low socio-economic status”.

Conclusions

Councils with established CWF schemes in New Zealand can be confident that their continuation does not pose risks to public health, and promotes improved oral health in their communities, reducing health inequalities and saving on lifetime dental care costs for their citizens. Councils where CWF is not currently undertaken can confidently consider this as an appropriate public health measure, particularly those where the prevalence and severity of dental caries is high. A forthcoming study from the Ministry of Health is expected to provide further advice on how large a community needs to be before CWF is cost-effective (current indications point to all communities of 1000+ people).

It is recommended that a review such as this one is repeated or updated every 10 years – or earlier if a large well-designed study is published that appears likely to have shifted the balance of health benefit vs health risk.

References

1. Dean, H.T. and E. Elvove, *Some Epidemiological Aspects of Chronic Endemic Dental Fluorosis*. Am J Public Health Nations Health, 1936. **26**(6): p. 567-75.
2. Connett, P. *50 Reasons to oppose fluoridation*. 2012 [cited 2014 31 Mar]; Available from: <http://fluoridealert.org/articles/50-reasons/>.
3. Fluoride Action Network. *FluorideAlert.org*. Available from: <http://fluoridealert.org>.
4. Bryson, C., *The Fluoride Deception*. 2004, New York, NY: Seven Stories Press.
5. Sandman, P.M., *Hazard versus outrage in the public perception of risk*, in *Effective Risk Communication*, V.T. Corvello, D.B. McCallum, and M.T. Pavlova, Editors. 1989, Plenum Press: New York.
6. Armfield, J.M. and H.F. Akers, *Risk perception and water fluoridation support and opposition in Australia*. J Public Health Dent, 2010. **70**(1): p. 58-66.
7. U.S. Department of Health and Human Services, *Proposed HHS recommendation for fluoride concentration in drinking water for prevention of dental caries*. Federal Register 2011. **76**(9): p. 2383-2388.
8. Health Canada, *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document - Fluoride*, 2010, Water, Air and Climate Change Bureau, Healthy Environments and Consumer Safety Branch, Ottawa.
9. Fairweather, A.A., et al., *Reference concentrations of cholecalciferol in animals: a basis for establishing non-target exposure*. New Zealand Journal of Zoology, 2013. **40**(4): p. 280-289.
10. Fawell, J., et al., *Fluoride in Drinking-water*, in *WHO Drinking-water Quality Series 2006*, World Health Organization: Geneva.
11. Marthaler, T.M. and P.E. Petersen, *Salt fluoridation--an alternative in automatic prevention of dental caries*. Int Dent J, 2005. **55**(6): p. 351-8.
12. Kunzel, W. and T. Fischer, *Rise and fall of caries prevalence in German towns with different F concentrations in drinking water*. Caries Res, 1997. **31**(3): p. 166-73.
13. Kunzel, W., et al., *Decline of caries prevalence after the cessation of water fluoridation in the former East Germany*. Community Dent Oral Epidemiol, 2000. **28**(5): p. 382-9.
14. Petersen, P.E., R.J. Baez, and M.A. Lennon, *Community-oriented administration of fluoride for the prevention of dental caries: a summary of the current situation in Asia*. Adv Dent Res, 2012. **24**(1): p. 5-10.
15. Petersen, P.E., *World Health Organization global policy for improvement of oral health--World Health Assembly 2007*. Int Dent J, 2008. **58**(3): p. 115-21.
16. British Fluoridation Society, *The extent of water fluoridation*, in *One in a million: the facts about water fluoridation, 3rd edition 2012*, British Fluoridation Society.
17. Fordyce, F.M., et al., *A health risk assessment for fluoride in Central Europe*. Environ Geochem Health, 2007. **29**(2): p. 83-102.
18. Edmunds, W.M. and P.L. Smedley, *Fluoride in natural waters*, in *Essentials of Medical Geology. Revised edition*, O. Selinus, Editor. 2013, Springer: London.
19. Gowda, S., *Pre- and post-water fluoridation oral health survey in Northland/Te Tai Tokerau: Final report*, 2009, Northland District Health Board: Whangarei.
20. Ministry of Health, *Guidelines for drinking-water quality management for New Zealand 2013. Third edition*, 2013, Ministry of Health: Wellington.
21. World Health Organization, *Guidelines for drinking-water quality - Fourth edition*, in *Water Sanitation Health 2011*, Geneva. p. 668.
22. Thomson, W.M., *Personal communication*, 2014.
23. WINZ - Water Information for New Zealand, *Fluoride in drinking water 2012-2013. Data Source: WINZ 6, Annual Survey data, extracted 4 June 2014*. ESR Water Group, 2014.
24. Watercare Services Limited, *Annual water quality report 2012*, 2012: Auckland.
25. Harland, C., et al., *Hydrofluorosilicic acid and water fluoridation.*, 2014, New Zealand Institute of Chemistry: Christchurch.
26. New Zealand Institute of Chemistry, *Production of Chemicals: Hydrofluorosilicic acid and water fluoridation*, in *Chemical processes in New Zealand*. 1998.

27. Jackson, P., P. Harvery, and W. Young, *Chemistry and bioavailability aspects of fluoride in drinking water*, 2002: Marolow, Bucks.
28. Finney, W.F., et al., *Reexamination of hexafluorosilicate hydrolysis by ¹⁹F NMR and pH measurement*. *Environ Sci Technol*, 2006. **40**(8): p. 2572-7.
29. Irish Expert Body on Fluorides and Health, *Forum on Fluoridation 2002* 2002, Stationery Office, Government of Ireland: Dublin. p. 296 p.
30. Ministry of Health, *Drinking-water Standards for New Zealand 2005 (Revised 2008)*, 2008, Ministry of Health: Wellington.
31. Coplan, M.J., et al., *Confirmation of and explanations for elevated blood lead and other disorders in children exposed to water disinfection and fluoridation chemicals*. *Neurotoxicology*, 2007. **28**(5): p. 1032-42.
32. Maas, R.P., et al., *Effects of fluoridation and disinfection agent combinations on lead leaching from leaded-brass parts*. *Neurotoxicology*, 2007. **28**(5): p. 1023-31.
33. Urbansky, E.T. and M.R. Schock, *Can fluoridation affect lead(II) in potable water? Hexafluorosilicate and fluoride equilibria in aqueous solution*. *International Journal of Environmental Studies*, 2000. **57**: p. 597-637.
34. Scientific Committee on Health and Environmental Risks (SCHER), European Commission Directorate-General for Health & Consumers, *Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water*, 2011, European Commission: Brussels.
35. Ministry of Health, *Annual Report on Drinking-water Quality 2012-2013*, 2014, Ministry of Health: Wellington.
36. National Research Council. Committee on Toxicology, *Health effects of ingested fluoride*, 1993, National Academy of Sciences: Washington, D.C.
37. Agency for Toxic Substances and Disease Registry (ATSDR), *Toxicological profile for fluorides, hydrogen fluoride, and fluorine*, 2003, U.S. Department of Health and Human Services, Public Health Service: Atlanta, GA.
38. Public Health England, *Delivering better oral health: an evidence-based toolkit for prevention. Third edition*, 2014.
39. Cressey, P., S. Gaw, and J. Love, *Estimated dietary fluoride intake for New Zealanders*, 2009, Institute of Environmental Science & Research Limited (ESR): Christchurch.
40. Taves, D.R., *Dietary intake of fluoride ashed (total fluoride) v. unashed (inorganic fluoride) analysis of individual foods*. *Br J Nutr*, 1983. **49**(3): p. 295-301.
41. Cao, J., et al., *Brick tea fluoride as a main source of adult fluorosis*. *Food Chem Toxicol*, 2003. **41**(4): p. 535-42.
42. Food Standards Australia New Zealand, *Australia New Zealand Food Standards Code - Standard 2.9.1 - Infant Formula Products*, 2009.
43. National Health and Medical Research Council; Ministry of Health, *Nutrient Reference Values for Australia and New Zealand, including Recommended Dietary Intakes*, 2006, Australian Government.
44. EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA), *Scientific opinion on dietary reference values for fluoride*. *EFSA Journal*, 2013. **11**(8): p. 3332.
45. Institute of Medicine, Food and Nutrition Board, *Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*, 1997, Standing Committee on the Scientific Evaluation of dietary reference intakes, Food and Nutrition Board, Institute of Medicine: Washington, D.C.
46. Committee on Fluoride in Drinking Water, *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*, 2006, National Research Council: Washington, DC, USA. p. 529.
47. Cressey, P., *Dietary fluoride intake for fully formula-fed infants in New Zealand: impact of formula and water fluoride*. *J Public Health Dent*, 2010. **70**(4): p. 285-91.
48. Filipsson, M., T. Oberg, and B. Bergback, *Variability and uncertainty in Swedish exposure factors for use in quantitative exposure assessments*. *Risk Anal*, 2011. **31**(1): p. 108-19.
49. U.S. Environmental Protection Agency, Health and Ecological Criteria Division, and Office of Water, *Fluoride: dose-response analysis for non-cancer effects*, 2010, EPA Washington, D.C.
50. Maguire, A., et al., *Fluoride intake and urinary excretion in 6- to 7-year-old children living in optimally, sub-optimally and non-fluoridated areas*. *Community Dent Oral Epidemiol*, 2007. **35**(6): p. 479-88.
51. U.S. Environmental Protection Agency, Health and Ecological Criteria Division, and Office of Water, *Fluoride: Exposure and Relative Source Contribution Analysis*, 2010, EPA: Washington, D.C.
52. D-A-CH (Deutschland- Austria- Confoederatio Helvetica), *Referenzwerte für die Nährstoffzufuhr (Reference values for nutrient intake)*, 2012: Frankfurt/Main.

53. Shimonovitz, S., et al., *Umbilical cord fluoride serum levels may not reflect fetal fluoride status*. J Perinat Med, 1995. **23**(4): p. 279-82.
54. Ron, M., et al., *Fluoride concentration in amniotic fluid and fetal cord and maternal plasma*. Eur J Obstet Gynecol Reprod Biol, 1986. **21**(4): p. 213-8.
55. Opydo-Szymaczek, J. and M. Borysewicz-Lewicka, *Transplacental passage of fluoride in pregnant polish women assessed on the basis of fluoride concentrations in maternal and cord blood plasma*. Fluoride, 2007. **40**(1): p. 46-50.
56. Chlubek, D., R. Poreba, and B. Machalinski, *Fluoride and calcium distribution in human placenta*. Fluoride, 1998. **31**(3): p. 131-136.
57. Brambilla, E., et al., *Oral administration of fluoride in pregnant women, and the relation between concentration in maternal plasma and in amniotic fluid*. Arch Oral Biol, 1994. **39**(11): p. 991-4.
58. Opinya, G.N., et al., *Intake of fluoride and excretion in mothers' milk in a high fluoride (9 ppm) area in Kenya*. Eur J Clin Nutr, 1991. **45**(1): p. 37-41.
59. International Programme on Chemical Safety. World Health Organization, *Fluorides. Environmental Health Criteria 227*, 2002, World Health Organization: Geneva.
60. Whitford, G.M., *Fluoride metabolism and excretion in children*. J Public Health Dent, 1999. **59**(4): p. 224-8.
61. Whitford, G.M., *Intake and metabolism of fluoride*. Adv Dent Res, 1994. **8**(1): p. 5-14.
62. Waterhouse, C., D. Taves, and A. Munzer, *Serum inorganic fluoride: changes related to previous fluoride intake, renal function and bone resorption*. Clin Sci (Lond), 1980. **58**(2): p. 145-52.
63. Cury, J.A. and L.M. Tenuta, *How to maintain a cariostatic fluoride concentration in the oral environment*. Adv Dent Res, 2008. **20**(1): p. 13-6.
64. Maguire, A., et al., *Bioavailability of fluoride in drinking water: a human experimental study*. J Dent Res, 2005. **84**(11): p. 989-93.
65. Whitford, G.M., et al., *Pharmacokinetics of ingested fluoride: lack of effect of chemical compound*. Arch Oral Biol, 2008. **53**(11): p. 1037-41.
66. Ministry of Health, *Our oral health: Key findings of the 2009 New Zealand Oral Health Survey*, 2010, Ministry of Health: Wellington.
67. Ministry of Health, *Health Loss in New Zealand: A report from the New Zealand Burden of Diseases, Injuries and Risk Factors Study, 2006-2016*, 2013, Ministry of Health: Wellington.
68. Page, L.A. and W.M. Thomson, *Dental caries in Taranaki adolescents: a cohort study*. N Z Dent J, 2011. **107**(3): p. 91-6.
69. Selwitz, R.H., A.I. Ismail, and N.B. Pitts, *Dental caries*. Lancet, 2007. **369**(9555): p. 51-9.
70. Marinho, V.C., et al., *Fluoride toothpastes for preventing dental caries in children and adolescents*. Cochrane Database Syst Rev, 2003(1): p. CD002278.
71. Levine, M., *Topics in Dental Biochemistry*. Topics in Dental Biochemistry, 2011: p. 1-307.
72. Featherstone, J.D., *Prevention and reversal of dental caries: role of low level fluoride*. Community Dent Oral Epidemiol, 1999. **27**(1): p. 31-40.
73. Buzalaf, M.A., et al., *Mechansims of action of fluoride for caries control*, in *Fluoride and the Oral Environment*, M.A. Buzalaf, Editor. 2011, Karger: Basel. p. 97-114.
74. Ekstrand, J. and A. Oliveby, *Fluoride in the oral environment*. Acta Odontol Scand, 1999. **57**(6): p. 330-3.
75. Leverett, D.H., et al., *Caries risk assessment by a cross-sectional discrimination model*. J Dent Res, 1993. **72**(2): p. 529-37.
76. Featherstone, J.D., *Delivery challenges for fluoride, chlorhexidine and xylitol*. BMC Oral Health, 2006. **6 Suppl 1**: p. S8.
77. Robinson, C., *Fluoride and the caries lesion: interactions and mechanism of action*. Eur Arch Paediatr Dent, 2009. **10**(3): p. 136-40.
78. Ingram, G.S., E.A. Agalamanyi, and S.M. Higham, *Caries and fluoride processes*. J Dent, 2005. **33**(3): p. 187-91.
79. Singh, K.A., A.J. Spencer, and D.S. Brennan, *Effects of water fluoride exposure at crown completion and maturation on caries of permanent first molars*. Caries Res, 2007. **41**(1): p. 34-42.
80. Singh, K.A., A.J. Spencer, and J.M. Armfield, *Relative effects of pre- and posteruption water fluoride on caries experience of permanent first molars*. J Public Health Dent, 2003. **63**(1): p. 11-9.
81. Slade, G.D., et al., *Associations between exposure to fluoridated drinking water and dental caries experience among children in two Australian states*. J Public Health Dent, 1995. **55**(4): p. 218-228.
82. Slade, G.D., et al., *Caries experience among children in fluoridated Townsville and unfluoridated Brisbane*. Aust N Z J Public Health, 1996. **20**(6): p. 623-9.

83. Spencer, A.J., J.M. Armfield, and G.D. Slade, *Exposure to water fluoridation and caries increment*. Community Dent Health, 2008. **25**(1): p. 12-22.
84. Public Health Service, *Review of Fluoride: Benefits and Risks. Report of the Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs*, 1991, Dept of Health and Human Services.
85. Public Health Commission, *Water Fluoridation in New Zealand: An analysis and monitoring report*, 1994: Wellington.
86. Centers for Disease Control and Prevention, *Recommendations for using fluoride to prevent and control dental caries in the United States*. MMWR Recomm Rep, 2001. **50**(RR-14): p. 1-42.
87. Medical Research Council, *Water fluoridation and health. Working group report*, 2002: London.
88. Scientific Advisory, Institute National de Sante Publique du Quebec,, *Water fluoridation: An analysis of the health benefits and risks*, 2007, Institute National de Sante Publique du Quebec: Quebec.
89. McDonagh, M., et al., *A systematic review of public water fluoridation*, 2000, NHS Centre for Reviews and Dissemination, University of York: York, UK.
90. McDonagh, M.S., et al., *Systematic review of water fluoridation*. BMJ, 2000. **321**(7265): p. 855-9.
91. National Health and Medical Research Council, *A systematic review of the efficacy and safety of fluoridation*, 2007, Australian Government: Canberra.
92. Truman, B.I., et al., *Reviews of evidence on interventions to prevent dental caries, oral and pharyngeal cancers, and sports-related craniofacial injuries*. Am J Prev Med, 2002. **23**(1 Suppl): p. 21-54.
93. Community Preventive Services Task Force. *Preventing Dental Caries: Community Water Fluoridation. Task Force Finding and Rationale Statement*. The Community Guide 2013 [cited 2014 20 July]; Available from: <http://www.thecommunityguide.org/oral/supportingmaterials/RRfluoridation.html>.
94. Whelton, H., et al., *North South Survey of Children's Oral Health in Ireland 2002, 2006*, Republic of Ireland, Department of Health and Children; Northern Ireland, Department of Health Social Services and Public Safety; WHO Collaborating Centre for Oral Health Services Research University, College Cork: Dublin. p. 176.
95. Public Health England, *Water fluoridation: Health monitoring report for England 2014*. , 2014, Department of Health: London.
96. Do, L.G., et al., *Dental caries and fluorosis experience of 8-12-year-old children by early-life exposure to fluoride*. Community Dent Oral Epidemiol, 2014.
97. Johnson, N., et al., *Effectiveness of water fluoridation in caries reduction in a remote Indigenous community in Far North Queensland*. Aust Dent J, 2014.
98. Institute of Medicine (U.S.). Committee on Examination of the Evolving Science for Dietary Supplements. and Institute of Medicine (U.S.). Food and Nutrition Board., *Evolution of evidence for selected nutrient and disease relationships*. The compass series. 2002, Washington, D.C.: National Academy Press. ix, 87 p.
99. Petersen, P.E. and M.A. Lennon, *Effective use of fluorides for the prevention of dental caries in the 21st century: the WHO approach*. Community Dent Oral Epidemiol, 2004. **32**(5): p. 319-21.
100. World Health Organization, *Inadequate or excess fluoride: A major public health concern*, in *Preventing disease through healthy environments:2010*, Public Health and Environment. World Health Organization: Geneva.
101. World Health Organization and International Programme on Chemical Safety. *Inadequate or excess fluoride*. 2014 [cited 2014 30 July]; Available from: http://www.who.int/ipcs/assessment/public_health/fluoride/en/.
102. Kanagaratnam, S., et al., *Enamel defects and dental caries in 9-year-old children living in fluoridated and nonfluoridated areas of Auckland, New Zealand*. Community Dent Oral Epidemiol, 2009. **37**(3): p. 250-9.
103. Gowda, S.S., et al., *Dental caries experience of children in Northland/Te Tai Tokerau*. N Z Dent J, 2009. **105**(4): p. 116-20.
104. Mackay, T.D. and W.M. Thomson, *Enamel defects and dental caries among Southland children*. N Z Dent J, 2005. **101**(2): p. 35-43.
105. Lee, M. and P.J. Dennison, *Water fluoridation and dental caries in 5- and 12-year-old children from Canterbury and Wellington*. N Z Dent J, 2004. **100**(1): p. 10-5.
106. Kamel, M.S., W.M. Thomson, and B.K. Drummond, *Fluoridation and dental caries severity in young children treated under general anaesthesia: an analysis of treatment records in a 10-year case series*. Community Dent Health, 2013. **30**(1): p. 15-8.
107. Hopcraft, M.S., et al., *Dental caries experience in young Australian Army recruits 2008*. Aust Dent J, 2009. **54**(4): p. 316-22.

108. Hopcraft, M.S. and M.V. Morgan, *Pattern of dental caries experience on tooth surfaces in an adult population*. Community Dent Oral Epidemiol, 2006. **34**(3): p. 174-83.
109. Griffin, S.O., et al., *Effectiveness of fluoride in preventing caries in adults*. J Dent Res, 2007. **86**(5): p. 410-5.
110. Whelton, H., et al., *Oral health of Irish adults 2000-2002. Final Report - April 2007*, U.o.C. WHO Collaborating Centre for Oral Health Services Research, Editor 2007, Department of Health and Children: Dublin.
111. Slade, G.D., et al., *Effects of fluoridated drinking water on dental caries in Australian adults*. J Dent Res, 2013. **92**(4): p. 376-82.
112. Neidell, M., K. Herzog, and S. Glied, *The association between community water fluoridation and adult tooth loss*. Am J Public Health, 2010. **100**(10): p. 1980-5.
113. Evans, R.W., et al., *Relationship between fluoridation and socioeconomic status on dental caries experience in 5-year-old New Zealand children*. Community Dent Oral Epidemiol, 1984. **12**(1): p. 5-9.
114. Slade, G.D., et al., *Influence of exposure to fluoridated water on socioeconomic inequalities in children's caries experience*. Community Dent Oral Epidemiol, 1996. **24**(2): p. 89-100.
115. Sagheri, D., J. McLoughlin, and J.J. Clarkson, *A comparison of dental caries levels in two communities with different oral health prevention strategies stratified in different social classes*. J Public Health Dent, 2007. **67**(1): p. 1-7.
116. McGrady, M.G., et al., *The association between social deprivation and the prevalence and severity of dental caries and fluorosis in populations with and without water fluoridation*. BMC Public Health, 2012. **12**: p. 1122.
117. Wright, J.C., et al., *The cost-effectiveness of fluoridating water supplies in New Zealand*. Aust N Z J Public Health, 2001. **25**(2): p. 170-8.
118. Cobiac, L.J. and T. Vos, *Cost-effectiveness of extending the coverage of water supply fluoridation for the prevention of dental caries in Australia*. Community Dent Oral Epidemiol, 2012. **40**(4): p. 369-76.
119. Griffin, S.O., K. Jones, and S.L. Tomar, *An economic evaluation of community water fluoridation*. J Public Health Dent, 2001. **61**(2): p. 78-86.
120. O'Connell, J.M., et al., *Costs and savings associated with community water fluoridation programs in Colorado*. Prev Chronic Dis, 2005. **2 Spec no**: p. A06.
121. Campaign, A.C., et al., *The impact of changing dental needs on cost savings from fluoridation*. Aust Dent J, 2010. **55**(1): p. 37-44.
122. Ciketic, S., M.R. Hayatbakhsh, and C.M. Doran, *Drinking water fluoridation in South East Queensland: a cost-effectiveness evaluation*. Health Promot J Austr, 2010. **21**(1): p. 51-6.
123. Tchouaket, E., et al., *The economic value of Quebec's water fluoridation program*. Z Gesundh Wiss, 2013. **21**: p. 523-533.
124. Kroon, J. and P.J. van Wyk, *A model to determine the economic viability of water fluoridation*. J Public Health Dent, 2012. **72**(4): p. 327-33.
125. Mascarenhas, A.K., *Risk factors for dental fluorosis: a review of the recent literature*. Pediatr Dent, 2000. **22**(4): p. 269-77.
126. World Health Organization, *Oral Health Surveys: Basic Methods*. Fifth ed. 2013, Geneva: World Health Organization.
127. Hong, L., et al., *Association of amoxicillin use during early childhood with developmental tooth enamel defects*. Arch Pediatr Adolesc Med, 2005. **159**(10): p. 943-8.
128. Aoba, T. and O. Fejerskov, *Dental fluorosis: chemistry and biology*. Crit Rev Oral Biol Med, 2002. **13**(2): p. 155-70.
129. Everett, E.T., *Fluoride's effects on the formation of teeth and bones, and the influence of genetics*. J Dent Res, 2011. **90**(5): p. 552-60.
130. Levy, S.M., et al., *Primary tooth fluorosis and fluoride intake during the first year of life*. Community Dent Oral Epidemiol, 2002. **30**(4): p. 286-95.
131. Levy, S.M., et al., *Associations between fluorosis of permanent incisors and fluoride intake from infant formula, other dietary sources and dentifrice during early childhood*. J Am Dent Assoc, 2010. **141**(10): p. 1190-201.
132. Fomon, S.J., J. Ekstrand, and E.E. Ziegler, *Fluoride intake and prevalence of dental fluorosis: trends in fluoride intake with special attention to infants*. J Public Health Dent, 2000. **60**(3): p. 131-9.
133. Erdal, S. and S.N. Buchanan, *A quantitative look at fluorosis, fluoride exposure, and intake in children using a health risk assessment approach*. Environ Health Perspect, 2005. **113**(1): p. 111-7.
134. Forsman, B., *Early supply of fluoride and enamel fluorosis*. Scand J Dent Res, 1977. **85**(1): p. 22-30.

135. Hujoel, P.P., et al., *Infant formula and enamel fluorosis: a systematic review*. J Am Dent Assoc, 2009. **140**(7): p. 841-54.
136. Berg, J., et al., *Evidence-based clinical recommendations regarding fluoride intake from reconstituted infant formula and enamel fluorosis: a report of the American Dental Association Council on Scientific Affairs*. J Am Dent Assoc, 2011. **142**(1): p. 79-87.
137. Australian Research Centre for Population Oral Health, *The use of fluorides in Australia: guidelines*. Aust Dent J, 2006. **51**(2): p. 195-199.
138. Wong, M.C., et al., *Cochrane review: Topical fluoride as a cause of dental fluorosis in children*. Evidence-Based Child Health, 2011. **6**(2): p. 388-439.
139. Beltran-Aguilar, E.D., S.O. Griffin, and S.A. Lockwood, *Prevalence and trends in enamel fluorosis in the United States from the 1930s to the 1980s*. J Am Dent Assoc, 2002. **133**(2): p. 157-65.
140. Evans, R.W. and J.W. Stamm, *Dental fluorosis following downward adjustment of fluoride in drinking water*. J Public Health Dent, 1991. **51**(2): p. 91-8.
141. Lo, E.C., R.W. Evans, and O.P. Lind, *Dental caries status and treatment needs of the permanent dentition of 6-12-year-olds in Hong Kong*. Community Dent Oral Epidemiol, 1990. **18**(1): p. 9-11.
142. Chankanka, O., et al., *A literature review of aesthetic perceptions of dental fluorosis and relationships with psychosocial aspects/oral health-related quality of life*. Community Dent Oral Epidemiol, 2010. **38**(2): p. 97-109.
143. McGrady, M.G., et al., *Adolescents' perceptions of the aesthetic impact of dental fluorosis vs. other dental conditions in areas with and without water fluoridation*. BMC Oral Health, 2012. **12**: p. 4.
144. Browne, D., et al., *The aesthetic impact of enamel fluorosis on Irish adolescents*. Community Dent Oral Epidemiol, 2011. **39**(2): p. 127-36.
145. Do, L. and A.J. Spencer. *Natural history of dental fluorosis in a longitudinal cohort study*. in IADR/AADR/CADR 91st General Session. 2013. Seattle, WA: J. Dent Res.
146. Zeiger, E., M.D. Shelby, and K.L. Witt, *Genetic toxicity of fluoride*. Environ Mol Mutagen, 1993. **21**(4): p. 309-18.
147. Morry, D.W. and C. Steinmaus, *Evidence on the carcinogenicity of fluoride and its salts*, 2011, Office of Environmental Health Hazard Assessment's Reproductive and Cancer Hazard Assessment Branch, California Environmental Protection Agency.
148. National Toxicology Program (NTP), *Toxicology and carcinogenesis studies of sodium fluoride in F344/N rats and B6C3F1 mice (drinking water studies)*, 1990, U.S. Department of Health and Human Services.
149. National Toxicology Program (NTP), *NTP Supplemental 2-year study of sodium fluoride in male F344 rats (CASRN 7681-49-4)*, in *Technical Report Series 1992*, U.S. Department of Health and Human Services.
150. Maurer, J.K., et al., *Two-year carcinogenicity study of sodium fluoride in rats*. J Natl Cancer Inst, 1990. **82**(13): p. 1118-26.
151. Maurer, J.K., et al., *Confounded carcinogenicity study of sodium fluoride in CD-1 mice*. Regul Toxicol Pharmacol, 1993. **18**(2): p. 154-68.
152. Knox, E.G., *Fluoridation of water and cancer: a review of the epidemiological evidence. Report of the Working Party*, 1985: London.
153. Takahashi, K., K. Akiniwa, and K. Narita, *Regression analysis of cancer incidence rates and water fluoride in the U.S.A. based on IACR/IARC (WHO) data (1978-1992)*. International Agency for Research on Cancer. J Epidemiol, 2001. **11**(4): p. 170-9.
154. Yang, C.Y., et al., *Fluoride in drinking water and cancer mortality in Taiwan*. Environ Res, 2000. **82**(3): p. 189-93.
155. Steiner, G.G., *Cancer incidence rates and environmental factors: an ecological study*. J Environ Pathol Toxicol Oncol, 2002. **21**(3): p. 205-12.
156. Gelberg, K.H., et al., *Fluoride exposure and childhood osteosarcoma: a case-control study*. Am J Public Health, 1995. **85**(12): p. 1678-83.
157. McGuire, S.M., et al., *Is there a link between fluoridated water and osteosarcoma?* J Am Dent Assoc, 1991. **122**(4): p. 38-45.
158. Moss, M.E., et al., *Osteosarcoma, seasonality, and environmental factors in Wisconsin, 1979-1989*. Arch Environ Health, 1995. **50**(3): p. 235-41.
159. Bassin, E.B., et al., *Age-specific fluoride exposure in drinking water and osteosarcoma (United States)*. Cancer Causes Control, 2006. **17**(4): p. 421-8.
160. Douglass, C.W. and K. Josphipura, *Caution needed in fluoride and osteosarcoma study*. Cancer Causes Control, 2006. **17**(4): p. 481-2.

161. Kim, F.M., et al., *An assessment of bone fluoride and osteosarcoma*. J Dent Res, 2011. **90**(10): p. 1171-6.
162. Comber, H., et al., *Drinking water fluoridation and osteosarcoma incidence on the island of Ireland*. Cancer Causes Control, 2011. **22**(6): p. 919-24.
163. Levy, M. and B.S. Leclerc, *Fluoride in drinking water and osteosarcoma incidence rates in the continental United States among children and adolescents*. Cancer Epidemiol, 2012. **36**(2): p. e83-8.
164. Blakey, K., et al., *Is fluoride a risk factor for bone cancer? Small area analysis of osteosarcoma and Ewing sarcoma diagnosed among 0-49-year-olds in Great Britain, 1980-2005*. International Journal of Epidemiology, 2014. **43**(1): p. 224-234.
165. National Fluoridation Information Service, *Community Water Fluoridation and Osteosarcoma – Evidence from Cancer Registries.*, 2013, National Fluoridation Information Service: Wellington.
166. Rao, H.V., et al., *A physiologically based pharmacokinetic model for fluoride uptake by bone*. Regul Toxicol Pharmacol, 1995. **22**(1): p. 30-42.
167. Turner, C.H., M.P. Akhter, and R.P. Heaney, *The effects of fluoridated water on bone strength*. J Orthop Res, 1992. **10**(4): p. 581-7.
168. Li, Y., et al., *Effect of long-term exposure to fluoride in drinking water on risks of bone fractures*. J Bone Miner Res, 2001. **16**(5): p. 932-9.
169. Levy, S.M., et al., *Effects of life-long fluoride intake on bone measures of adolescents: a prospective cohort study*. J Dent Res, 2014. **93**(4): p. 353-9.
170. Pereira, M., et al., *Memory impairment induced by sodium fluoride is associated with changes in brain monoamine levels*. Neurotox Res, 2011. **19**(1): p. 55-62.
171. Whitford, G.M., J.L. Whitford, and S.H. Hobbs, *Appetitive-based learning in rats: lack of effect of chronic exposure to fluoride*. Neurotoxicol Teratol, 2009. **31**(4): p. 210-5.
172. Choi, A.L., et al., *Developmental fluoride neurotoxicity: a systematic review and meta-analysis*. Environ Health Perspect, 2012. **120**(10): p. 1362-8.
173. Finkelman, R.B., H.E. Belkin, and B. Zheng, *Health impacts of domestic coal use in China*. Proc Natl Acad Sci U S A, 1999. **96**(7): p. 3427-31.
174. Borman, B. and C. Fyfe, *Fluoride and children's IQ*. N Z Med J, 2013. **126**(1375): p. 111-2.
175. Grandjean, P. and P.J. Landrigan, *Neurobehavioural effects of developmental toxicity*. Lancet Neurol, 2014. **13**(3): p. 330-8.
176. Broadbent, J.M., et al., *Community Water Fluoridation and Intelligence: Prospective Study in New Zealand*. Am J Public Health, 2014.
177. Gupta, R.S., et al., *The toxic effects of sodium fluoride on the reproductive system of male rats*. Toxicol Ind Health, 2007. **23**(9): p. 507-13.
178. Collins, T.F., et al., *Developmental toxicity of sodium fluoride in rats*. Food Chem Toxicol, 1995. **33**(11): p. 951-60.
179. Collins, T.F., et al., *Multigenerational evaluation of sodium fluoride in rats*. Food Chem Toxicol, 2001. **39**(6): p. 601-13.
180. Collins, T.F., et al., *Developmental toxicity of sodium fluoride measured during multiple generations*. Food Chem Toxicol, 2001. **39**(8): p. 867-76.
181. Sprando, R.L., et al., *Testing the potential of sodium fluoride to affect spermatogenesis in the rat*. Food Chem Toxicol, 1997. **35**(9): p. 881-90.
182. Sprando, R.L., et al., *Testing the potential of sodium fluoride to affect spermatogenesis: a morphometric study*. Food Chem Toxicol, 1998. **36**(12): p. 1117-24.
183. Ortiz-Perez, D., et al., *Fluoride-induced disruption of reproductive hormones in men*. Environ Res, 2003. **93**(1): p. 20-30.
184. Geng, Y., et al., *Sodium fluoride activates ERK and JNK via induction of oxidative stress to promote apoptosis and impairs ovarian function in rats*. J Hazard Mater, 2014. **272**: p. 75-82.
185. Zhou, Y., et al., *The toxicity mechanism of sodium fluoride on fertility in female rats*. Food Chem Toxicol, 2013. **62**: p. 566-72.
186. Erickson, J.D., et al., *Water fluoridation and congenital malformations: no association*. J Am Dent Assoc, 1976. **93**(5): p. 981-4.
187. Erickson, J.D., *Down syndrome, water fluoridation, and maternal age*. Teratology, 1980. **21**(2): p. 177-80.
188. Takahashi, K., *Fluoride-linked Down syndrome births and their estimated occurrence due to water fluoridation*. Fluoride, 1998. **31**(2): p. 61-73.
189. Whiting, P., M. McDonagh, and J. Kleijnen, *Association of Down's syndrome and water fluoride level: a systematic review of the evidence*. BMC Public Health, 2001. **1**(6).

190. Mitchell, E.A., J.M.D. Thompson, and B. Borman, *No Association between Fluoridation of Water-Supplies and Sudden-Infant-Death-Syndrome*. New Zealand Medical Journal, 1991. **104**(924): p. 500-501.
191. Dick, A.E., et al., *Water fluoridation and the sudden infant death syndrome*. New Zealand Medical Journal, 1999. **112**(1093): p. 286-289.
192. Bobek, S., S. Kahl, and Z. Ewy, *Effect of long-term fluoride administration on thyroid hormones level blood in rats*. Endocrinol Exp, 1976. **10**(4): p. 289-95.
193. Guan, Z.Z., et al., *Synergistic action of iodine-deficiency and fluorine-intoxication on rat thyroid*. Chin Med J (Engl), 1988. **101**(9): p. 679-84.
194. Zhao, W., et al., *Long-term Effects of Various Iodine and Fluorine Doses on the Thyroid and Fluorosis in Mice*. Endocr Regul, 1998. **32**(2): p. 63-70.
195. Susheela, A.K., et al., *Excess fluoride ingestion and thyroid hormone derangements in children living in Delhi, India*. Fluoride, 2005. **38**: p. 98-108.
196. Hosur, M.B., et al., *Study of thyroid hormones free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) in subjects with dental fluorosis*. Eur J Dent, 2012. **6**(2): p. 184-90.
197. Burgi, H., L. Siebenhuner, and E. Miloni, *Fluorine and thyroid gland function: a review of the literature*. Klin Wochenschr, 1984. **62**(12): p. 564-9.
198. Jooste, P.L., et al., *Endemic goitre in the absence of iodine deficiency in schoolchildren of the Northern Cape Province of South Africa*. Eur J Clin Nutr, 1999. **53**(1): p. 8-12.
199. Zipkin, I., et al., *Fluoride and calcification of rat aorta*. Calcif Tissue Res, 1970. **6**(3): p. 173-82.
200. Martin-Pardillos, A., et al., *Effect of water fluoridation on the development of medial vascular calcification in uremic rats*. Toxicology, 2014. **318**: p. 40-50.
201. Liu, H., et al., *Assessment of relationship on excess fluoride intake from drinking water and carotid atherosclerosis development in adults in fluoride endemic areas, China*. Int J Hyg Environ Health, 2014. **217**(2-3): p. 413-20.
202. Kousa, A., et al., *Geochemistry of ground water and the incidence of acute myocardial infarction in Finland*. J Epidemiol Community Health, 2004. **58**(2): p. 136-9.
203. Rogot, E., et al., *Trends in urban mortality in relation to fluoridation status*. Am J Epidemiol, 1978. **107**(2): p. 104-12.
204. Erickson, J.D., *Mortality in selected cities with fluoridated and non-fluoridated water supplies*. N Engl J Med, 1978. **298**(20): p. 1112-6.
205. Lantz, O., et al., *Fluoride-induced chronic renal failure*. Am J Kidney Dis, 1987. **10**(2): p. 136-9.
206. Ludlow, M., G. Luxton, and T. Mathew, *Effects of fluoridation of community water supplies for people with chronic kidney disease*. Nephrol Dial Transplant, 2007. **22**(10): p. 2763-7.
207. Lamberg, M., H. Hausen, and T. Vartiainen, *Symptoms experienced during periods of actual and supposed water fluoridation*. Community Dent Oral Epidemiol, 1997. **25**(4): p. 291-5.
208. Armstrong, W.D., L. Singer, and E.L. Makowski, *Placental transfer of fluoride and calcium*. Am J Obstet Gynecol, 1970. **107**(3): p. 432-4.
209. Beltran, E.D. and B.A. Burt, *The pre- and posteruptive effects of fluoride in the caries decline*. J Public Health Dent, 1988. **48**(4): p. 233-40.
210. Mitchell, S.C., et al., *Maternal transmission of mutans Streptococci in severe-early childhood caries*. Pediatr Dent, 2009. **31**(3): p. 193-201.
211. American Academy of Pediatric Dentistry, *Guideline on perinatal oral health care, in AAPD Clinical Guidelines 2011*.
212. Do, L.G. and A.J. Spencer, *Reconstituting infant formula with fluoridated water reduced deciduous caries experience*, in *The 9th World Congress on Preventive Dentistry 2009* 2009, IADR: Phuket.
213. Food Standards Australia New Zealand, *Final assessment report. Voluntary addition of fluoride to packaged water*, 2009.
214. Spak, C.J., U. Berg, and J. Ekstrand, *Renal clearance of fluoride in children and adolescents*. Pediatrics, 1985. **75**(3): p. 575-9.
215. Schiffli, H.H. and U. Binswanger, *Human urinary fluoride excretion as influenced by renal functional impairment*. Nephron, 1980. **26**(2): p. 69-72.
216. World Health Organization. *Risks to oral health and intervention: Fluorides*. [cited 2014 2 July]; Available from: http://www.who.int/oral_health/action/risks/en/index1.html.
217. World Health Organization, *Briefing on fluoride in drinking water*, 2006, WHO: Geneva.
218. European Food Safety Authority (EFSA), *Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the tolerable upper intake level of fluoride (Request No EFSA-Q-2003-018)*. The EFSA Journal, 2005. **192**: p. 1-65.

219. Rugg-Gunn, A.J. and L. Do, *Effectiveness of water fluoridation in caries prevention*. *Community Dent Oral Epidemiol*, 2012. **40 Suppl 2**: p. 55-64.
220. International Agency for Research on Cancer (IARC), *Fluorides (Inorganic, Used in Drinking-water)*, in *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 1987*, World Health Organization: Geneva. p. 208-210.

Abbreviations

AI = adequate intake

ATSDR = Agency for Toxic Substances and Disease Registry (USA)

CWF = community water fluoridation

dmft = decayed, missing, or filled primary (deciduous) teeth

DMFT = decayed, missing, or filled permanent teeth

DRV = dietary reference value

EFSA = European Food Safety Authority

EPA = Environmental Protection Agency (USA)

ESR = Environmental Science & Research (NZ)

HFA = hydrofluorosilicic acid; hexafluorosilicate

H₂SiF₆ = hydrofluorosilicic acid; hexafluorosilicate

IOM = Institute of Medicine (USA)

LOAEL = lowest observed adverse effect level

MAV = maximum acceptable value

MCLG = maximum contaminant level goal

MRL = minimal risk level

NaF = sodium fluoride

Na₂SiF₆ = sodium fluorosilicate

NHMRC = National Health and Medical Research Council (Australia)

NOAEL = no observed adverse effect level

NRC = National Research Council (USA)

NRV = nutrient reference value

NTP = National Toxicology Program (USA)

NZMoH = New Zealand Ministry of Health

PHE = Public Health England

TDI = tolerable daily intake reference dose

SCHER = Scientific Committee on Health and Environmental Risks (Europe)

UL = tolerable upper level of intake

WHO = World Health Organization

Appendix

Table A1. Study characteristics and levels of evidence criteria for epidemiological studies of community water fluoridation (CWF) – used in the UK NHS/York review[89] and the Australian NHMRC review. [91]

HIGH quality of evidence – minimal risk of bias
<ul style="list-style-type: none">• Prospective study design (not retrospective or cross-sectional), starting around the time of either initiation or discontinuation of CWF, and with a long follow up• Randomisation, or addressing and adjusting for multiple possible confounding factors• Blinded: fluoridation status of participants is unknown to those assessing outcomes.
MODERATE quality of evidence – moderate risk of bias
<ul style="list-style-type: none">• Studies that started within three years of the initiation or discontinuation of CWF, with a prospective follow up for outcomes.• Studies that measured and adjusted for at least one confounding factor (but less than 3)• Not blinded - fluoridation status of participants was known to those assessing primary outcomes, but other provisions were made to prevent measurement bias.
LOWEST quality of evidence – high risk of bias
<ul style="list-style-type: none">• Cross-sectional or retrospective studies using concurrent or historical controls• Studies that failed to adjust for confounding factors.

Table A2. Major reviews, guidelines, and oral health reports on community water fluoridation (CWF)

Review	Year	Scope of review/Inclusion criteria	Conclusions	
			CWF efficacy	CWF adverse effects
Public Health Service – USA [84]	1991	Comprehensive qualitative assessment of health benefits and risks, prepared by PHS Ad Hoc Subcommittee on Fluoride. Analysed NTP fluoride carcinogenicity studies, published studies on humans and animals, Public input was requested and submissions reviewed.	Fluoride has substantial benefits in the prevention of tooth decay. Numerous studies, taken together, clearly establish a causal relationship between water fluoridation and the prevention of dental caries. The health and economic benefits of water fluoridation accrue to individuals of all ages and socioeconomic groups, especially to poor children.	<ul style="list-style-type: none"> - CWF at optimal level does not pose a detectable cancer risk to humans. - More studies are needed to determine whether there is a link between CWF levels and bone fractures. - No indication of adverse effects in other organ systems. - Mild fluorosis has increased in all areas (fluoridated or not) due to introduction of additional fluoride sources
Public Health Commission - NZ [85]	1994	Review of the benefits and costs of CWF, with particular attention to recent scientific literature and NZ-related literature	Average individual lifetime benefit of CWF in NZ = prevention of 2.4-12.0 DMFT; At population level (with 50% of population exposed to CWF) = prevention of 58,000-267,000 DMFT/year in NZ. Greatest caries prevention benefit in lower SES groups, Māori, and children	<ul style="list-style-type: none"> - Possible small increased risk of hip fracture. - No evidence of link to cancer, except possible small increased risk of osteosarcoma cannot be ruled out. - Little/no adverse cosmetic impact from dental fluorosis; moderate fluorosis likely due to other fluoride sources - No scientific basis for concern about other health effects from CWF at 1 mg/L
NHS Centre for Reviews and Dissemination, University of York (UK) [89]	2000	Systematic review of 214 studies in all languages using strict quality criteria for inclusion. Cross-sectional studies were excluded. Overall the validity of the studies was considered moderate or low.	The best available evidence suggests that CWF does reduce caries prevalence, both as a proportion of children who are caries free and by the mean change in dmft/DMFT score. A beneficial effect was still evident in spite of the assumed exposure to non-water fluoride in all study populations after 1974	<ul style="list-style-type: none"> - Fluorosis of any degree was estimated to occur in 48% of people consuming water at 1.0 mg/L fluoride. - Bone fracture studies found no association with CWF - No clear association was found between CWF and cancer incidence or mortality (including bone cancers, thyroid cancer, and all cancer) - Insufficient evidence exists for other possible negative effects

Review	Year	Scope of review/Inclusion criteria	Conclusions	
			CWF efficacy	CWF adverse effects
Centers for Disease Control and Prevention (CDC) - US [86]	2001	Review/guideline on use of fluorides for prevention and control of dental caries in the US – looks at all modalities. Does not review safety.	Recommends that all persons drink water with an optimal fluoride concentration and brush teeth twice daily with fluoride toothpaste	Not assessed
Medical Research Council (MRC) – UK [87]	2002	Mostly reiterated York review but considered what future research could help inform risk management decisions on water fluoridation.	Conclusions as per those in York. Also found that water fluoridation reduced dental caries inequalities between high and low SES groups. Suggested studies needed to provide better estimate of effects of CWF against background of widespread use of fluoride toothpaste.	- Evidence suggests no link to cancer, and no effect on fracture risk (but cannot rule out the possibility of a small %change - either increase or a decrease - in hip fractures.) - No evidence of any other significant health effects
US Task Force on Community Preventive Services [92]	2002	Reviews 21 qualifying studies of CWF, including 15 starting of continuing CWF, 5 stopping or reducing CWF, and 1 with changes in both directions.	Strong evidence shows that CWF is effective in reducing the cumulative experience of dental caries within communities. Starting CWF decreased caries experience by 30-50%. Stopping CWF lead to ~17% increase in caries experience. CWF was cost saving in all studies.	Not assessed
Ireland Forum on Fluoridation [29]	2002	First major review of CWF in Ireland since it was introduced in 1964. Based on presentations by Irish and international experts examining scientific evidence representing views both for and against CWF. Also addressed issues of concern to the Irish public.	CWF has been very effective in improving oral health in the Irish population, especially children, but also adults and the elderly, and should continue as a public health measure	- Best available and most reliable evidence indicates that human health is not adversely affected by CWF at the maximum permitted fluoride level (1 mg/L) - There is evidence that dental fluorosis is increasing in Ireland.
Ireland North-South survey of children's oral health [94]	2002	Survey of oral health in fluoridated Republic of Ireland (RoI) compared with non-fluoridated Northern Ireland (NI)	CWF was the major contributor to lower decay rates in RoI compared with NI, despite worse oral health habits in RoI.	Fluorosis is increasing in Ireland, more so in fluoridated areas.

Review	Year	Scope of review/Inclusion criteria	Conclusions	
			CWF efficacy	CWF adverse effects
WHO – International Programme on Chemical Safety (IPCS) [59]	2002	Environmental Health Criteria report on the relationship between fluoride exposure and human health, to provide guidelines for setting exposure limits - focused on adverse effects	Not assessed	Effects on teeth and skeleton (both beneficial and harmful) are observed at exposures below those associated with other adverse health effects. Effects on bone are the most relevant with regard to assessing potential adverse effects of long-term exposure
WHO - Fluoride in Drinking Water [10]	2006	A detailed review and guideline primarily focusing on effects of high natural fluoride and its removal. Also reviews animal and in vitro evidence for adverse effects of fluoride exposure	Fluoride concentrations in drinking-water of about 1 mg/L are associated with a reduced incidence of dental caries, particularly in children, compared with lower water fluoride levels.	Although health effects of high natural fluoride are documented, no credible evidence was found that water fluoridation is associated with any adverse health effects aside from dental fluorosis
National Research Council (NRC) – US [46]	2006	Review of health effects associated with the US EPA's maximum contaminant level goal (MCLG) for fluoride (4 mg/L)	Not assessed	A threshold for severe dental fluorosis occurs at ~2 mg/L F in water. Other effects at the MCLG level were equivocal. Review concluded that the MCLG should be lowered
National Health and Medical Research Council (NHMRC) - Australia [91]	2007	Synthesis of evidence on efficacy and safety of different forms of fluoridation. Included York review + 5 additional studies since 1999	CWF remains the most effective and socially equitable means of achieving community-wide exposure to the caries preventive effects of fluoride.	- CWF is associated with dental fluorosis, but the majority is not of aesthetic concern. Prevalence reduced by more appropriate use of other fluoride sources - Minimal effect on fracture risk. Fluoridation at 0.6-1.1 mg/L may lower risk compared with higher and lower levels No clear association with cancer Insufficient evidence to conclude regarding other possible negative effects
Scientific Advisory, Institut National de Sante Publique du Quebec [88]	2007	Synthesis of current evidence with respect to safety and efficacy of CWF to determine whether Quebec fluoridation policy (CWF at 0.7 mg/L) needs to be reviewed or remain unchanged	CWF is the most effective and economical public health measure for preventing caries.	The scientific data currently available does not show that water fluoridation at concentrations deemed beneficial to dental health is harmful to humans.
Griffin et al. – [109]	2007	Systematic review of 9 studies of CWF effectiveness in adults 20-60+ years (n = 7,853 subjects).	Caries prevented fraction for lifetime exposure vs no exposure was 34.6% and 27.2% in 5 studies published after 1979	Not assessed

Table A2 continued				
Review	Year	Scope of review/Inclusion criteria	Conclusions	
			CWF efficacy	CWF adverse effects
Ireland adult oral health report [110]	2007	Survey designed to analyse the differences in oral health of Irish adults according to exposure to CWF.	Exposure to CWF has a statistically significant impact on number of teeth retained and caries experience in adults	Not assessed
Scientific Committee on Health and Environmental Risks (SCHER) report - EU [34]	2010	Critical review of available information on hazard profile and epidemiological evidence of adverse and/or beneficial effects of fluoride (particularly evidence since 2005 or any evidence not considered by SCCP [212] and EFSA [218] panels	CWF reduces caries prevalence and severity, especially among children from low SES groups. However, topical fluoride application (toothpaste or varnish) is the most effect in preventing tooth decay.	<ul style="list-style-type: none"> - Acknowledges risk for mild dental fluorosis in children. - Concludes that typical human fluoride exposures do not influence thyroid function, IQ, or reproductive capacity. - Fluoride cannot be classed as to carcinogenicity. CWF is not expected to lead to unacceptable risks to the environment.
US EPA Dose-Response analysis of non-cancer effects [49]	2010	Technical analysis of human dose-response data on dental and skeletal fluorosis, and skeletal fractures	Not assessed	Severe dental fluorosis may be experienced by a small % (0.5%) of populations exposed to F at 2 mg/L. No clear evidence that F at this level will cause other types of adverse health effects (skeletal fluorosis or bone fractures)
2009 Oral Health Survey - NZ [66]	2010	Detailed survey of oral health status in New Zealand. Not designed as an in-depth CWF study, but data examined for any protective effect against caries, and impact on prevalence and severity of dental fluorosis	Overall, children and adults living in fluoridated areas had significantly lower lifetime experience of dental decay (ie, lower dmft/DMFT) than those in non-fluoridated areas. CWF cost-effectively provides benefits above and beyond those from other fluoride sources alone (eg, toothpaste and tablets).	Overall prevalence of moderate fluorosis was very low (~2%; no severe fluorosis was found), and no significant difference in the prevalence of moderate fluorosis (or any of the milder forms of fluorosis) between people living in fluoridated and non-fluoridated areas.
Health Canada Drinking Water Guidelines [8]	2010	Encompasses all major reviews, + case reports and clinical studies. Based on Health Canada's review of available science, as supported by the Expert Panel Meeting on fluoride.	A fluoride concentration of 0.7 mg/L in drinking water provides optimal dental health and is protective against adverse effects	The weight of evidence does not support a link between exposure to fluoride in drinking water at 1.5 mg/L and any adverse health effects including cancer, immunotoxicity, reproductive and/or developmental toxicity, genotoxicity, and/or neurotoxicity

Table A2 continued

Review	Year	Scope of review/Inclusion criteria	Conclusions	
			CWF efficacy	CWF adverse effects
Rugg-Gunn and Do [219]	2012	Review of studies pre and post 1990	Effect of CWF on caries reduction is smaller in studies post 1990 vs earlier. Studies analysing continuous vs non-continuous residency in CWF areas clearly show the caries preventive effect increases with higher % of life exposed to fluoridated water	Not addressed
Public Health England [95]	2014	Water fluoridation Health monitoring report for England	<p>CWF areas vs non CWF areas</p> <ul style="list-style-type: none"> -45% fewer hospital admissions for caries in children aged 1-4y -15% fewer 5 year olds with caries (28% taking into account SES and ethnicity) -11% fewer 12 year olds with caries (21% adjusting for SES/ethnicity) 	<ul style="list-style-type: none"> -No significant effect of general health, hip fracture, osteosarcoma, overall cancer, Down's syndrome, or all cause mortality -Kidney stones, bladder cancer lower in CWF areas. -Dental fluorosis higher in CWF areas but still low overall (1% vs 0.2%)

Table A3. Cancer data – major reviews, recent studies, and key animal data

Major reviews	Year	Conclusions
UK Working Party on Fluoridation of Water and Cancer [152]	1985	Extensive analysis of cancer epidemiological evidence found an absence of demonstrable effects on cancer rates following long-term exposures to naturally elevated or artificially fluoridated water - permits conclusion of safety of fluoridated water.
International Agency for Research on Cancer (IARC)/WHO [220]	1987	Studies show no consistent trend of higher cancer rates in CWF areas, but evidence inadequate to draw firm conclusions. Fluorides labeled “non-classifiable as to their carcinogenicity in humans.”
Public Health Service – USA [84]	1991	Animal studies “fail to establish an association between fluoride and cancer.” Population-based studies (n >50 over 40 years) indicate “Optimal fluoridation of drinking water does not pose a detectable cancer risk to humans.” An evaluation by NCI of osteosarcomas using nationwide age-adjusted incidence data from the entire SEER database for the years 1973-1987 found a slightly increased incidence in young males in fluoridated vs. non-fluoridated areas, but “an extensive analysis reveals that it is unrelated to the introduction and duration of fluoridation.”
National Research Council (NRC), USA [36]	1993	“Laboratory data are insufficient to demonstrate a carcinogenic effect of fluoride in animals.” “The weight of the evidence from epidemiological studies completed to date does not support the hypothesis of an association between fluoride exposure and increased cancer risk in humans.”
NHS Centre for Reviews and Dissemination, University of York (UK) [89]	2000	“No clear association between water fluoridation and incidence or mortality of bone cancers, thyroid cancer, or all cancers was found.”
WHO – International Programme on Chemical Safety (IPCS) [59]	2002	“In spite of the large number of studies conducted in a number of countries, there is no consistent evidence to demonstrate any association between the consumption of controlled fluoridated drinking-water and either morbidity or mortality from cancer”
WHO - Fluoride in Drinking Water [10]	2006	Conclusion unchanged from 2002 WHO-IPCS report[59]
National Research Council (NRC) – US [46]	2006	Data from humans, genotoxicity assays, and studies of mechanisms of actions in cell systems indicate “the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed.”
National Health and Medical Research Council (NHMRC) - Australia [46]	2007	Included 4 additional studies + York review. Conclusions unchanged from York review [46] This analysis includes the case-control study of Bassin et al. [89]
California EPA, [147]	2011	The hypothetical mechanisms of fluoride carcinogenicity are considered to be plausible, but overall, the current body of epidemiologic evidence on the carcinogenicity of fluoride is considered inconclusive.
Public Health England [95]	2014	No differences were found between fluoridated and non-fluoridated areas in overall cancer rate or osteosarcoma incidence. Bladder cancer rates were lower in fluoridated areas than in non-fluoridated areas.
Recent studies	Year	Conclusions
Bassin et al. [159] (+comment [89])	2006	Preliminary data suggested that exposure to fluoride in drinking water was linked to increased risk of osteosarcoma in boys but not girls. Analysis of full study data did not support this conclusion.
Kim et al. [161]	2011	Fluoride levels in bone samples from osteosarcoma tumors were the same as in other bone cancers that did not show increased risk with CWF.
Comber et al. [89]	2011	Data from 1994–2006 on osteosarcoma incidence from the Northern Ireland Cancer Registry (NICR) and the National Cancer Registry of Ireland (NCRI) were analysed, with cases divided into ‘fluoridated/non-fluoridated groups based on residence at time of diagnosis. No significant differences were observed between fluoridated and non-fluoridated areas in either age-specific or age-standardised incidence rates of osteosarcoma.

Table A3 continued		
Recent studies	Year	Conclusions
Levy and Leclerc [163]	2012	Used cumulative osteosarcoma incidence rate data from CDC Wonder database and SEER 9 cancer registries categorised by CWF status between 1992 and 2006 – concluded that water fluoridation status in the continental U.S. has no influence on osteosarcoma incidence rates during childhood and adolescence. The study provides no evidence that young males are at greater risk of osteosarcoma from fluoride in drinking water than females of the same age group.
Blakey et al. [164]	2014	Ecological analysis using high-quality population-based data on osteosarcoma and Ewing sarcoma cases diagnosed in Great Britain between 1980 and 2005. Fluoride levels were assigned on a small-area basis, allowing improved classification of exposure. Found no evidence of association between these cancers and fluoride in drinking water (whether from CWF or naturally occurring at optimal level)
Key animal studies		
National Toxicology Program (NTP, USA [148])	1990	Statistically significant increases in osteosarcomas observed in male rats drinking water with up to 175 mg/L fluoride, but not in female rats or male or female mice similarly exposed.
National Toxicology Program (NTP, USA [149])	1992	Findings from previous NTP study not replicated in male rats of the same strain receiving a higher fluoride dose (250 mg/L), also via drinking water, for 2 years
Maurer et al. [150]	1990	No treatment-related tumor findings were observed in two-year diet studies in male and female Sprague-Dawley rats