



Fluoride and Oral Health

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The discovery during the first half of the 20th century of the link between natural fluoride, adjusted fluoride levels in drinking water and reduced dental caries prevalence proved to be a stimulus for worldwide on-going research into the role of fluoride in improving oral health. Epidemiological studies of fluoridation programmes have confirmed their safety and their effectiveness in controlling dental caries. Major advances in our knowledge of how fluoride impacts the caries process have led to the development, assessment of effectiveness and promotion of other fluoride vehicles including salt, milk, tablets, toothpaste, gels and varnishes. In 1993, the World Health Organization convened an Expert Committee to provide authoritative information on the role of fluorides in the promotion of oral health throughout the world (WHO TRS 846, 1994). This present publication is a revision of the original 1994 document, again using the expertise of researchers from the extensive fields of knowledge required to successfully implement complex interventions such as the use of fluorides to improve dental and oral health. Financial support for research into the development of these new fluoride strategies has come from many sources including government health departments as well as international and national grant agencies. In addition, the unique role which industry has played in the development, formulation, assessment of effectiveness and promotion of the various fluoride vehicles and strategies is noteworthy. This updated version of 'Fluoride and Oral Health' has adopted an evidence-based approach to its commentary on the different fluoride vehicles and strategies and also to its recommendations. In this regard, full account is taken of the many recent systematic reviews published in peer reviewed literature.

Sections:

1. Introduction	69	11. Fluoride toothpastes	85
2. Presence of fluoride in the environment	70	12. Topical fluorides (other than toothpaste)	88
3. Fluoride metabolism and excretion	72	13. Multiple fluoride exposure	90
4. Fluoride in teeth and bone	73	14. Fluorides and adult dental health	90
5. Biomarkers of fluoride exposure	75	15. Recommendations	91
6. Caries prevention and enamel fluorosis	77	Annexe 1. Worldwide totals for populations with artificially and naturally fluoridated water	92
7. Fluoride in drinking-water	78	Annexe 2. Worldwide use of fluoridated salt	94
8. Fluoridated salt	81	Annexe 3. Worldwide use of fluoridated milk	95
9. Fluoridated milk	83	Acknowledgments	95
10. Fluoride supplements (tablets and drops)	84	References	95

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1. Introduction

At the 2007 WHO World Health Assembly, a resolution was passed that universal access to fluoride for caries prevention was to be part of the basic right to human health (Petersen, 2008). There are three basic fluoride delivery methods for caries prevention; community based (fluoridated water, salt and milk), professionally administered (fluoride gels, varnishes) and self-administered (toothpastes and mouth-rinses). Whilst the effectiveness of these different methods is considered separately in this publication, it is important to note that combinations of different methods are in use in many communities throughout the world. For example, in the recent review of fluoride use in twenty Asian countries

this diversity of approach was evident (Petersen and Phantumvanit, 2012).

In revising the 1994 edition of "Fluorides and Oral Health" the increasing emphasis on an evidence-based approach is fully taken into account. In this respect the findings of published systematic reviews underpin the evidence to support the conclusions reached. In addition, account is taken of the fact that many complex public health programmes and interventions are not amenable to measurement using the classical randomised control clinical trial design; the findings of observational studies are also relevant in assessing the value of these interventions (Downer, 2007; O'Mullane *et al.*, 2012; Rugg-Gunn *et al.*, 2016; von Elm *et al.*, 2008).

Research suggests that fluoride is most effective in caries prevention when a low level of fluoride is constantly maintained in the oral cavity. Important reservoirs of this fluoride are in plaque, saliva, on the surfaces of the oral soft tissue, and in a loosely bound form on the enamel surfaces. Strategies that provide regular, low-level exposure to fluoride in the community such as fluoridated water, salt, milk and fluoride toothpaste are superior, in terms of making fluoride widely available in a cost-effective way, compared with professional applications, notably of high-concentration fluoride gels and varnishes. The method of action of these latter products is also based on the maintenance of a continuous low level of fluoride at the enamel surface through slow release of fluoride from the calcium fluoride deposits formed on the tooth surface at the time of application. They are most appropriate for selective use on individuals who are susceptible to caries.

Fluoride is effective at controlling caries because it acts in several different ways. When present in dental plaque and saliva, it delays the demineralization and promotes the remineralization of incipient enamel lesions, a healing process before cavities become established. Fluoride also interferes with glycolysis, the process by which cariogenic bacteria metabolize sugars to produce acid. In higher concentrations, it has a bactericidal action on cariogenic and other bacteria. Studies suggest that, when fluoride is ingested during the period of tooth development, it makes teeth more resistant to subsequent caries development. Fluoridated water also has a significant topical effect in addition to its systemic effect (Hardwick *et al.*, 1982). It is well known that salivary and plaque fluoride (F) concentrations are directly related to the F concentration in drinking water. This versatility of action adds to fluoride's value in caries prevention. Aiding remineralization is likely to be fluoride's most important action.

The goals of community-based public health programmes, therefore, should be to implement the most appropriate means of maintaining a constant low level of fluoride in as many mouths as often as possible. There is clear evidence that when this goal is achieved through long-term exposure of a population to fluoride, whether it be from drinking-water, salt, milk, or topically applied fluorides including fluoride toothpastes, or from combinations of topically applied fluorides with either fluoridated water, salt or milk, it results in decreased numbers of carious lesions in that population. Many scientific studies demonstrate that, when a population is first exposed to fluoride in this way, a decline in caries incidence among the younger members of the community will be evident after about two years. There is also growing evidence that these strategies also lead to a reduction in caries levels in adults.

Experience has shown that it can be difficult to achieve effective fluoride-based caries prevention without the development of some degree of enamel fluorosis, which refers to changes in the appearance of tooth enamel, caused by sub-surface porosity as a result of hypoplasia or hypomineralization. These changes are caused by long term ingestion of fluoride during the time the teeth are forming. This means that whatever methods are chosen to maintain the low level of fluoride in the mouth, the results may be accompanied by some degree of enamel fluorosis. The public health administrator seeks to maximize caries reduction while minimizing fluorosis, though in many communities the relative priority accorded to these outcomes will vary. It should also be noted that fluorosis is not the only type of disturbance found in dental enamel; enamel opacities can result from a

large number of causes unrelated to fluoride use. Diagnostic skill is required to distinguish between the various causes of defects in enamel development.

Fluoride is being used widely on a global scale although few developing countries have large-scale fluoridation programmes in operation. The use of fluoride toothpaste is almost universal in developed countries and is deemed to have played a major role in the large reduction in dental caries seen since the 1970s. However, in developing countries, even where the use of fluoride toothpaste is becoming more common, its use is not the norm.

Extensive water fluoridation programmes have been introduced in Australia, Brazil, Chile, Canada, Hong Kong, China, Malaysia, New Zealand, the Republic of Ireland, Singapore, Spain, the UK, the USA and elsewhere. (See Annexe 1 for more detailed information about the extent of water fluoridation worldwide.)

Fluoridated salt is widely used in parts of Europe, for example Switzerland, France, Germany, and the Czech Republic, and used very extensively throughout Latin America, in, for example, Belize, Bolivia, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, Jamaica, Mexico, Peru, and Uruguay among many other countries. (See Annexe 2 for more detailed information about the extent of salt fluoridation worldwide.)

Milk fluoridation programmes targeted at children are currently in operation in Chile, Thailand, the Russian Federation and the UK (Annexe 3).

2. Presence of fluoride in the environment

2.1 Introduction

The effect of the widespread presence of fluoride in its various forms in different environments has been investigated in depth over the last 20 years. Summaries of these investigations have been published (Camargo 2003; International Programme on Chemical Safety 2002; SCHER Report 2011).

2.2 Fluorides in the lithosphere

Fluorine is the most electronegative of all chemical elements and is therefore never encountered on Earth in the elemental form. Combined chemically in the form of fluorides, fluorine is seventeenth in the order of frequency of occurrence of the elements, and represents about 0.06-0.09% of the earth's crust. Fluoride may occur in a wide variety of minerals, in rock and soil, including fluorspar, cryolite, apatite, mica, hornblende, and a number of pegmatites such as topaz and tourmaline. Volcanic and sub-volcanic rocks, as well as salt deposits of marine origin, also contain significant amounts of fluoride - up to 2500 mg/kg. Certain minerals of particular commercial importance, such as cryolite used for the production of aluminium and rock phosphates used for the production of fertilizers, can have a fluoride content up to 4.2% (42,000 mg/kg). Waters with high fluoride content are usually found at the foot of high mountains and in areas with geological deposits of marine origin. Typical examples are the geographical belt from the Syrian Arab Republic through Jordan, Egypt, Libya, Algeria, Morocco, and the Rift Valley of East Africa. Another belt stretches from Turkey through Iraq, the Islamic Republic of Iran, and Afghanistan to India, northern Thailand, China and Japan. Similar areas can be found in the Americas and South Africa (Fawell *et al.*, 2006).

There is an obvious abundance of fluoride in the world, but it should be remembered that most of it is firmly bound to minerals and other chemical compounds and is therefore not biologically available. The availability of free fluoride ions in the soil is governed by the natural solubility of the fluoride compound in question, the acidity of the soil, the presence of other minerals or chemical compounds, and the amount of water present. Fluoride concentrations in soil increase with depth. In a study of 30 different soils in the United States of America, 20-500 mg of F⁻ per kg were found at depths of 0-7.5 cm and levels of 20-1620 mg of F⁻ per kg at depths of 0-30 cm. Idaho and Tennessee soils had unusually high fluoride concentrations: 3870 mg of F⁻ per kg and 8300 mg of F⁻ per kg, respectively. In high mountain areas, the fluoride content of the soil is usually low.

2.3 Fluorides in water

Owing to the universal presence of fluorides in the earth's crust, all water contains fluorides in varying concentrations. The bulk of the water normally available to humans is involved in the hydrological cycle, which means that it originates in the sea. Seawater itself contains fluoride at levels of 0.8-1.4 mg/L. The fluoride content of water obtained from lakes, rivers, or artesian wells is for the most part below 0.5 mg/l, although concentrations as high as 95 mg/l have been recorded in the United Republic of Tanzania. Water trapped in sediments since their deposition and thermal waters associated with volcanoes and epithermal mineral deposits usually have fluoride levels of 3-6 mg/L. The highest natural fluoride concentration ever found in water was recorded in Lake Nakuru in the Rift Valley in Kenya, namely 2800 mg/l. The soil at the lake shore contained up to 5600 mg/l, and the dust in the huts of the local inhabitants contained 150 mg/kg.

The general geological formation of an area is not an indicator of the concentration of fluoride in groundwater. There are significant variations in the distribution of rocks with readily leachable fluoride. It has been observed that, even within one village community, different wells often show widely divergent fluoride contents, apparently as a result of differences in the local hydrogeological conditions. Groundwater may show variations in fluoride content depending on the presence of fluoride-containing formations at different depths.

2.4 Fluorides in air

Fluorides can also be widely distributed in the atmosphere, originating from the dusts of fluoride-containing soils and from gaseous industrial waste. In addition, in some parts of China, high fluoride concentrations in indoor air have been reported as a result of the use of fluoride-rich coal for drying, curing and cooking of food (Fawell *et al.*, 2006).

2.5 Fluorides and pollution

The principal sources of pollution are industries and mining. The fluoride content in the air in some factories can reach a level as high as 1.4 mg/m³ and in the neighbourhood of such factories a level of 0.2 mg/m³ in air may be attained. Some 90% of the air samples taken in an industrial city in the Federal Republic of Germany in 1955 and 1965 contained fluoride concentrations of 0.5-3.8 µg/m³ (International Programme on Chemical Safety, 2002). The fluoride content in the air in non-industrial areas has been found to be from 0.05 to 1.90 µg/m³. In the event of inadequate

emission control, environmental pollution can be expected. This has occurred in the past in industrialized countries and, unless strong controls are adhered to, is likely to occur in developing countries pursuing a policy of industrialization without proper environmental safeguards.

Problems have occurred in the mining of phosphates and fluor spar, when fluoride-rich dust has been blown over long distances by the wind and deposited on plants, thereby entering the food-chain. The use of pesticides containing fluoride can have a similar effect, and their use should be limited to the greatest extent possible. With regard to soil and surface water, the use of fertilizers and the discharge of industrial waste into rivers and streams are important sources of undesirable fluoride.

2.6 Fluorides in foods and beverages

Extensive reviews on food borne fluoride show that the fluoride concentration in unprocessed foods is usually low (0.1-2.5 mg/kg). However, products in which skeletal tissue has been inadvertently or intentionally included during processing can have high fluoride concentrations. For example, a fluoride concentration range of 21-761 mg/kg has been reported in fish protein concentrate.

Leaves of the tea plant have a fluoride concentration ranging from 3.2 to 400 mg/kg, while its infusions contain up to 8.6 mg/L depending on the infusion time and the amount and variety of tea; an average value for commonly used brands being about 1.5 mgF/L when prepared using distilled water (Malinowska *et al.*, 2008). Other features of special interest are traditional culinary practices, as in East Africa, where fluoride-containing trona (hydrous sodium carbonate) is used as a tenderizer to shorten the cooking time of vegetables. Similar habits are found among peoples of northern Africa, while in China studies have found an association between the use of fluoride-rich coal for cooking, heating and drying of food, and high daily fluoride intakes from food. Food can acquire fluoride from fluoridated water during cooking for example rice and pasta and this source of fluoride ingestion should not be overlooked.

In countries with large water fluoridation programmes, fluoridated water may be used in food processing, raising the fluoride content of the processed food above that of products for which low fluoridated water has been used. This is particularly important when baby foods are prepared and means that details of the ingredients, including fluoride, should be printed on the packages.

2.7 Desalination and household water treatment plants

While certain industrial activities can increase the fluoride content of the food-chain, processes such as desalination can result in a reduction of fluoride in the diet (WHO, 2005). In the Gulf States, for example, many communities used to obtain their water from boreholes, sometimes with a high fluoride content. Now desalinated seawater is used, from which almost all the fluoride is removed during treatment. Concern has been expressed over some water-purification devices for household use which are based on reverse osmosis, because under certain operating conditions, they can remove fluoride from the water. Such devices are generally designed for the removal of microbiological and solid matter rather than for chemical purification.

2.8 The ecological impact of fluoridated water

A number of publications have considered the ecological impact of fluoridated water (Camargo, 2003). Recently the EU Scientific Committee on Health and Environmental Risks (SCHER) included a summary of these publications in its final report of its review of any new evidence on the hazard profile, health effects and human exposure to fluoride and fluoridating agents of drinking water (SCHER, 2011). The Committee assessed whether the fluoridation of drinking water specifically leads to adverse ecological impacts. The presence of fluorosilicates in drinking water due to the use of hexafluorosilicic acid or hexafluorosilicate for fluoridation, is very low as fluorosilicates and other species are rapidly hydrolyzed in water to fluoride and silica (sand). The SCHER review focussed on the environmental exposures arising from the use of fluoridated water as drinking water, for personal hygiene, washing clothes and washing dishes as reported in the publication by (Osterman, 1990). Most of this flows to the environment in drainage water and via sewage treatment works. Based on the physico-chemical characteristics of fluoride, the contamination of soil and the atmosphere from fluoridated water was deemed to be very limited and the SCHER assessment was confined to aquatic effects on fish, invertebrates and algae in fresh and sea waters. Based on three types of evidence: a simplistic risk assessment, mass balance modelling, and a modified EUSES analysis (EC 2004), the Committee concluded that adding fluoride to drinking water at concentrations between 0.8 mg F/L and the WHO reference dose of 1.5 mg F/L, does not result in unacceptable risk to water organisms.

2.9 Bottled water

Sales of bottled water have increased dramatically in recent years in many countries. The fluoride content of these bottled waters, which come from many different sources, is highly variable, which means that consumption of fluoride from bottled water is difficult to measure in the community. Manufacturers of bottled water should be encouraged to list the mineral content of their products, fluoride included, on the label to assist consumers. Where fluoride content is high, some jurisdictions take further regulatory steps to restrict children's exposure to undesirably high quantities of fluoride. In regions where the fluoride concentration in bottled waters used by the community is low and there is a water fluoridation policy, the addition of fluoride to local mineral waters may be considered in order to confer the caries preventive benefit to their consumers. For example, in Mongolia children are given bottled water in school containing 0.5 mg/L F.

2.10 Summary

1. Most fluoride is found in the form of chemical compounds, and the availability of free fluoride ions in soils and water is not uniform.
2. Although all groundwaters contain fluoride in varying concentrations, there can be major differences within a relatively small area and at different depths of boreholes. Seasonal variations have also been reported.
3. There can be significant environmental pollution with fluoride that comes from unprotected mines, industrial emission, coal burning, fertilizers and pesticides.

4. The fluoride content of foods and beverages is significantly affected by the fluoride concentration in the water used during processing.
5. Adding fluoride to drinking water at recommended concentrations for the control of dental caries does not pose a risk for water organisms.

3. Fluoride metabolism and excretion

3.1 Introduction

The health effects of ingested fluoride have been considered by a number of bodies, the most recent of which include the Royal Society of New Zealand and the Office of the Prime Minister's Chief Science Advisor (2014); European Food Safety Authority 2013; European Commission Scientific Committee on Health and Environmental Risks report (SCHER, 2011); National Academy of Sciences Report (2006). A recent monograph edited by Buzalaf (2011), also covered this topic.

3.2 Fluoride absorption

Approximately 90% of the fluoride ingested each day is absorbed from the alimentary tract, with higher proportions from liquids than from solids. The half-time for absorption is approximately 30 minutes, hence peak plasma concentrations usually occur within 30-60 minutes. Absorption across the oral mucosa is limited and probably accounts for less than 1% of the daily intake. Absorption from the stomach occurs readily and is inversely related to the pH of the gastric contents, and most of the remaining fluoride that enters the intestine will be absorbed rapidly. High concentrations of dietary calcium and other cations that form insoluble complexes with fluoride can reduce fluoride absorption from the gastrointestinal tract (Buzalaf and Whitford, 2011).

3.3 Fluoride in plasma

There are two general forms of fluoride in human plasma. The ionic form, detectable by the ion-specific electrode, is the one of interest in dentistry, medicine, and public health. Ionic fluoride is not bound to proteins, to other components of plasma, or to soft tissues. The other form consists of several fat-soluble organic fluoro-compounds, which can be contaminants derived from food processing and packaging. The concentration of ionic fluoride in soft and hard tissues is directly related to the amount and duration of ionic fluoride intake, but that of the organic fluoro-compounds is not.

Where water is the main source of fluoride intake, fasting plasma concentrations of healthy young or middle-aged adults when expressed as micromoles per litre ($\mu\text{mol/L}$) - are roughly equal numerically to the fluoride concentrations in drinking water when expressed as milligrams per litre (mg/L). Plasma fluoride concentrations tend to increase slowly over the years provided that intake remains relatively constant, reflecting the increase of the concentration of fluoride in bone with age. Fluoride balance i.e. the numerical difference between total daily intake and total daily excretion, can be positive or negative especially in infants and young children. Plasma and all tissue concentrations tend to increase when the balance is positive and decrease when it is negative.

3.4 Tissue distribution

A steady-state exists between the fluoride concentrations in plasma or extracellular fluid and those in the intracellular fluid of most soft tissues. Intracellular fluoride concentrations are lower, but they change proportionately and simultaneously with those of plasma. With the exception of calcified tissues and the kidneys, which concentrate fluoride in the renal tubular fluid, tissue-to-plasma fluoride concentration ratios are less than 1.0.

The fluoride concentrations of several of the specialized body fluids, including gingival crevicular fluid, ductal saliva and urine, are also related to those of plasma in a steady-state manner. The mechanism underlying the transmembrane migration of fluoride, like that for absorption from the stomach, appears to be the diffusion equilibrium of hydrogen fluoride, so that factors that change the magnitude of transmembrane or transepithelial pH gradients will affect the tissue distribution of fluoride accordingly.

Approximately 99% of the body burden of fluoride is associated with calcified tissues. Of the fluoride ingested, approximately 55% will be retained by children and approximately 36% by adults and the remainder of the absorbed fluoride will be excreted in urine. Thus, children retain a higher proportion of ingested fluoride compared with adults (Villa *et al.*, 2010). Increased retention in children is due to the large surface area provided by numerous and loosely organized developing bone crystallites, which increase the clearance rate of fluoride from plasma by the skeleton. Accordingly, the peak plasma-fluoride concentrations and the areas under the time-plasma concentration curves, especially during the period of skeletal development and growth, are directly related to both the age of the individual and fluoride intake.

Fluoride is strongly but not irreversibly bound to apatite and other calcium phosphate compounds that may be present in calcified tissues. In the short term, fluoride may be mobilized from the hydration shells and the surfaces of bone crystallites (and presumably dentine and developing enamel crystallites) by isoionic or heteroionic exchange. In the long term, the ion is mobilized by the normal process of bone remodelling. It has been reported that human serum fluoride concentrations were increased following administration of parathormone hormone and decreased by administration of thyrocalcitonin (Waterhouse *et al.*, 1980). There is some evidence for a circadian rhythm in plasma fluoride concentrations that appears to involve the renal and hormonal systems.

3.5 Fluoride excretion

About 10% of the daily intake of fluoride is not absorbed and is excreted in the faeces, except in subjects with high calcium diets when up to 25% can be excreted by this route. The elimination of absorbed fluoride occurs almost exclusively via the kidneys. Data from the 1940s seemed to show that the amount of fluoride excreted in sweat could nearly equal urinary fluoride excretion under hot moist conditions. However more recent data obtained with modern analytical methods indicate that sweat fluoride concentrations are very low and similar to those of plasma (about 1-3 $\mu\text{mol/L}$ or 0.019-0.057 mg/L). Therefore, sweat is probably a quantitatively minor route for fluoride excretion even under extreme environmental conditions.

The clearance rate of fluoride from plasma is essentially equal to the sum of the clearances by calcified tissues and kidneys. In patients with compromised renal function in which the glomerular filtration rate falls chronically to 30% of normal, fluoride excretion might decline sufficiently to result in increased soft and hard-tissue fluoride concentrations. Such increases, however, are not known to result in adverse health effects. Fluoride is freely filtered through the glomerular capillaries and undergoes tubular reabsorption in varying degrees. The renal clearance of fluoride is directly related to urinary pH and, under some conditions, to urinary flow rate. As in the cases of gastric absorption and transmembrane migration, the mechanism for the tubular reabsorption of fluoride appears to be the diffusion of hydrogen fluoride. Thus, factors that affect urinary pH, such as diet, drugs, metabolic or respiratory disorders, and altitude of residence, have been shown to affect, or can be expected to affect, the extent to which absorbed fluoride is retained in the body.

3.6 Summary

1. Absorption of fluoride from the stomach occurs readily and is inversely related to the pH of the gastric contents. Most of the fluoride not absorbed from the stomach will be absorbed from the intestine.
2. About 10% of the daily fluoride intake is not absorbed from the gastro-intestinal tract and elimination of absorbed fluoride occurs almost exclusively via the kidneys.
3. Fasting plasma fluoride concentrations in healthy young or middle-aged adults expressed as $\mu\text{mol/L}$ are roughly equal, numerically, to the fluoride concentration in drinking-water expressed as mg/L . For example, if the water fluoride concentration is 1.0 mg/L then the plasma concentration would be approximately 1.0 $\mu\text{mol/L}$ (or 0.019 mg/L).
4. Approximately 99% of fluoride in the body is associated with calcified tissues.
5. The proportion of ingested fluoride retained in the body (i.e. the balance) is approximately 55% in children and 36% in adults.

4. Fluoride in teeth and bone

4.1 Introduction

The well-known phenomenon of a strong affinity between fluoride and biological apatite is based on the ease of chemical substitution of the hydroxyl component of calcium hydroxyapatite by fluoride. Pure fluorapatite contains approximately 3.7% (37,000 mg/kg) fluoride by weight; up to about one-third of the total hydroxyl ions in enamel can be replaced by fluoride ions. Normal human apatite tissue, i.e. bone and tooth tissue, never approximates to pure fluorapatite, although fluoride substitution varies considerably, being dependent on the tissue-fluoride environment at the time of calcification. Once formed, the apatite /fluorhydroxyapatite remains chemically stable until the tissue is resorbed, remodelled, or otherwise metabolized although the incorporation of a small amount of fluoride is possible by diffusion and adsorption to the crystal structure (Buzalaf *et al.*, 2011).

4.2 Fluoride in teeth

The fluoride concentration in teeth reflects the overall availability of fluoride during tooth formation and will vary depending on the time of exposure to and intake of fluoride. The highest fluoride concentrations in enamel are found at the surface and can be around 2000mg/kg in persons residing in non-fluoridated regions (representing a 6% replacement of OH⁻ by F⁻ in hydroxyapatite) and 3000mg/kg (8% replacement of OH⁻ by F⁻) in fluoridated areas. These concentrations fall sharply after the outermost 10-20 µm of enamel to levels ranging from hundreds of mg/kg to around 50 mg/kg, depending on whether the area is fluoridated or not (Pessan and Buzalaf, 2011). Beyond this depth the fluoride content remains fairly constant up to the enamel-dentine junction, in contrast with bone and dentine where accumulation of fluoride continues throughout life. Once human enamel is fully formed its fluoride concentration can only be permanently altered at subsurface regions, as a result of trauma caused, for example, by caries, erosion, or abrasion. In the outermost surface layers, however, fluoride concentrations are independent of de- and remineralisation processes and can increase due to diffusion of fluoride from the oral environment which can vary according to exposure to ingested fluoride sources, therapeutic agents, saliva and dental plaque. In contrast to enamel, dentine continues to accumulate fluoride throughout life. The fluoride content of dentine is derived entirely by the systemic route.

Within the dentine, the fluoride concentration is generally higher than that of the majority of enamel and tends to increase gradually from the enamel-dentine junction to the dentine pulpal surface. This may provide some benefit in combination with additional sources of fluoride, since a higher fluoride concentration is required in dentine to inhibit demineralisation and enhance remineralisation, compared with enamel.

4.3 Fluoride in bone

The normal turnover of bone during remodelling leads to a change in fluoride content that reflects plasma fluoride at the time; this, in turn, reflects the fluoride bioavailability from absorbed food, drink, and inhalation.

Variables influencing the fluoride content of bone include fluoride intake, age, and bone type (cancellous or cortical). The rate of increase in bone fluoride levels is greatest in young people during periods of bone growth and least in older people. Bone fluoride levels reflect a lifetime cumulative history of exposure to the element.

Confusion arises over two claims: one, that fluoride stimulates new bone growth and hence is useful therapeutically in controlling osteoporosis, and the other, that it is the cause of increasing prevalence of hip fractures in the elderly. In many countries, both osteoporosis and hip fractures have an enormous medical and social cost, and prevention, rather than treatment, is the key to reducing the impact of this problem. These issues are discussed in more detail in the following sections.

4.4 Fluoride, osteoporosis and prevention of associated fractures

The potential of fluoride to increase bone mineralization

as fluorapatite has been the basis for treatment, or the potential prevention of osteoporotic conditions. Despite long-term, empirically based adult therapy using high sodium fluoride doses (40 mg or more daily) results in reversing or preventing the progression of osteoporosis have failed to elicit general medical recognition that it constitutes a valid and useful treatment regimen. Four randomized clinical trials provide important information on the safety and efficacy of sodium fluoride treatment of postmenopausal osteoporosis following vertebral fracture (Gordon and Corbin, 1992). While many studies have shown that a daily regimen of high levels of sodium fluoride will increase bone mass, this has not led to a significant reduction in the occurrence of vertebral bone fractures. On the basis of the data from these trials, the United States Food and Drug Administration in October 1989, did not accept sodium fluoride as a therapy for osteoporosis and concluded that its use for the treatment of osteoporotic bone fractures is ineffective. There are therefore differences between health authorities in Europe and the United States of America regarding the use of fluoride for the treatment of osteoporosis. More recently, the use of sustained release intermittent sodium fluoride and monofluorophosphate has shown some promise. However at this time, due to lack of long term definitive data, fluoride is not recommended as a first or second line therapy for the treatment of osteoporosis or the prevention of associated fractures (McLaughlin *et al.*, 2006).

Some studies of long-term exposure to fluoride in drinking-water at optimal levels for caries prevention have implicated fluoride as a causative factor in the incidence of hip fractures in the elderly, while other similar studies have implicated fluoride exposure at optimal levels as providing a preventive effect. Independent reviews of these contemporary studies conclude that they fail to establish an adequate basis for concluding that fluoride levels in drinking-water for caries prevention are related to hip fractures and bone health (Hillier *et al.*, 2000; McDonagh *et al.*, 2000; Phipps *et al.*, 2000). The closeness of the confidence limits around the null effect is impressive; RR at 1.00 with 95% CI of 0.94-1.06.

A study in Sweden (Näsman *et al.*, 2013) used nationwide registers to investigate the association between hip fracture and long term exposure to fluoridated water at different levels from low <0.3mg/L to high ≥1.5mg/L for 473,277 adults born in Sweden between 1900 and 1919. The analysis of 60,773 hip fractures among the cohort revealed no association with chronic fluoride exposure.

A recent review of the health effects of fluoride on health (Royal Society of New Zealand and the Office of the Prime Minister's Chief Science Advisor, 2014) concluded that "on the available evidence there is no appreciable risk of bone fractures arising from Community Water Fluoridation".

4.5 Fluoride and skeletal fluorosis

Endemic skeletal fluorosis is known to occur in several parts of the world. Crippling forms of the disease associated with the highest levels of fluoride exposure are a significant cause of morbidity. Many millions of people, mainly in India and China, are at risk of crippling skeletal fluorosis (Fawell *et al.*, 2006).

Skeletal fluorosis is associated predominantly with the consumption of drinking water containing elevated levels of fluoride. Other important associated factors include climate, nutritional status and diet, and exposure to other substances that modify the absorption of fluoride. In parts of China, the indoor burning of fluoride-rich coal and consumption of high levels of brick tea are also implicated. Occupational exposure to elevated concentrations of fluoride in the air may also be a cause.

Public health authorities should monitor the fluoride level in local water supplies, and examine the population for signs of excessive fluoride exposure (e.g. moderate and/or severe enamel fluorosis and crippling skeletal fluorosis). Where unsafe levels of fluoride are found in drinking water supplies, and a safe low fluoride supply cannot be provided as an alternative or a source for blending, treatment to remove fluoride from drinking water supplies (see Section 8.6) should use chemicals of a grade suitable for use in drinking-water supply as outlined in the WHO Guidelines for Drinking-water Quality (Fawell *et al.*, 2006).

4.6 Fluoride and osteosarcoma

Claims of osteosarcoma induced by fluoride are based on equivocal evidence from studies of rats which received extremely high amounts of fluoride. A study conducted in the late 1980s concluded that the incidence of osteosarcoma was increased in male rats when fed very high doses of sodium fluoride (100 mg/L and 175 mg/L) for 2 years (National Toxicology Program, 1990). Many descriptive and case control studies in which exposure to fluoride from drinking water was determined by self-reported or ecological level data have failed to demonstrate an association. One exploratory analysis reported an increased risk among a subset of males recruited from existing cases of osteosarcoma in 11 hospitals in the US between 1989 and 1992 and exposed to fluoridated water during childhood (Bassin *et al.*, 2006). The study estimated fluoride exposure in water from questionnaires and residential histories and type of drinking water used. Caution is urged when interpreting the results of this study because of lack of consistency of findings in a later cohort (1993–2000) studied in similar settings (Douglass and Joshipura, 2006). The later cohort was the subject of a more recent publication which reported on a cohort of 137 cases of osteosarcoma and 51 tumour controls which were identified in 9 hospitals across the US between 1993 and 2000 (Kim *et al.*, 2011). Fluoride exposure was measured directly in samples of bone taken adjacent to the tumour or from the iliac crest hence misclassification of fluoride exposure was likely to be minimal. No significant association between bone fluoride levels and risk of osteosarcoma was found. The main strength of this study is the use of direct bone fluoride concentration as the measure of fluoride exposure rather than the use of estimated fluoride intake.

An Irish study found no significant differences between fluoridated and non-fluoridated areas in either age-specific or age-standardised incidence rates of osteosarcoma (Comber *et al.*, 2011). A research team from the Universities of Newcastle upon Tyne, Leeds and Oxford (Blakey *et al.*, 2014), who analysed osteosarcoma (n=2,566) and Ewing sarcoma (n=1,650) cases in people aged up to 50 that occurred across the whole of the UK between 1980 and 2005, found no statistically significant difference in the rates of

incidence between fluoridated and non-fluoridated areas.

On the basis of recent published reviews and peer reviewed publications there is no evidence that fluoride levels in drinking water at concentrations aimed at controlling dental caries is associated with increased risk of osteosarcoma or any other kind of bone cancer in humans.

4.7 Summary

1. The bulk of fluoride in enamel reflects its availability in the pre-eruptive, tooth-formative period. Post-eruptive exposure is reflected mainly in the outer layer of enamel.
2. Public health authorities should monitor the fluoride level in local water supplies, and examine the population for signs of excessive fluoride exposure.
3. Bone fluoride content increases with age. The rate of increase is more rapid in young people during periods of growth, but, as fluoride balance is achieved, the uptake slows and eventually approaches or reaches a steady state, when fluoride intake is constant.
4. With respect to hip fracture and bone health, there is no scientific evidence for altering current public health policy on the use of fluorides for caries prevention.
5. Studies of osteosarcoma in humans have failed to identify any correlation with fluoride exposure.

5. Biomarkers of fluoride exposure

5.1 Introduction

A fluoride biomarker is of value primarily for identifying and monitoring deficient or excessive intakes of biologically available fluoride. Details of biological markers of fluoride exposure have been published recently (Rugg-Gunn *et al.*, 2011; Pessan and Buzalaf, 2011). Knowledge of fluoride exposure, as indicated by an appropriate biomarker during pre-eruptive periods of tooth formation, allows assessment of the potential for later development of fluorosis, while knowledge of exposure post-eruptively provides a guide to the potential level of protection from caries. Fluoride biomarkers may also serve to assess the impact of water fluoridation on bone quality and other physiological conditions.

5.2 Biomarkers of contemporary and recent fluoride ingestion, patterns of fluoride ingestion: plasma, bone, saliva, urine, nails and hair

Contemporary biological markers assess present, or very recent, exposure to fluoride: fluoride concentrations in blood, bone surface, saliva, milk, sweat and urine have been considered (Rugg-Gunn *et al.*, 2011). A number of studies relating fluoride concentration in plasma to fluoride dose have been published, but at present there are insufficient data on plasma fluoride concentrations across various age groups to determine the 'usual' concentrations. Although bone contains 99% of the body burden of fluoride, attention has focused on the bone surface as a potential marker of contemporary fluoride exposure. From rather limited data, the ratio of surface-to-interior concentrations of fluoride may be preferred to whole bone fluoride concentration. Fluoride concentrations in the parotid and submandibular/sublingual ductal saliva follow the plasma fluoride concentration,

although at a lower concentration. At present, there are insufficient data to establish a normal range of fluoride concentrations in ductal saliva as a basis for recommending saliva as a marker of fluoride exposure. Sweat and human milk are unsuitable as markers of fluoride exposure. A substantial portion of ingested fluoride is excreted in urine (see Section 3). Plots of daily urinary fluoride excretion against total daily fluoride intake suggest that daily urinary fluoride excretion is suitable for estimating fluoride intake for groups of people, but not for individuals. While fluoride concentrations in plasma, saliva and urine have some ability to assess fluoride exposure, present data are insufficient to recommend using fluoride concentrations in these body fluids as biomarkers of contemporary fluoride exposure for individuals. Daily fluoride excretion in urine can be considered a useful biomarker of contemporary fluoride exposure for groups of people, and standards for urinary fluoride excretion indicating low, optimal and high fluoride exposure are available (Rugg-Gunn *et al.*, 2011; WHO, 2014).

Studies examining contemporaneous relationships between total daily fluoride intake, daily urinary fluoride excretion and the fraction of the fluoride ingested which is retained have been undertaken over the last 40 years. These were recently collated (Villa *et al.*, 2010). Studies involving 212 children aged less than seven years and 283 adults aged 18-75 years were included. The data for children and adults were studied separately, assuming that 90% of the fluoride ingested was absorbed. The main conclusion drawn from these data is that when the daily fluoride intake is above 0.5mgF/day for children and 2mgF/day for adults the constant proportion of fluoride retained is of the order of 55% in children and 36% in adults. The participants in the studies included in this report all consumed Westernised diets. Dietary practices are one of a number of factors known to influence urinary fluoride excretion. For example more vegetarian diets, cause urine to be more alkaline which in turn leads to increased urinary fluoride excretion (Buzalaf and Whitford, 2011; Zohouri and Rugg-Gunn, 2000). There is a need for more research into fluoride intake and excretion in people consuming non-Westernised, vegetarian diets.

Measuring daily fluoride ingestion directly in population groups by collection and analysis of solids and liquids consumed or completion of dietary diaries requires considerable subject compliance and can be expensive. A reasonable estimate of daily fluoride ingestion can be obtained based on its relatively constant relationship with daily urinary fluoride excretion (Rugg-Gunn *et al.*, 2011). Studies of urinary fluoride levels are ideal for assessing the intake of fluoride in populations. More particularly, such studies also provide a basis for decisions on the use of fluoride for caries prevention. The procedures to follow when monitoring urinary fluoride excretion in communities have been published by the World Health Organization (WHO, 2014).

The concentrations of fluoride in nails and hair appear to be proportional to intake over longer periods of time. To this extent their concentrations reflect average plasma fluoride concentrations over time. Nails grow at about 0.1 mm/day so the average plasma concentration and fluoride intake over a 1-3-week period 3 to 4 months earlier can be estimated from the analysis of single nail clipping. Fluoride

in hair could be used to estimate intake over longer periods. Although potentially promising tools for estimating fluoride exposure, refinements of the sampling methods for these human tissues and improved testing technology are needed. Additional research should clarify the physiological factors that can influence fluoride uptake and accumulation in these tissues (Pessan and Buzalaf, 2011).

5.3 Historical biological markers for exposure to fluoride: bone and teeth

As described in section 3.4, the body burden of fluoride is best reflected in the calcified tissues, although enamel is not the tissue of choice because most of its fluoride is incorporated during tooth formation. After tooth eruption, exposure to widely fluctuating concentrations of fluoride in the oral cavity significantly affects fluoride levels in the surface layers of enamel, where the highest concentrations of fluoride are found. Bone fluoride concentrations are more reliable indicators of long-term fluoride exposure and body burden, although fluoride is not uniformly distributed throughout bone. For example, cancellous bone usually has higher fluoride concentrations than cortical bone.

The fluoride concentrations of dentine are similar to those of bone and, as in bone, they tend to increase over the years provided that fluoride intake does not decline. Dentine, especially coronal dentine, may be the best marker for estimating chronic fluoride intake and the most suitable indicator for fluoride body burden. This tissue does not normally undergo resorption, and it seems to continue accumulating fluoride slowly throughout life, since it is permeated by extracellular fluid. Dentine is usually protected from exposure to fluoride in the oral cavity by the covering enamel or cementum and in practical analytical terms it is also more easily obtained than bone. No gold standard for total fluoride exposure is available that can be used to validate dentine fluoride as a biomarker of cumulative fluoride exposures, particularly one that is easily obtainable for a large population over a number of years.

5.4 Fluorosis as a biomarker

Epidemiological studies by Dean and colleagues in the 1930s demonstrated clearly the relationship between the prevalence and severity of enamel fluorosis in human teeth and the level of fluoride in water supplies (Dean, 1936). These and other studies have shown that in a population there is a direct relationship between the degree of fluorosis and the plasma and bone fluoride levels on the one hand, and the concentration of fluoride in drinking-water on the other hand. These studies suggest that fluorosis can be used as a biomarker for the level of fluoride exposure in populations during the time of enamel formation. An increased level of fluorosis in both fluoridated and non-fluoridated communities has been used to indicate increased historical exposure to fluoride in these communities, despite constant fluoride levels in the drinking-water. This increased exposure to fluoride was found in part to result from unintentional ingestion of fluoride toothpaste, underlining the value of using fluorosis as a biomarker, but only for exposure during tooth formation. In the case of fluorosis of permanent incisors, prevalence and severity of dental fluorosis are a reflection of fluoride intake during the first three years of life (Levy *et al.*, 2010).

5.5 Summary

1. Daily urinary fluoride excretion is suitable for estimating fluoride intake for groups of people but not for individuals. Values have been published for low, optimal and high exposure. In this regard it is important to emphasise that concentration (mg/L) and excretion (mg/time period) are not the same. WHO has published a manual providing guidelines on the technical procedures related to fluoride excretion analysis.
2. Clinical enamel fluorosis is the most convenient biomarker, but it only records the effects of ingestion of fluorides in the first 6 years of life, limiting its use to an estimation of historical exposure to fluoride when dental enamel is forming.
3. Enamel fluorosis can be used as a biomarker for the level of fluoride exposure in populations during the time of enamel formation whereas fluoride concentrations in dentine and whole bone provide information of exposure over decades or a lifetime.
4. Concentrations of fluoride in hair and nails as potential biomarkers for exposure during recent weeks or months, merit further study.
5. Further studies of fluoride excretion related to non-Westernised diets, variable urinary flow rates and pH are warranted.

6. Caries prevention and enamel fluorosis

6.1 Introduction

Studies conducted in the United States of America during the late 1930s and early 1940s in communities with varying levels of naturally occurring fluoride in the drinking-water found that, at 1 mg of fluoride per litre, the reduction in the prevalence of dental caries was approximately 50% compared with communities with less than 0.1 mg of fluoride in their drinking water. This reduction was associated with very mild/mild forms of enamel fluorosis in a small percentage of the population - about 10% (Dean 1942). At the time this low prevalence of fluorosis was deemed not to represent a public health problem; if it was even noticed, it was considered acceptable and far preferable to the severe dental caries it largely replaced. It is worth noting that the balance between the benefit of caries prevention and risk of very/mild fluorosis is also relevant when considering use of other fluoride strategies. For example since there is evidence that young children can swallow a sizeable proportion of toothpaste placed on the brush, the decision on fluoride concentrations, frequency of use, amount of fluoride toothpaste to be used and age of commencement should take account of the risk of developing dental caries and the risk of mild enamel fluorosis (Forum on Fluoridation, 2002; Do and Spencer, 2007; Wong *et al.*, 2011).

In the past 30 years our understanding of the method of action of fluoride in the prevention of dental caries has changed (Groenveld *et al.*, 1990). Recent evidence from extensive Australian studies indicate that in the case of caries in first permanent molars both the pre-eruptive and post-eruptive effects are needed to obtain maximum caries prevention (Singh and Spencer, 2004; Singh *et al.*, 2007).

6.2 Controlling enamel fluorosis

Achieving the best possible caries prevention usually requires the use of population-based programmes such as adding fluoride to drinking-water, salt or milk and the widespread use of fluoride toothpastes. The question therefore arises whether the maximum caries preventive effect can be achieved without the appearance of some degree of very mild fluorosis in the target population. In communities served with optimally fluoridated water supplies, a small proportion of the population will continue to be affected by very mild/mild fluorosis, evident as diffuse white lines and patches, which is not aesthetically damaging and which usually cannot be seen by the untrained eye (Chankanka *et al.*, 2010).

A study of children aged 11 to 13 years in two UK cities which used improved methodology to assess levels of dental fluorosis, found that the percentage of children with a fluorosis score of TF3 was 6% in fluoridated Newcastle and 1% in non-fluoridated Manchester. However, the prevalence of higher scores (TF4 or greater) was very low in both cities - 1% in fluoridated Newcastle and 0.2% in non-fluoridated Manchester. Of these, very few children were seen with a score of TF5, - 0.1% in fluoridated Newcastle and 0.2% in non-fluoridated Manchester - and no children were found with higher TF scores (McGrady *et al.*, 2012).

In communities where additional sources of fluorides are available, such as fluoride toothpaste or fluoride supplements which can be swallowed by young children, the prevalence of unaesthetic forms of fluorosis will increase. For example, in many parts of the United States of America much of the noticeable rise in the prevalence of fluorosis can be accounted for by physicians prescribing fluoride supplements for children resident in fluoridated communities or by young children swallowing fluoride toothpaste. However other countries with extensive use of fluoride toothpastes but without a tradition of prescribing fluoride tablets, have not experienced a rise in aesthetically unacceptable enamel fluorosis.

Several approaches to reducing the risk of fluorosis from ingestion of toothpaste have been taken: guidelines in some countries recommend the use of a "smear" of fluoride toothpaste (0.1mg) for all children under the age of 3 years and a pea-size amount (0.25 mg) over the age of 3 years (SIGN 2014; Public Health England, 2014; ADA Council on Scientific Affairs, 2014); other countries adopt a risk-based approach to the use of fluoride toothpaste for young children, and recommend deferring the use of fluoride toothpaste until a child is aged between 18 and 36 months (depending on the country) unless the child has been assessed as being at increased risk of developing caries (Forum on Fluoridation, 2002; Health Canada, 2010; Australian Research Centre for Population Oral Health, 2012). In addition, some guidelines recommend the use of low fluoride toothpaste for young children (EAPD, 2009; Australian Research Centre for Population Oral Health, 2012).

The association between the use of infant formula feed reconstituted with optimally fluoridated water and enamel fluorosis has been the subject of debate in recent years. In the systematic review of the relationship between use of infant formula and enamel fluorosis, Hujoel *et al.*, (2009) concluded that the "evidence that the fluoride in the infant formula caused enamel fluorosis was weak, as other mechanisms could explain the observed association." An evidence based clinical review was published recently (Berg *et al.*, 2011). It was concluded

“...that when dentists advise parents and caregivers of infants who consume powdered or liquid concentrate infant formula as the main source of nutrition, they can suggest the continued use of powdered or liquid concentrate infant formulas reconstituted with optimally fluoridated drinking water while being cognizant of the potential risks of enamel fluorosis development.” Enamel fluorosis on the aesthetically important anterior teeth is caused by excessive fluoride ingestion in the first five years with the most critical period being the first three years. Thus all sources of fluoride ingestion should be considered and in areas where infant formula is reconstituted with fluoridated water parents or guardians should be advised to take particular care to avoid the ingestion of fluoride toothpaste by their children for these first critical years to limit the total fluoride ingestion (see section 11.4).

Enamel fluorosis is being monitored regularly in many communities. Over the past 20 years different indices and technologies have been developed for recording the first, barely perceptible diffuse white lines in enamel that are associated with fluoride ingestion, and it is now feasible to measure these changes reliably in epidemiological studies. The World Health Organization Oral Health Surveys Basic Methods includes photographs which depicts examples of the various degrees of enamel fluorosis to aid examiners on scoring such condition during epidemiological surveys (Petersen and Baez, 2013).

6.3 Summary

1. Enamel fluorosis should be monitored regularly, using indices sensitive enough to detect early changes in enamel following minor changes in fluoride intake. It is worth noting that urinary fluoride assessments are capable of detecting changes in contemporaneous fluoride intake some 6 years earlier than examination for enamel fluorosis in permanent teeth.
2. When mild or more severe fluorosis is found to a significant extent in a community, steps should be taken to reduce fluoride ingestion by children with developing teeth.

7. Fluoride in drinking-water

7.1 Introduction

The first studies linking the natural fluoride content of drinking-water with reduced caries prevalence appeared in the 1930s. The practice of adjusting the natural concentration of fluoride in drinking water to improve dental health began in 1945 in the city of Grand Rapids in the USA. Since then hundreds of millions of people worldwide have regularly consumed artificially fluoridated water: currently around 380 million, plus approximately 50 million whose drinking water supplies naturally contain optimal fluoride concentrations (Annexe 1). Studies from many different countries over the past 60 years are remarkably consistent in demonstrating substantial reductions in caries prevalence as a result of water fluoridation. One hundred and thirteen studies into the effectiveness of artificial water fluoridation in 23 countries conducted before 1990, recorded a modal percent caries reduction of 40 to 50% in primary teeth and 50 to 60% in permanent teeth (Murray *et al.*, 1991).

More recently, systematic reviews summarizing these extensive databases have confirmed that water fluoridation substantially reduces the prevalence and incidence of dental

caries in primary and permanent teeth (McDonagh *et al.*, 2000; Truman *et al.*, 2002; Australian Government, NHMRC, 2007; Iheozor-Ejiobar *et al.*, 2015). Although percent caries reductions recorded have been slightly lower in 59 post-1990 studies compared with the pre-1990 studies, the reductions are still substantial. A review of studies conducted in ten countries between 1990 and 2000 on individuals ranging from 3 to 44 years of age reported average caries reductions of between 30% and 59% in primary teeth and between 40% and 49% in permanent teeth (Rugg-Gunn and Do, 2012).

The method of action of fluoride in the prevention of dental caries is predominantly post-eruptive and topical. Fluoride that is present in the oral fluids during an acidic challenge inhibits demineralisation of surface enamel as well as speeding up the process of remineralisation when the pH balance is re-established (Buzalaf *et al.*, 2011). However, the pre-eruptive effect of ingested fluoride is also confirmed as being important; findings from Australia and the Netherlands for example support the pre-eruptive effect of fluoride in reducing caries levels in pit and fissure surfaces of permanent teeth (Groeneveld *et al.*, 1990; Singh *et al.*, 2007).

7.2 Impact on a population, limitations, and implementation

Provided that a community has a piped water supply, water fluoridation is the most effective method of reaching the whole population, so that all social classes benefit without the need for active participation on the part of individuals. Water fluoridation has been endorsed by the world's leading science and health organizations, including WHO, the International Association for Dental Research (IADR) and FDI World Dental Federation.

The crucial requirement for community water fluoridation is a well-established, centralized, piped, water supply. Unfortunately in most developing countries, where caries tends to be increasing, centralized water distribution is often lacking, even in densely populated urban areas, and is rarely found in rural regions.

Water fluoridation proposals sometimes attract opposition from a minority of local residents. It is important therefore that the general public is properly informed of the benefits and safety of the proposals, and that they are confident that the proposal has the support of their leading health authorities and of the government. The promotion of and safe implementation of water fluoridation should be considered a multi-professional activities in which dentists, engineers, chemists, nutritionists, physicians and other health sector-related professionals participate.

7.3 Economics, health, and safety

An effective community fluoridation programme requires; a, suitable equipment available in a treatment plant or pumping station, including continuous power supply; b, a constant supply of a suitable fluoride-containing chemical; c, workers in the water treatment plant able to maintain the system and keep adequate records (American Water Works Association, 2004; Drinking Water Inspectorate, 2005) and, d, sufficient funding for the initial installation and running costs (British Fluoridation Society, 2012; Truman *et al.*, 2002). It follows that the level of dental caries must be sufficiently high, or the risk of an increasing prevalence of caries sufficiently serious, to justify the investment.

Provided that a large population is served, the cost per head can be very small, especially if the initial cost of equipment is spread out over a period of 5-10 years. All fluoridation plants should have effective fail-safe systems with well-defined limits for the precision of measurements. In order to prevent overdosage, the plant must have a safety mechanism that stops the addition of fluoride automatically if the flow of water through the treatment plant is diminished suddenly (Griffin *et al.*, 2001). A US economic evaluation (Griffin *et al.*, 2001) estimated that the reduction in the cost of restorative dental treatment exceeded the cost of fluoridation in communities of all sizes and in all scenarios based on assumed reductions of tooth decay from 12% to 29%.

The question of possible adverse general health effects caused by exposure to fluorides taken in optimal concentrations throughout life has been the object of thorough medical investigations which have failed to show any impairment of general health. For example, the Knox Report (1985) and the York Review (McDonagh *et al.*, 2000) concluded the absence of demonstrable effects on cancer rates in the face of long-term exposures to naturally elevated concentrations of fluoride in water; the absence of any demonstrable effect on cancer rates following the artificial fluoridation of water supplies; the large human populations observed; and the consistency of findings from many different sources of data in many different countries; which leads to the conclusion, that in these respects the fluoridation of drinking water is safe. Reviews conducted in the United Kingdom, Australia, Canada, the US and New Zealand did not identify credible scientific evidence of harm to health from water fluoridation schemes (Australian Government, National Health and Medical Research Council, 2007; Centers for Disease Control and Prevention, 2001; Health Canada, 2010; McDonagh *et al.*, 2000; Medical Research Council, 2002; Sutton *et al.*, 2015). A recent review by the Royal Society of New Zealand and the Office of the New Zealand Prime Minister's Chief Science Adviser (2014) concluded that there are no adverse health effects of any significance arising from water fluoridation and that the safety margins are such that no subset of the population is at risk because of fluoridation.

A report by the EU Commission's Scientific Committee on Health and Environmental Risks on the health effects of fluoride in drinking water found no evidence of harm to health. It found nothing to link fluoride in water at the levels ordinarily found within the EU with endemic skeletal fluorosis, osteosarcoma, thyroid disorders or negative effects on human reproductive capacity and neurodevelopment (SCHER, 2011).

Public Health England (PHE, 2014) analysed data from all the fluoridated and non-fluoridated areas of England and found no evidence of a difference between them in the rate of hip fractures, all-cause cancer, osteosarcoma or Down's syndrome. The same analysis found a lower rate of kidney stones and bladder cancer in fluoridated areas than non-fluoridated areas, although PHE points out that no conclusions about cause and effect can be drawn. Selection of these indicators was based on the evidence base, theoretical plausibility, potential impact on population health, quality and availability of data, and validity of the indicator.

It is important that ongoing surveillance of general health be maintained in fluoridated and non-fluoridated communities. The structured use of health registers, for example cancer and hip fracture registers, is an important and improving source of information for this purpose.

7.4 Legal aspects and public acceptance

Legislation providing for water fluoridation is of two types. It may be mandatory, requiring a ministry of health or communities of a certain size to fluoridate their public water supplies if they are below the accepted fluoride concentrations level. Alternatively, legislation may be of the permissive or "enabling" type, empowering the ministry of health or a local government body to institute fluoridation. In some countries national legislation or local jurisdictions may require formal public consultations to give members of the communities potentially affected by the proposals the opportunity to voice their opinions prior to a decision being made by the statutorily responsible body. This may involve consultative methods such as opinion polls, public meetings, invitations to respond in writing and referenda, the outcomes of which are then used to help shape the final decision.

7.5 Appropriate concentrations of fluoride in drinking-water

Determination of the most appropriate levels of fluoride in drinking water is crucial if the measure is to be both effective and receive public acceptance. This knowledge is important both for communities intending to begin fluoridation, and for those with excessive natural fluoride which require partial de-fluoridation. The use of an ion-specific electrode as an effective method for monitoring fluoride levels in drinking-water is generally accepted as the accepted gold standard method.

Dean's research from over 60 years ago established 1.0 mg/L as the most appropriate concentration of fluoride in drinking-water. By "most appropriate", was meant the concentration at which a substantial caries reduction could be achieved while limiting enamel fluorosis to an acceptable prevalence and severity. Because people in hot climates drink more water than those in moderate climates, this figure of 1.0 mg/L was modified into a range (0.7-1.2 mg/L); the higher the average temperature in a community, the lower the recommended level of fluoride in the drinking-water. The United States Public Health Service in 1962 adopted this range as a standard for fluoride concentration in drinking-water, and since then this standard has been widely used.

By the 1990s, however, it became clear that these standards were not appropriate for all parts of the world. Even in the United States of America, where they were developed, the advent of air-conditioning, the increased consumption of processed soft drinks and processed foods, and the increasing availability of other sources of fluoride, especially use of fluoride toothpastes from the 1970s onwards, were rendering obsolete the assumptions upon which the range was based. In other parts of the world, especially the tropical and subtropical areas of Africa and Asia, the variety of dietary practices found in many different races and cultures meant that the recommended range had probably never been appropriate.

Certainly it was found that the prevalence and severity of fluorosis in several Asian regions were unduly high when these guidelines were followed. Hong Kong, for example, has adjusted the fluoride concentration in its drinking-water several times since water fluoridation began there in 1961, using different concentration in the hot and cooler seasons and then endeavouring to find an appropriate year-long concentration. According to the United States Public Health Service guidelines, the most appropriate concentration for Hong Kong would be around 0.8 mg/L. However, fluorosis in children was found to be still unacceptably high at that level and the concentration was reduced in several stages to 0.5 mg/L in 1988 (Ho *et al.*, 2011).

It can be stated that the recommended levels of fluoride in drinking-water according to annual temperature, as listed in the United States Public Health Service guidelines of 1962, are not appropriate for use in tropical and subtropical areas of the world. Because higher than expected levels of fluorosis have followed their application, it seems that the recommended range is too high for these areas. The level of 1.0 mg/L should be seen as an upper limit, even in a cold climate, and 0.5 mg/L, now used in Hong Kong and recommended in the Gulf States, may be an appropriate lower limit. The increase in the level of enamel fluorosis in permanent incisors, attributable to the increased use and swallowing of fluoride toothpaste by young infants and children has led to some countries reducing fluoride levels in drinking water e.g. in the Republic of Ireland fluoride levels in drinking water were reduced in 2008 from 0.8-1 ml/L with a target of 0.9 mg/L to 0.6-0.8 with a target of 0.7 mg/L. (Forum on Fluoridation, 2002). Communities in other countries, for example in Australia and in Canada, have made similar adjustments to levels of fluoride in drinking water in recent years, with a view to controlling the occurrence of enamel fluorosis. However, the need for reductions in target levels has not been indicated in all countries with fluoridation schemes. Decisions need to reflect local circumstances in the light of the monitoring of enamel fluorosis levels, the prevalence and severity dental caries and the commonly available sources of fluoride to children during periods of tooth formation.

7.6 Removal of excessive fluoride in drinking water

Excessive concentration of fluoride in drinking water in developing countries are a serious public health problem because it can lead to high concentrations of generalised fluorosis. There are many water filter systems and treatment methods available to remove excess fluoride from water. However, many of these systems can be difficult to implement and therefore the supply of alternative sources of water with low fluoride content, if available, should be regarded as the first option. In cases where alternative sources are not available de-fluoridation of water is the only option.

There are several different de-fluoridation methods and what may work in one community may not work in another community. It is essential that care be taken to select the appropriate de-fluoridation method in order to ensure that a sustainable solution to the fluorosis problem is achieved (Fawell *et al.*, 2006). There are five established defluoridation methods: bone charcoal, contact precipitation, Nalgonda,

activated alumina, and clay. In addition advanced treatment technologies such as reverse osmosis, electrodialysis and distillation are available on the market. Defluoridation of drinking water is technically feasible at point of use (at the tap), for small communities of users and also for large drinking water supplies. Point of use systems are generally installed to produce sufficient quantities of treated water for drinking and cooking requirements for several persons.

Bone charcoal is a blackish porous granular material, its major components being calcium phosphate (57-80%), calcium carbonate (6-10%) and activated carbon (7-10%). In contact with water, the bone charcoal absorbs a wide range of pollutants and specifically has the ability to take up fluoride from water. Water treated with bone charcoal can have a foul taste and may be rejected by the users consequently the design of a system which uses bone charcoal requires careful planning. One of the constraints of the bone charcoal defluoridation method is that in some communities religious beliefs preclude the use of animal bones; in these instances this method is unacceptable.

Contact precipitation is a technique by which fluoride is removed from the water through addition of calcium and phosphate compounds and then bringing the water in contact with an already saturated bone charcoal medium. Although it has only been implemented to date at village level in Tanzania and Kenya, contact precipitation is probably suitable for implementation on a wider scale. The construction of contact precipitation plants is relatively straightforward when properly supervised by persons experienced in the process (Fawell *et al.*, 2006).

The Nalgonda process was adapted and developed in India for both community and household water systems. The aluminium sulphate and lime process has a long history and was initially proposed for de-fluoridation of water when excessive fluoride in water became a health concern in the USA as the agent responsible for mottling of teeth (Boruff, 1934).

The process is based upon aluminium sulphate coagulation flocculation/sedimentation reaction where the dosage is designed to ensure removal of fluoride from water. The aluminium sulphate is dissolved and added to the water under efficient stirring in order to ensure initial complete mixing. Aluminium hydroxide micro-flocs are produced rapidly and gathered into larger easily settling flocs. Thereafter the mixture is allowed to settle. During this flocculation process many kinds of micro-particles and negatively charged ions including fluoride are partially removed by electrostatic attachment to the flocs.

Discarding sludge from the Nalgonda process can lead to environmental health problems as the sludge is quite toxic because it contains the removed fluoride in a concentrated form. The process for discarding the sludge requires careful planning. The Nalgonda method requires skilled workers and a reliable electricity supply.

Activated alumina comprises aluminium grains prepared with an adsorptive surface. When water passes a packed column of activated alumina, pollutants and other components in the water are adsorbed onto the surface of the grains. The design criteria for activated alumina can be challenging. Also it was previously considered that this process was costly due to the high cost of chemicals and availability in the market. This is no longer the case:

experience mainly from India, Thailand and China indicates that activated alumina may, under certain conditions, be affordable for low income communities. The system was patented as early as 1936 and since then activated alumina has become the subject of several patents and because of commercial interests is the most widely advocated technique worldwide.

The ability of clay to remove pollutants from water has been known for centuries and is believed to have been used at domestic level in ancient Egypt. Clay is an earthy sedimentary material and is mainly composed of fine particles of hydrous aluminium silicates and other minerals and impurities. It is plastic when moist, retains its shape when dried and is extremely hard when fired; properties used when making pottery, bricks and tiles. There has been a suggestion that some soils are more efficient than others in the ability to cleanse water but this is debatable. An important consideration when using clay as a de-fluoridation material is that many soils are heavily polluted and therefore any clay to be used for de-fluoridation prior to producing drinking water should be tested for presence of toxic materials and other possible pollutants. The introduction of the clay technology for de-fluoridation requires rigorous attention to detail.

7.7 Requirements for implementation of water fluoridation

1. A prevalence of dental caries in the community that is high or moderate, or firm indications that the caries level is increasing.
2. Attainment by the country (or area of a country) of a moderate level of economic and technological development.
3. Availability of a municipal water supply reaching a large proportion of homes.
4. Evidence that people drink water from the municipal supply rather than water from individual wells, rainwater tanks or other sources.
5. Availability of the equipment needed in a treatment plant or pumping station.
6. Availability of a reliable supply of a fluoride-containing chemical of acceptable quality.
7. Availability of trained workers in the water treatment plant who are able to maintain the system and keep adequate records.
8. Availability of sufficient funding for initial installation and running costs.

7.8 Summary

1. Community water fluoridation is safe and cost-effective and should be introduced and maintained wherever socially acceptable and feasible.
2. The optimum fluoride concentration will normally be within the range 0.5-1.0 mg/L.
3. The technical operation of water-fluoridation systems should be monitored and recorded regularly.
4. Surveys of dental caries and enamel fluorosis should be conducted periodically. For effective surveillance the World Health Organization suggests that clinical oral health surveys should be conducted regularly every five to six years in the same community or setting.

8. Fluoridated salt

8.1 Introduction

Use of salt fluoridation for dental caries prevention began in Switzerland in the mid 1950s and has expanded to several countries around the world (Marthaler 2005; Petersen and Lennon, 2004). A study in China of fluoridated salt (200-250ppm) was found to be an effective and safe way to prevent dental caries in primary teeth and remained effective on permanent first molars after the programme had stopped for 1-4 years (Petersen *et al.*, 2008).

When most salt for human consumption is fluoridated, the community effectiveness of salt fluoridation approximates that of water fluoridation (Marthaler and Petersen, 2005). The first studies of the effects on the incidence and prevalence of dental caries of fluoride added to ingested salt were carried out from around 1965 to 1985 in Colombia, Hungary and Switzerland, with rather similar results to those observed after the introduction of water fluoridation. Fluoridated salt reaches the consumer through several channels, including domestic salt, meals at schools, large kitchens and in bread; fluoridated salt exerts both a systemic and topical effect. In Colombia, Costa Rica, Jamaica, and the Canton of Vaud in Switzerland, most, if not all, of these channels are used; in France and Germany the focus is on fluoridating domestic salt. The island of Jamaica provides another interesting example, because virtually all salt destined for human consumption on the island has been fluoridated since 1987. A renal fluoride excretion study conducted in Jamaica in 2008 indicated that the current fluoride exposure assures virtual freedom from enamel fluorosis, while the targeted decline of caries has been met or has surpassed expectations. At this time, there is obviously no reason to change the salt fluoridation scheme conditions as they have been maintained over twenty one years in Jamaica (Baez *et al.*, 2010).

The use of fluoridated salt as a community preventive agent for dental caries prevention has increased steadily since 1986. Significant development has occurred in the Americas where Colombia, Costa Rica, Jamaica, Mexico and Uruguay have more than 20 years of documented community experience with population coverage up to 98%. Other countries such as Belize, Bolivia, Cuba, Dominican Republic, Ecuador, Peru and Venezuela have active programmes, and an estimated further five are in the process of implementing this approach. Fluoridated salt is also available in certain countries that do not have identified programmes, such as Trinidad and Tobago and other Caribbean and Latin American countries.

These studies have shown caries reductions, acceptability by the public, no increase in individual salt consumption, no proven related increase in enamel fluorosis, no other negative health impacts reported, and very low per capita costs. Belarus has illustrated the added impact on caries reductions by adding fluoridated salt to existing oral health promotion programmes.

The Center for Global Development, Washington DC in 2004 cited the Jamaica salt fluoridation programme as one of the 17 most relevant public health initiatives taken worldwide in recent years (Levine, 2004).

8.2 Impact on a population and implementation (Annexe 2)

The efficacy and impact of salt fluoridation depend upon the programme implementation. However, factors such as distribution, marketing, pricing and method of implementation affect community coverage, impact and health. For example, Jamaica prohibited the importation and sale of all non-fluoridated salt for human consumption and achieved reported caries reductions of up to 82% in 12 year olds. The reduction in dental caries observed represented biological factors-including the use of fluorides-in combination with secular trends. However, it is highly possible that the most important factor in this reduction was the consumption, beginning in 1987, of fluoridated salt (Warpeha *et al.*, 2001).

Mexico has achieved national fluoride coverage of its 112 million population through fluoridated and iodized salt and fluoridated water. Uruguay has legislated that a specific percentage of domestic salt for human consumption be fluoridated, and the German programme has incentives for the addition of fluoride to salt.

Depending on the method of implementation, part of, or whole, populations may be covered. The minimum level of implementation is fluoridation of domestic salt only, as practised in France and Germany. In Switzerland fluoridated domestic salt containing 250 mg F/kg has been available in addition to nonfluoridated salt since 1983; under these conditions, 75% of the domestic salt sold between 1987-1991 was fluoridated. Varying levels of implementation using multiple products are in place in Costa Rica, Jamaica and Switzerland. When the salt for bakeries and institutions is fluoridated, as well as all domestic salt, population coverage is virtually complete. When only some domestic salt is fluoridated, consumers retain more choice but community effectiveness is diminished.

Fluoridated salt raises ambient oral fluoride concentration throughout life in a manner similar to water fluoridation (Whitford, 2005). A small study of Swiss military conscripts supports the hypothesis of continued effectiveness (Menghini *et al.*, 1991). Among conscripts from western Switzerland, those who had not benefited from fluoridated salt had 10.2 DMF (decayed, missing, or filled) teeth while those from the canton of Vaud who had consumed fluoridated salt from the age of 5 years onwards had only 7.1 DMF teeth. A recent meta-analysis of 11 databases indicated that salt fluoridation was effective in the prevention of dental caries (Yengopal *et al.*, 2010).

Implementation of a comprehensive national fluoridation programme through water and salt is more difficult when there are multiple drinking-water sources which have a naturally optimal or excessive fluoride concentration. Various mechanisms can be utilized to exercise control of the distribution network. Implementation of epidemiological surveillance is critical. An essential element is the census of water supplies and mapping of fluoride so that regulations can be implemented to prohibit distribution of fluoridated salt to communities where fluoride concentration in water is optimal or above optimal. Also, salt fluoridation requires refined salt produced with modern technology and a level of technical expertise adapted from that used in adding iodine to salt. However, technology is available for adding fluoride and iodine to coarse granular salt. Because ensuring

a uniform distribution of fluoride within manufactured salt and the possibility of settling, the fluoride concentration in salt at the point of purchase or use should be monitored.

8.3 Economics, health, safety and limitations.

Costs are minimal compared to treatment costs of water fluoridation and coverage can be universal. Effective programme implementation depends upon collaboration between health authorities, salt processors, distributors, and the community. Cost-benefit studies conducted in the region of the Americas comparing anticipated fluoridation costs versus economic resources that will no longer be needed on dental treatment after implementation of salt fluoridation indicated benefits were considerably higher than the investment required for implementing the programme (Gillespie and Baez, 2005).

One concern expressed is that promotion of the dental benefits of fluoridated salt would be unacceptable and contradictory to public health messages that encourage the reduction of consumption of salt to decrease the risk of hypertension. However, those who raise this objection rather misunderstand the approaches used in France, Switzerland and elsewhere. Currently the major programmes are using potassium fluoride, rather than sodium (associated with hypertension) fluoride as the added ingredient, and the populations of these countries are not encouraged to consume more salt to improve their dental health. Individual table salt consumption has not increased and no adverse effects from the small amount of sodium noted. The "automatic" or passive effect of fluoridated salt is well accepted by the consumer. In other words, people do not need to change their usual behaviour to benefit, they simply need to change the product. Indeed, reduced consumption of salt could and should be encouraged and, where this is successful, the concentration of fluoride in salt could simply be increased appropriately if necessary.

In Switzerland fluoridated salt is available at the same price as other kinds of salt, including iodized salt; hence there is no extra cost to the consumer. Price differences in other countries vary considerably in comparison with iodized or non-iodized salt, dependent upon local policies, regulations, and the market. In early Hungarian studies, 350 mg/kg was added, the highest concentration yet reported for human use. At present 200 to 250 mg/kg is used in nearly all programmes.

8.4 Legal aspects and public acceptance

EU legislation recently re-approved the use of fluorides as a food additive and specifically approved sodium and potassium fluoride (the most frequently used compounds) as approved food additives (EU Regulations, 2009; Götzfried, 2006). Europe has several countries with salt fluoridation programmes, although few have a large market share except Switzerland and Germany. The WHA Resolution (WHO, 2007) on Oral Health (WHA 60.17) approved the use of salt fluoridation as an alternative to water fluoridation where this was not feasible for any reason. It is not recommended where other ingested fluoride programmes are in place.

8.5 Requirements for application

1. Moderate or high dental caries prevalence, or the expectation that caries prevalence will increase.
2. Predominance of low-fluoride drinking-water.

3. Multiple sources of water posing a serious economic obstacle to water fluoridation.
4. Lack of political and community will and resources to fluoridate drinking-water.
5. Centralized salt production or recognised sites producing domestic salt with experience of including and monitoring additives.
6. Coordination between health agencies, salt producers, marketers, distributors, and the community, with inclusion of appropriate monitoring programmes, is suggested for effective implementation. An adequate epidemiological surveillance system for salt fluoridation has been developed and as for any public health programme using fluoride for dental caries prevention, it is an essential programme component (Baez, 2001).
7. In the absence of local or national capability to produce fluoridated salt, the importation of fluoridated salt, or the addition of fluoride to imported domestic salt for human consumption, can be used. Coordination and monitoring similar to national production should be required.

8.6 Summary

1. Salt fluoridation should be considered where water fluoridation is not feasible for technical, financial or sociocultural reasons. It can be used for small groups or large populations, is very economical and, where necessary, provides freedom of choice.
2. The optimum concentration must be determined on the basis of salt intake studies and an assessment of fluoride exposure. A concentration of 200 mg F/kg salt may be regarded as a minimum when several types of salt (domestic and salt for bakeries, restaurants and other large kitchens) are fluoridated, but twice this concentration may be appropriate when only domestic salt is fluoridated.
3. The technical operations of salt fluoridation systems should be monitored and recorded regularly. In addition, the correct concentration and homogeneity (i.e. that the added fluoride salt is evenly distributed throughout the mixture) should be periodically ascertained in the packages offered to the consumer.
4. The fluoride concentration should appear on all salt packages.
5. Surveys of dental caries and dental enamel fluorosis should be conducted periodically. Urinary fluoride excretion should be monitored before and after programme commencement to assess the appropriateness of the fluoride dosage.

9. Fluoridated milk.

9.1 Introduction

Milk is an essential food in early life and continues to provide benefit from childhood and adolescence through to old age. Many government agencies subsidise the provision of milk to children and school milk programmes exist in many countries; these programmes are supported by the World Health Organization (WHO) and the Food and Agriculture Organisation (FAO). The provision of milk in schools is often integrated into national health promoting school programmes, and has been shown to reduce inequalities in the health of children (Baker *et al.*, 1980).

The concept of milk as a vehicle for fluoride emerged in the early 1950s (Bánóczy and Rugg-Gunn, 2009).

9.2 Impact of fluoridated milk

Since 1986, the WHO International Programme for Milk Fluoridation has promoted and supported programmes aimed at demonstrating the feasibility for community use of fluoridated milk for caries prevention. Various channels have been used to target fluoridated milk to children attending kindergartens and schools, in Bulgaria, Russia and Thailand to children consuming powdered milk and milk-cereal distributed as part of a National Complementary Feeding Programme in Chile, and to older adults at risk of root caries attending a specialist dental clinic in Sweden (Peterson *et al.*, 2011).

9.3 Implementation

A substantial amount of non-clinical research has been published demonstrating the bioavailability of fluoride in milk and the biological plausibility of milk fluoridation (Edgar, 2009; Villa, 2009a). Three systematic reviews have been published of the clinical effectiveness of milk fluoridation (Yeung *et al.*, 2015; National Health and Medical Research Council, 2007; Cagetti *et al.*, 2013). All studies considered in these three systematic reviews reported a reduction in dental decay among those consuming/receiving fluoridated milk. A wider ranging review of the clinical effectiveness of milk fluoridation in preventing dental caries listed 18 studies conducted in 12 countries (Bánóczy *et al.*, 2013). Of these, nine demonstrated caries prevention in primary teeth and 12 in the permanent dentition. A very recent study also showed that fluoridated milk delivered daily in schools in Bulgaria resulted in substantially lower caries development compared with children in schools receiving milk without added fluoride (Petersen *et al.*, 2015). The totality of the evidence suggests that milk fluoridation is effective in the prevention of dental caries. The reviews suggest that children should begin to drink fluoridated milk from an early age, preferably before 4 years, in order to reduce caries in primary teeth. In addition they recommend that children should continue to drink fluoridated milk while their first permanent molars erupt in order to protect these teeth.

The implementation of community-based milk fluoridation programmes has been described by Woodward (2009), including a simple questionnaire to be answered when assessing the feasibility of a milk fluoridation programme. In excess of one and a half million children worldwide currently consume fluoridated milk (Annexe 3) and the experience gained in this international programme has provided considerable knowledge on the practical aspects. The wider collaboration of national and local governments, dairies, schools and health professionals are an important feature of the successful programmes. The daily dosage varies from 0.50mg to 0.85mg fluoride per child (Annexe 3) with children drinking around 200 ml of fluoridated milk per day for about 200 days per year. The dose will depend on age and background fluoride exposure – the latter being evaluated by questionnaire and measurement of urinary fluoride excretion (Villa, 2009b). Recently a study of fluoridated milk intake in 3 to 4 and 6 to 7 year old children in schools in north-east England indicated that compliance was high at greater than 90% in each of the groups studied (Walls *et al.*, 2012).

The legal framework for the addition of fluoride to milk has been documented (Woodward, 2009). Programmes can allow for personal consent for inclusion, if this is deemed appropriate. Types of milk vary within and between countries. For example, powdered milk is used in Chile, fresh pasteurised milk in several countries and UHT milk in Thailand. These differences reflect cultural and local logistical considerations and do not affect fluoride availability and effectiveness. The addition of fluoride to milk is a simple process (Villa, 2009a) and the cost of fluoridated milk is usually the same as non-fluoridated milk. Overall, the cost of the programmes in Chile, Thailand and the UK is around 2 to 3 US\$ per child per year (Woodward, 2009; Marinho *et al.*, 2007, 2011; Bánóczy *et al.*, 2013). The safety of milk fluoridation has been established (Marinho *et al.*, 2003; Villa, 2009b). WHO has published a manual to assist those considering implementing milk fluoridation programmes (Bánóczy *et al.*, 2009).

9.4 Summary

1. In a community with a well-developed milk distribution system, such as a school milk programme, the technical procedures for producing fluoridated milk are straightforward.
2. Encouraging results regarding caries reductions have been reported with fluoridated milk in children and a recent study in older adults suggests that this also might be a promising area of research.
3. Further research on starting age, dosage and the minimum number of intakes per year should be encouraged.
4. The cost is low at about 2 to 3 US dollars per child per year. Risk of adverse effects is very low as the dose is constant and related to age and background fluoride exposure.

10. Fluoride supplements (tablets and drops)

10.1 Introduction

Studies on the use of fluoride supplements, drops and chewable tablets, in the control of dental caries in communities with non-fluoridated water supplies have been reported regularly in the scientific literature for the last 45 years. A number of systematic and other reviews have concluded that the quality of the reviewed studies was generally low and the evidence of a caries preventive effect on the primary and permanent dentitions was inconsistent. Different dosage regimes have been recommended over the years. Recently updated dosage regimens have been published for Europe (Espelid 2009), New Zealand (Coop *et al.*, 2009) and the US (Rozier *et al.*, 2010). These recommendations take account of the balance between the benefits of the use of fluoride drops or tablets and the risk of developing unsightly mild fluorosis in permanent incisors (Ismail and Husson 2008). The level of fluoride in the drinking water, the incidence of fluorosis in the permanent incisors of the community, the age at which infants should start taking fluoride drops or tablets, the amount of fluoride in each drop or tablet, usually taken once a day, the estimated caries risk status of the child and the pattern of sales and use of fluoride toothpastes are some of the factors which are taken into account by groups of experts who have drawn up dosage regimens. Countries need to consider carefully whether to recommend the use of fluoride supplements (drops and tablets) in view of uncertainties about compliance and the

risk of fluorosis if children under the age of 6 years take more than the advised dose.

10.2 Impact on a population, limitations, and implementation

The use of fluoride tablets can be either at home or in school-based programmes. Daily administration of tablets at home requires a very high level of parental motivation, and campaigns to encourage parents to give their children fluoride supplements have not been successful in many countries, the impact being least in the economically underprivileged sections of a community. Results of home-based trials have to be interpreted with caution, because the attitude to oral health of the parents who give their children supplements from birth is likely to be more favourable than that of those who begin supplementation late. School-based programmes used to be prevalent in Europe but are much less common now.

There is no logistic problem in the production of fluoride tablets but there has been considerable discussion as to the optimum dosage of fluoride tablets and drops. Reports on numerous different dosage regimens have been published in various communities; all are based on empirical estimates rather than on the results of rigorous scientific studies and the evidence supporting particular recommendations are generally low.

10.3 Economics, health, and safety

Where fluoride supplements are prescribed individually by dentists, the cost of tablets is considerably greater than when they are purchased in bulk and administered in supervised school programmes. In such programmes, the teachers' supervising time is usually not included in the cost of the programme, although it is obvious that supervision is a real and important cost. The actual cost of supervision will vary greatly from one country to another, with different labour charges and cultures.

The objective of any systemic fluoride administration is to obtain the maximum caries-preventive effect with a minimum risk of fluorosis. In the past, fluoride tablet dosages have been calculated in an attempt to duplicate the fluoride intake of people receiving optimally fluoridated drinking-water, although a review of water consumption in the United Kingdom revealed that children drink considerably less from public water supplies than was assumed previously (Rugg-Gunn *et al.*, 1987; Zohouri *et al.*, 2004). Thus earlier estimates that children aged 3 years ingest 1 mg F⁻/day from fluoridated water were almost certainly too high.

Obviously fluoride tablets should be kept out of reach of young children, and should be packaged in child-proof containers. In some countries the number of tablets in a container is limited so that there can be no more than 120 mg of sodium fluoride in any one container; this seems a prudent safety precaution.

10.4 Legal aspects and public acceptance

In some countries, fluoride tablets are available only on prescription from a physician or a dentist. In other countries fluoride tablets are available over the counter. In Canada, the Food and Drug Regulations prohibit the over-the-counter sale of a tablet containing fluoride if the largest dosage would result in a daily intake of more than 1 mg of fluoride ion.

In the United States of America, the Food and Drug Administration has banned the making of claims that dietary fluoride supplements for pregnant women are effective in reducing dental caries in the infant, since such benefits have not been established.

10.5 Enamel fluorosis and fluoride supplements

Fluoride from tablets is ingested and absorbed at one time of day and this is physiologically different from ingestion of fluoride from water or salt where absorption is spread throughout the day. Animal experiments have shown that fluoride given once a day is more likely to cause enamel fluorosis than the same amount of fluoride given intermittently throughout the day. Some recent studies have indicated that the ingestion of fluoride supplements can be a risk factor for enamel fluorosis (as can the inadvertent ingestion of fluoride-containing dentifrices and mouth-rinses). The stage of enamel development most vulnerable to excessive fluoride intake is the transitional stage, which occurs between the late secretory and early maturation stages. Consistent evidence accumulated in the US over the years shows that fluoride tablets used during the first 3 years of life increased the risk of developing fluorosis; the first year of life appears to be the period of highest risk for incisors (Buzalaf and Levy, 2011).

10.6 Dosage schedule

There has been a general trend towards lowering the fluoride supplement dose, particularly in the early months of life. A further problem is the complexity of most dosage schedules, particularly if there are a number of children of different ages in the family. In addition, fluoride supplements have been found to be ineffective as a public health measure because compliance with the daily regimen can be poor and the children who use them are normally from the more oral-health-conscious families. The possibility of an increased risk of enamel fluorosis has led some experts to conclude that:

- fluoride supplements have limited application as a public health measure;
- a dose of 0.5 mg F/day should be prescribed only for individuals at risk, and starting only at the age of 3 years;
- labelling should advise that fluoride supplements should not be used before 3 years of age unless prescribed by a dentist.

On the other hand, particularly in countries where there is a high level of caries in the primary dentition, many dentists feel that it is most important to maximize the caries preventive properties of fluoride supplements.

Recently recommended dosage schedules in Europe, New Zealand and the US exemplify the variation in approaches (Rozier *et al.*, 2010; Espelid, 2009; European Academy of Paediatric Dentistry, 2009).

In the case of Europe it is recommended that no fluoride supplements be prescribed before the age of two years; 0.25 mg F/day for age 2-6 years and 0.5 mg F/day for age 7-18 years. In addition it is recommended that if the level of fluoride in drinking water is 0.3mgF/L or above, further systemically administered fluoride regimes are not advised.

In New Zealand the recommended dosage schedule is: no fluoride tablets under 3 years; 0.25 mg F/day for 3-5 year-olds; 0.5 mg F/day for 6-8 year olds and 1 mg F/day

for 9 year-olds and older. It is recommended that tablets should be chewed or sucked or dissolved in a drinking liquid.

In the US in the case of water supplies containing <0.3mg/L F it is recommended that no fluoride tablets be prescribed before the age of 6 months, between 6 months and 3 years 0.25 mg F/ per day, 3-6 year 0.50 mg F/day and 6-16 years 1mg F/day. For water supplies with 0.3-0.6 mg/L F fluoride drops or tablets should not be prescribed before the age of 3 years, between 3-6 years 0.25 mg/day and between 6-16 years 0.5 mg F/day.

10.7 Summary

1. Fluoride supplements have limited application as a public health measure.
2. In areas where there is particular concern about caries in the primary and permanent dentitions, a dosage regimen that takes into account the fluoride content of the total exposure to fluorides from water and other sources and the prevalence of fluorosis in the community should be determined.
3. Prescribed supplements should be issued in child-proof containers. The quantity of sodium fluoride in all the tablets in any one container should not exceed 120 mg.
4. Recommendations regarding dosage schedules vary in different communities and depend on factors such as levels of caries and enamel fluorosis, pattern of use of fluoride toothpaste and legislation.

11. Fluoride toothpastes

11.1 Introduction

The use of cleaning agents for teeth in the form of powders, creams and pastes has been part of personal grooming since antiquity (Lippert, 2013). However, it was only in the second half of the 20th century, with the successful incorporation of fluoride, that toothpaste acquired a therapeutic anti-caries effect in addition to a cleansing effect. Since then, various fluoride compounds have been added to toothpaste, either singly or in combination, including sodium fluoride, acidulated phosphate fluoride, stannous fluoride, sodium monofluorophosphate and amine fluoride (Lippert, 2013).

The effectiveness of fluoride toothpaste at preventing caries has been demonstrated in several systematic reviews (Marinho *et al.*, 2003a; Twetman, 2009; Twetman *et al.*, 2003; Wright *et al.*, 2014). Based on meta-analysis of 70 trials of moderate quality, the review by Marinho *et al.* (2003a) reported a reduction of 24% in caries increment in permanent teeth with the use of fluoride toothpaste and concluded that there was "...clear evidence that fluoride toothpastes are efficacious in preventing caries." This review also found that the effect of fluoride toothpaste increased with increasing frequency of brushing (twice a day more effective than brushing once a day), increased baseline level of caries and with increasing fluoride concentration, but that the effect of fluoridated toothpaste is in addition to the effect of fluoridated water.

Fluoride toothpaste is now the most widely used method for maintaining a constant low level of fluoride in the oral environment (Goldman *et al.*, 2008) and its widespread use is considered to have played an important role in the decline in dental caries in industrialised countries in recent decades (Brathall *et al.*, 1996). In many countries, fluoride-containing toothpastes make up more than 95% of all toothpaste sales.

In 2006, total sales of all toothpastes at retail sales price was US\$14,827 billion, growing to 20,486 billion in 2011 (Information provided by Euromonitor International in 2012).

11.2 Toothpaste formulation

During the past 60 years there have been considerable improvements in fluoride toothpaste formulation, which have resulted in increased effectiveness in improving oral health. The main fluoride compounds currently found in toothpastes are sodium fluoride and sodium monofluorophosphate, although stannous fluoride and amine fluoride are also used (Pessan *et al.*, 2011). The development of flavours to suit different cultures is increasing the worldwide acceptability of toothpastes.

From a public health viewpoint, it is essential that only toothpaste formulations that are adequately supported by properly conducted clinical trials should be promoted. It is essential that the manufacturing process includes adequate quality assurance procedures to ensure that fluoride is present in the toothpaste at the concentration stated on the tube and that it is available for caries prevention. For example interaction between an active agent (e.g sodium fluoride) and an incorrectly chosen calcium abrasive can lead to a considerable reduction in available fluoride and a short shelf-life.

The competitiveness in the world market for fluoride toothpastes is likely to ensure that research and development will continue in these areas, thereby improving the oral health promotion potential of future formulations. The highly competitive nature of the oral care market and the promotion of toothpastes by the different manufacturing companies has no doubt contributed to their increased use worldwide. The positive role of the oral health care industry in promoting oral health has been considerable.

11.3 Fluoride concentrations in toothpastes

In 1977 the European Commission suggested that an upper limit of 1,500 ppm fluoride be placed on toothpastes sold over the counter without prescription. It is now generally accepted that the fluoride concentration of 'standard' toothpaste is between 1,000 and 1,500 ppm and this is a standard recommended by WHO. In some countries, 'low fluoride' toothpastes containing less than 1,000 ppm F (usually in the range 400 – 550 ppm F) are marketed for children. 'High fluoride' toothpastes containing more than 1,500 ppm F (usually in the range 2,000 to 5,000 ppm F) are available on prescription for older children and adults at increased risk of caries.

A systematic review of the effectiveness of different concentrations of fluoride toothpaste (Walsh *et al.*, 2010) confirmed the caries-preventive benefits of using fluoride toothpaste compared to placebo in permanent teeth, but only at concentrations of 1,000ppm and above. Comparison of the relative effectiveness of toothpastes with different fluoride concentrations indicated a dose-response relationship, with effectiveness increasing with increasing fluoride concentration.

11.4 Fluoride toothpastes and young children

Parents are encouraged to start cleaning their child's teeth as soon as the first tooth appears, and recent evidence suggests that in industrialized countries many parents begin to use a fluoride toothpaste regularly with their children from a young age, in many instances before the age of 1 year.

Young children are unable to spit out effectively and can ingest 80-100% of the fluoride dispensed at each brushing (Cochran *et al.*, 2004). Consequently toothpaste is a significant source of ingested fluoride during the critical period of permanent tooth development (Buzalaf and Levy, 2011).

A systematic review of topical fluoride as a cause of dental fluorosis in children found weak unreliable evidence that starting the use of fluoride toothpaste in children under 12 months of age may be associated with an increased risk of fluorosis. The evidence for its use between the age of 12 and 24 months was equivocal (Wong *et al.*, 2010). There is stronger evidence that higher levels of fluoride (1,000 ppm or more) in toothpaste are associated with an increased risk of fluorosis when used with children under 5 or 6 years of age (Wong *et al.*, 2010; Wright *et al.*, 2014). However, this is the fluoride concentration for which a definite caries-preventive effect has been demonstrated (Walsh *et al.*, 2010). Because the fluorosis recorded in studies included in the systematic reviews was confined to the very mild grades and was not aesthetically compromising, the use of fluoride toothpastes should continue to be promoted in communities, whether or not they are served with fluoridated water, fluoridated salt or fluoridated milk. To reduce the risk of fluorosis, guidelines that recommend use of toothpaste containing 1,000 ppm F for young children tend to limit the amount used to a "smear" (equivalent to 0.1mg F) (Public Health England, 2014; Scottish Intercollegiate Guidelines Network, 2014) or to the size of a grain of rice (Health Canada, 2010). It is important that children should be supervised when brushing to ensure appropriate use of toothpaste.

In some countries low concentration fluoride toothpastes for young children are being marketed, even though the caries-preventive efficacy of these products has not been established in randomised controlled trials (Walsh *et al.*, 2010).

The production of toothpaste with candy-like flavours should be discouraged as this may lead to excessive ingestion of fluoride by young children. Similarly toothpastes containing fluoride at 1,500 ppm or more should not be used by young children, as this may also lead to excessive ingestion of fluoride.

Guidance on the use of fluoride toothpaste for young children varies from country to country. The greatest variation is found in the age at which its use should begin and recommendations on concentration of fluoride and amount of toothpaste to place on the brush. Variation in guidance can be expected where background exposure to other forms of fluoride differ among the target population groups. Important variables to bear in mind when issuing guidance on fluoride toothpaste use for young children are background fluoride exposure and caries risk among the population at which the advice is targeted.

11.5 Constraints and barriers to using fluoride toothpaste

11.5.1 Cost

While fluoride toothpastes are now the most widely used delivery system for applying fluoride to teeth, in order to be effective, toothpaste must be purchased and used appropriately. The availability and use of fluoride toothpaste has not been uniform and is less likely among underprivileged groups.

Cost also remains a barrier to their widespread use in many communities (Goldman *et al.*, 2008). Hence, for much of the world, the development of affordable and effective fluoride toothpastes is a major priority.

The WHO Oral Health Programme has promoted the development and use of 'affordable' fluoride toothpastes for developing countries. An 'affordable' toothpaste is one that is available at a price that allows people on a low income to purchase it. A school-based programme using 'affordable' fluoride toothpaste in Indonesia demonstrated that companies can manufacture effective toothpastes that are also of low cost. Meanwhile, since the use of fluoride toothpastes is a public health measure, it is highly desirable that effective fluoride toothpastes are exempt from the duties and taxation applied to cosmetics, to encourage greater use worldwide (Jones *et al.*, 2005).

The WHO Global Oral Health Programme is currently undertaking further demonstration projects in Africa, Asia and Europe to assess the effects of affordable fluoride toothpaste, milk fluoridation and salt fluoridation (Petersen, 2004).

11.5.2 Socio-cultural, religious and geographic constraints

The availability of fluoride toothpaste, even if 'affordable', does not of itself guarantee uptake and use by the majority of a population. Culturally determined hygiene practices, and actual or perceived religious restrictions, can have a significant impact on the use of products such as toothpaste. Furthermore, populations in developing countries may not have access to fluoride toothpaste for practical or economic reasons, and experience from Africa suggests this is particularly true for rural populations.

Rapid changes in global disease patterns closely linked to changing lifestyles, including increased consumption of diets rich in sugars, urgently demand the development of culturally sensitive oral health promotion strategies to increase the use of fluoride toothpaste in countries and communities where its use has previously been uncommon.

11.6. Factors facilitating the organization of fluoride toothpaste programmes

In both developed and developing countries, the disadvantaged and socially marginalised suffer the greatest burden of disease. Strategies to address such inequalities in oral health will depend to a large extent on oral health service resources available locally. In the UK for example, the National Health Service has developed free fluoride toothpaste programmes targeted at the socially disadvantaged where tooth decay rates in children are unacceptably high.

In most developing countries such programmes would be unaffordable. However, local studies have demonstrated that specially-formulated affordable fluoride toothpastes are effective in caries prevention, and WHO policy supports measures to make such affordable fluoride toothpaste available in developing countries. In some parts of the developing world school-based toothbrushing programmes with commercially available fluoride toothpastes are in place, such as China (Min *et al.*, 2007) and Southern Thailand (Petersen *et al.*, 2015). Elsewhere the use of fluoride toothpaste has been encouraged by incorporating it into

existing oral hygiene practices - for example, programmes involving fluoride application using a chewing-stick (*miswak*) have been developed in communities where this form of tooth-cleaning is commonly practised.

Finally, since oral health is important to general health, and risk factors are often common to both, the WHO global strategy for prevention and control of non-communicable disease has promoted the 'common risk factor' approach to manage the prevention and control of oral diseases. WHO will provide technical and policy support to enable countries to integrate oral health promotion with general health promotion (Petersen, 2004). Proper evaluation of health promotion activity is important, and good evidence of efficacy will facilitate the development of good practice (Petersen and Kwan, 2004).

11.7 Manner of use of fluoride toothpaste

The manner in which fluoride toothpaste is used has an important influence on its effectiveness in caries prevention. This is not surprising since the primary function of fluoride toothpaste is to bring the fluoride ion into contact with enamel, dental plaque and, in the case of adults, exposed root dentine. Several recent studies have shown that frequency of use of a fluoride toothpaste is inversely related to caries incidence, and the method of rinsing following brushing has also been shown to affect caries inhibition: thorough mouth-rinsing with water after brushing the teeth increases the oral clearance of fluorides and may reduce the caries-preventive effect (Parnell and O'Mullane, 2013). A number of studies have attempted to link effectiveness with the amount of toothpaste habitually used on the brush, but to date, there is little evidence that the two are related.

11.8 Summary

1. Every effort must be made to develop affordable fluoride toothpastes for general use in developing countries and amongst the socially deprived. Since the use of fluoride toothpastes is a public health measure, it would be in the ultimate interest of countries to exempt them from the duties and taxation applied to cosmetics.
2. Everyone should be encouraged to brush daily with a fluoride toothpaste. Brushing frequency is positively related to caries prevention.
3. The caries preventive effectiveness of fluoride toothpastes is positively related to fluoride concentration in the toothpaste. The effectiveness of toothpastes with less than 1000 ppm fluoride is uncertain due to the limited number of studies available. More research into the effects of fluoride toothpastes at lower levels of fluoride concentration is needed, particularly on primary teeth. Fluoride toothpaste tubes should carry advice that, for children under the age of 6 years, brushing should be supervised and only a very small amount or smear (less than 5 mm, 'pea' sized) should be placed on the brush or the chewing-stick. Research on methods of controlling the amount of toothpaste placed on the brush (for example, by restricting the size of tube orifice and size of brush) should be encouraged.

4. The use of toothpastes with candy-like flavours or containing fluoride at 1500 ppm or more by children under 6 years of age should not be encouraged.
5. Important variables to bear in mind when issuing guidance on fluoride toothpaste use for young children are background fluoride exposure and caries risk among the population to which the advice is targeted.
6. Further research on the effectiveness of fluoride toothpastes on root-surface caries is required.
7. The effectiveness of other methods of using fluoride toothpaste (such as supervised school tooth-brushing and chewing-stick programmes) should be assessed and their adoption encouraged where they are acceptable.

12. Topical fluorides (other than toothpaste)

12.1 Introduction

Topical fluorides are defined as “delivery systems which provide fluoride to exposed surfaces of the permanent and primary dentition, at elevated concentrations for a local protective effect and are therefore not intended for ingestion.” (Marinho *et al.*, 2003b). Topical fluorides can be divided into two broad categories: a, professionally applied (e.g. varnish, gel, foam, slow-release devices and solutions) and, b, self-applied (e.g. toothpaste and mouthrinse). With the exception of fluoride toothpaste, which is the most widely used topically applied fluoride worldwide, topical fluorides are usually recommended for individuals or populations who are considered to be at moderate or high caries risk, after taking into account other exposures to fluoride.

12.2 Fluoride varnishes

Fluoride varnishes were developed to prolong the contact time of fluoride on the tooth surface. Varnishes typically contain high concentrations of fluoride, are available both as low viscosity and high viscosity preparations and are for professional application only. The fluoride formulations and concentrations found in most commercially available varnishes include: 5% sodium fluoride; 0.9% difluorosilane; and, 6% sodium fluoride plus 6% calcium fluoride (56,300 ppm F).

A recently updated Cochrane review of 22 trials of moderate quality, found that fluoride varnish, applied two to four times a year, is associated with a reduction of 43% in caries in permanent teeth and 37% in primary teeth of children and adolescents, compared to placebo or no treatment (Marinho *et al.*, 2013). This substantial caries-inhibiting effect of varnish was not influenced by caries level of the population or by exposure to other sources of fluoride. There is agreement that more high quality trials on the efficacy of fluoride varnish at preventing caries are required, particularly in the primary dentition (Carvalho *et al.*, 2010; Poulsen, 2009) and for adults (Petersson *et al.*, 2004). The optimum application frequency for fluoride varnish has yet to be established, with most studies reporting from one to four applications per year.

Although the fluoride concentration is typically very high, the nature of varnish lends itself to controlled, precise application to specific tooth surfaces. A single 0.25 ml ap-

plication of fluoride varnish with 22,600 ppm F contains 5.65 mg of fluoride ion, which is well below the probably toxic dose (PTD) for fluoride of 5 mg/kg body weight, even if all the varnish dispensed is swallowed. A recent study of the pharmacokinetics of fluoride in six toddlers aged 12 to 15 months after application of 5% sodium fluoride varnish concluded that “occasional application of fluoride varnish following American Academy of Pediatrics guidance is safe for toddlers” (Milgrom *et al.*, 2014).

In countries with widespread fluoridated water such as Australia, Republic of Ireland and the United States, fluoride varnish is recommended only for patients at elevated risk of caries, whereas in countries with limited or no water fluoridation such as England and Scotland, fluoride varnish is recommended for all children and young adults, with the frequency of application increased for those at elevated risk of caries.

Because fluoride varnish is quick and easy to apply, it is increasingly being recommended for use in young or pre co-operative children as part of an individual treatment plan and also as part of community-based fluoride varnish programmes targeted at high caries risk populations. Although originally only applied by dentists and dental hygienists, fluoride varnish is now applied by trained dental nurses, and, in some countries, by trained non-dental healthcare professionals as a means of increasing access to this preventive intervention particularly for very young children (Moyer, 2014; Okunseri *et al.*, 2009).

There is limited evidence for the effectiveness of fluoride varnishes at reducing dentine hypersensitivity (Merika *et al.*, 2006; Ritter *et al.*, 2006).

12.3 Fluoride gels

Fluoride gel is available for professional use, and also for self-application. It has a viscous texture and has the advantage that it can be applied in a tray to treat an entire dental arch at one time. Other methods of application include using cotton wool buds, floss or a toothbrush. The concentration of fluoride in gel typically ranges from 5,000 ppm to 12,300 ppm and formulations with low pH (acidulated phosphate fluoride (APF) gel) and neutral pH (sodium fluoride) gels are available. APF gel is the most widely used professionally applied fluoride gel. Neutral gels are recommended for patients with porcelain restorations to avoid the possibility of a low pH gel etching these restorations.

The effectiveness of fluoride gels at preventing caries in permanent teeth of children is established (Marinho *et al.*, 2002). However, in children at low caries risk, fluoride gel application may not provide any additional benefit. Fluoride gel is therefore recommended for children (and adults) at increased risk of developing caries.

The application time for professionally applied gels is 4 minutes and the frequency of application is up to 4 times a year, depending on caries risk. The technique for professional application of fluoride gel should aim to minimise the risk of swallowing the gel (European Academy of Paediatric Dentistry, 2009). This can be achieved by having the patient sitting upright during application, applying the gel to one arch at a time, using suction throughout the procedure and encouraging the patient to spit out any residual gel after application.

Self-applied fluoride gel is applied more frequently, either daily or weekly, and is recommended for high risk individuals, such as those undergoing fixed appliance orthodontic treatment or patients with hyposalivary function. Patients using self-applied fluoride gels should follow the manufacturer's instructions carefully, to ensure appropriate use of the product. Self-applied fluoride gel may also be used in school-based caries-preventive programmes 6-12 times a year.

Because of the possibility of excessive ingestion of fluoride from gel, particularly in young children, guidelines on the use of fluoride gel generally recommend a threshold age, below which fluoride gel should not be applied. This varies between 6 years of age (Weyant *et al.*, 2013; European Academy of Paediatric Dentistry, 2009) and 10 years of age (Australian Research Centre for Population Oral Health, 2006).

12.4 Fluoride foam

Fluoride foam is a relatively recent product which has the same fluoride concentration (12,300 ppm), pH (3-4) and method of application (tray) as conventional APF gel. The main advantage of foam over gel is that less material needs to be used (Whitford *et al.*, 1995) and therefore the patient's risk of ingesting excess fluoride is reduced. However, few studies have evaluated its effectiveness at preventing caries and consequently there is insufficient evidence for fluoride foam to be recommended for routine caries prevention.

12.5 Slow-release fluoride devices

The objective of a slow-release fluoride device is to produce a consistent level of fluoride intra-orally, over a long period of time (1-2 years) without the need for regular professional involvement or patient compliance.

The intra-oral devices currently in use are of two types: the copolymer membrane device and the fluoride glass bead device. The devices are usually attached to the buccal surface of a posterior tooth either by direct bonding, or by means of an orthodontic band or plastic bracket.

While there is evidence from *in vivo* trials that slow release fluoride devices can produce a sustained increase in salivary fluoride levels (Toumba *et al.*, 2009) to date there is insufficient evidence from randomised control trials to determine the caries-inhibiting effect of slow-release fluoride devices (Chong *et al.*, 2014).

12.6 Silver diamine fluoride

Silver diamine fluoride ($\text{Ag}(\text{NH}_3)_2\text{F}$) has been advocated as an agent to arrest cavitated caries lesions in addition to preventing the formation of new lesions, particularly in resource-poor situations where access to dental care is limited (dos Santos *et al.*, 2012). Silver diamine fluoride (SDF) is a low-cost product that is quick and simple to apply, even in very young children, and can be used by trained non-dental health professionals. SDF is commercially available at concentrations from 10% up to 38%, with the latter concentration containing 44,800ppm fluoride. The mechanism of action of SDF is thought to be through a combination of remineralisation (formation of fluorapatite) and anti-microbial effects of silver (Rosenblatt *et al.*, 2009). Evidence for the effectiveness of SDF at

preventing and arresting caries is currently limited in both quantity and quality. Further well-designed trials that can overcome the problem of blind outcome assessment, and that take into account any potential adverse effects and the safety of SDF are required to establish if SDF has a role in the management of caries.

12.7 Fluoride mouthrinses

Commercial or over-the-counter mouthrinses represent one of the fastest growing sectors of the oral care industry in recent years. In the UK for example, sales of mouthrinse increased by 44% between 2005 and 2010 (www.mintel.com). Mouthrinses containing fluoride are recommended as part of a caries-preventive strategy for high caries risk individuals, such as patients undergoing orthodontic treatment or patients with hyposalivary function. These mouthrinses typically contain 100 – 500 ppm F and are used once or twice daily. Fluoride mouthrinse containing 900 ppm F has traditionally been used in weekly or fortnightly school-based mouthrinsing programmes in children in non-fluoridated areas with high caries prevalence. These two distinct regimens (individual daily use and community-based weekly/fortnightly use) are sometimes referred to as the low potency/high frequency technique and the high potency/low frequency technique, respectively - use of fluoride mouthrinse at these two main strengths and rinsing frequencies is associated with clear reduction in caries of the order of 26% in children, regardless of other sources of fluoride (Marinho *et al.*, 2003c). There is also some evidence for the effectiveness of fluoride mouthrinse at preventing root caries (Twetman *et al.*, 2004). Recent Swedish guidelines on adult oral health have recommended the daily use of 900 ppm F mouthrinse for adults at increased risk of caries (National Board of Health and Welfare (Socialstyrelsen) Sweden, 2011), marking the introduction of a third mouthrinsing regimen – high potency/high frequency.

Although fluoride mouthrinsing programmes using 225 ppm F operate in over 60% of preschools and kindergartens in Japan (Komiyama *et al.*, 2014), the use of fluoride mouthrinse is not generally recommended for children below the age of 6 or 7 years of age, because most young children lack the ability to spit out effectively. At this age, there is little or no danger of acute toxic reactions with mouthrinse for home use, which typically contains 225 – 450 ppmF as long as it is used in accordance with manufacturer's instructions and is stored out of reach of young children. The margin of safety for acute toxicity with school-based 900-ppm fluoride mouthrinse is wide (10 ml contains 9 mg F) which is over 10 times lower than the probably toxic dose (PTD) for a 6-year-old child of average weight (20kg).

The ethanol content of home-use mouthrinses is also of concern, particularly for children and for those wishing to avoid alcohol (FDI Commission, 2002). Alcohol-free formulations are increasingly being made available, and should be recommended.

Where fluoride toothpaste is in widespread use, fluoride mouthrinse should ideally be used at a different time to toothbrushing to maintain intra-oral fluoride levels (Australian Research Centre for Population Oral Health, 2006; Public Health England, 2014).

12.8 Summary

1. Professionally applied and high fluoride self-administered topical fluorides are generally indicated for persons and groups with moderate and high caries activity and for patients with special needs, especially in communities with low exposure to fluoride.
2. Fluoride varnishes and silver diamine fluoride offer advantages of ease of use and the potential to be applied to very young children by trained non-dental health professionals. However, further high-quality evidence for the effectiveness of both modalities preventing or arresting caries in primary teeth is required.
3. In communities with low exposure to fluoride, school-based fluoride rinsing programmes are recommended, but their adoption should be based on the cost of implementation and the caries status of the community.

13. Multiple fluoride exposure

Most clinical trials involving the use of fluorides in caries prevention have tested a single product. In many parts of the world, however, exposure to fluoride from multiple sources is the rule rather than the exception: e.g. people in fluoridated areas brush their teeth with fluoride toothpastes, and anyone anywhere can have a significant, but usually unknown, intake of systemic fluoride from food and drink in addition to their use of fluoride toothpaste.

Exposure to multiple sources of fluoride can be beneficial or undesirable. It can be beneficial in the sense that fuller advantage is being taken of the several ways in which fluorides act to prevent caries, but it can also increase the potential for fluorosis. Some multiple exposure is controlled, as when a dentist applies fluoride gel or varnish to a caries-susceptible patient who is using a fluoride toothpaste, but some exposure, for example to fluoride in food and drinks and inappropriate use of fluoride toothpastes is not. It is the uncontrolled systemic exposure to fluoride, sometimes from unsuspected sources, that is the principal public health concern. Periodic monitoring of fluoride exposure in a population, in order to determine whether systemic exposure is low, optimal or high, as well as regular monitoring of fluorosis prevalence and severity in children (see Section 5), enables those responsible for public health to determine whether further action is called for. WHO emphasizes that public health actions are needed to provide sufficient fluoride intake in areas where fluoride exposure is suboptimal for prevention of dental caries, while additional recommendations are given on reducing excess fluoride in areas where severe adverse health effects are common (WHO, 2010).

Use of more than one form of fluoride in a caries-prevention programme usually provides additive benefits (Marinho *et al.*, 2004) but sometimes the cost-effectiveness is low. For example, if fluoridated mouthrinsing is introduced to children with low to moderate caries activity who drink fluoridated water and brush regularly with fluoride toothpaste, the minor additional benefit may be not worth the operational costs of the programme. By contrast, fluoridated mouthrinsing among children with high caries prevalence who have no other exposure to fluoride would

clearly be cost-effective. Dental public health administrators should be aware of the total fluoride exposure in the population before introducing any fluoride programme for caries prevention. The likely cost-effectiveness of any such programme has to be judged in the light of existing exposure and caries prevalence in the target population.

13.1 Summary

1. Exposure to fluoride from multiple sources in young children, whether controlled or uncontrolled, can be both beneficial in terms of reduced caries and undesirable in terms of risk of enamel fluorosis. However only one form of systemic fluoride, (water, salt, milk or tablets/drops) should be used.
2. Those responsible for dental public health should be aware of the total fluoride exposure in the population before introducing any additional fluoride programme for caries prevention, and the cost-effectiveness of such programmes should be carefully considered.

14. Fluorides and adult dental health

Since the use of fluorides, whether through community programmes, professionally applied or self-applied, have been shown to be effective in reducing dental caries in children and adolescents, it is not unreasonable to speculate that this public health measure would, in the long term, have a positive impact on the oral health of adults. There is increasing evidence that this in fact is the case. A systematic review of the effectiveness of self- and professionally applied fluoride and water fluoridation among adults was reported recently (Griffin *et al.*, 2007). Using a random effects model to estimate the effect size (absolute difference in annual caries increment or relative risk ratio) for all adults aged 20 or more years and for adults aged 40 or more years, 20 studies satisfied the inclusion criteria. Amongst studies published after or during 1980, any fluoride (self- and professionally applied or water fluoridation) annually prevented 0.29 (95%CI:0.16-0.42) carious coronal and 0.22 (95%CI:0.08-0.37) carious root surfaces. The prevented fraction for water fluoridation was 27% (95% CI:19%-34%). The authors concluded that these findings suggest that fluoride prevents caries among adults of all ages. In a national survey of adult dental health in the Republic of Ireland in 2002, the sample examined included random samples of 35-44 year old life-time residents of fluoridated and non-fluoridated communities (Whelton *et al.*, 2007). Using multivariate analysis to take account of confounding factors, exposure to fluoridated water supplies was significant in reducing the odds of being in the high risk group.

Two recent studies conducted amongst Australian defence force recruits (Mahoney and Slade, 2008; Hopcraft *et al.*, 2009) have reported significantly lower mean DMFT levels amongst recruits who had been life-time residents of fluoridated communities. For example, the latter reported a cross-sectional study involving 1,084 Australian Army recruits aged 17-35 years. Data were obtained from a clinical dental examination including bitewing radiographs, and a questionnaire elicited socio-demographic data and history on lifetime exposure to fluoridated drinking water.

Recruits with lifetime exposure to fluoridated drinking water had 25 per cent less caries experience compared with recruits who had no exposure to fluoridated drinking water after adjusting for the effects of age, gender, education and socio-economic status. Similar results were obtained in the study undertaken by Mahoney and Slade (2008) involving 876 army personnel aged 17-36 years. The authors concluded that the degree of lifetime exposure to fluoridated drinking water was inversely associated with DMFT in a dose-response manner. More recently a systematic review on the effectiveness of supplemental fluoride use for moderate and high caries risk adults was undertaken (Gibson *et al.*, 2011). A comprehensive search of the literature was completed using multiple databases. Studies included were randomized control trials (RCT) or clinical trials conducted in moderate or high caries risk adult populations, evaluating self- or professionally applied fluoride with the outcomes of caries reduction/remineralization. Sodium fluoride rinses, toothpastes, gels and varnishes each showed a positive effect in preventing dental caries in high risk adults. The evidence regarding sodium fluoride varnish is related primarily to root caries and older adults.

A widely used measure of adult oral health is the extent of loss of natural teeth. Neidell *et al.* (2010) undertook an analysis of the data collected in annual surveys conducted by the Center for Disease Control in 24 states in the USA. Using data collected from 1995 to 1999, the authors estimated the internal regression model relating community water fluoridation (CWF) with tooth loss. The results indicated that CWF levels in the county of residence at the time of respondents' birth was significantly related to tooth loss but the respondents' current CWF levels were not. In addition the impact of CWF exposure was larger for individuals of lower socioeconomic status. This study suggests the benefits of CWF may be larger than previously believed and that CWF had a lasting improvement in racial/ethnic and economic disparities in oral health. In the adult survey conducted in the Republic of Ireland (Whelton *et al.*, 2007) two measures of tooth loss were adopted in the analysis which included a multivariate approach to take account of confounding factors. The percentage of adults aged 35-44 years who were edentulous was found to have declined substantially in the period 1990-2002 in life-time residents of both fluoridated and non-fluoridated communities. In 1990, the percentage edentulous of the fluoridated group was 2.4 compared with 6.1 in the non-fluoridated group. The corresponding 2002 figures were 0.3% and 1.2%. A widely used measure of retention/loss of natural teeth is the percentage with 20 or more natural teeth present. The figures for the Republic of Ireland for this outcome measure in 2002 were 92.4% in the fluoridated group compared with 83.2% in the non-fluoridated group. A similar finding was reported by Berta *et al.* (2009) in a study of 1,159 adults aged 35-44 years in Brazil. The percentage in this study with 20 or more teeth present was 64.8% in the fluoridated group compared with 56.8% in the non-fluoridated.

Whilst the above studies are consistent in showing that the use of fluorides is effective in improving the oral health of adults, further studies are recommended.

15. Recommendations

1. Community water fluoridation is safe, effective in caries prevention and very likely to be cost effective and should be introduced and maintained wherever it is socially acceptable and feasible. The optimum water fluoride concentration will normally be within the range 0.5-1.0 mg/L.
2. Salt fluoridation, at a minimum concentration of 250 mg F/kg salt, should be considered as a practical alternative wherever water fluoridation is not socially acceptable or feasible.
3. Encouraging results have been reported with milk fluoridation. Milk fluoridation programmes are very cost-effective particularly when part of a national or community school health programme or when implemented within the context of a diet and nutrition scheme.
4. There is a need to carry out detailed fluoride mapping of existing water sources, as well as hydrological studies to show flow lines, and hydrogeochemical surveys in areas where fluorosis is endemic. Governments in the affected areas should establish clear guidelines on exploitation of groundwater so that sinking boreholes in high fluoride zones can be avoided.
5. Countries that have industries that emit fluoride into the atmosphere or have mines of fluoride-rich minerals should introduce and enforce environmental protection measures.
6. Dietary practices that increase the risks of infants and young children being overexposed to fluoride from all sources should be identified and appropriate action taken to reduce fluoride exposure to an optimal level.
7. Periodic urinary fluoride monitoring in a population, as well as regular monitoring of enamel fluorosis prevalence and severity in children enables those responsible for dental public health to adjust exposure to fluoride if needed.
8. In view of the endemic nature of unsightly enamel fluorosis in a number of regions, research on the development of affordable technology for partial defluoridation in households and communities is recommended.
9. The effectiveness of caries-preventive programmes should be assessed when existing and new schemes are introduced.
10. Fluoride tablets and drops have limited application as a public health measure. In areas with medium to low caries prevalence a conservative prescribing policy should be adopted. In areas with high caries prevalence, a dosage regimen should be used that takes into account age of the child and fluoride exposure including the fluoride content of the drinking-water.
11. Only one systemic fluoride measure should be used at any one time in a community or on an individual basis unless the child is at high risk for dental caries.

12. WHO recommends use of effective fluoridated toothpaste at the level of 1000 to 1500 ppm F. Because fluoride toothpastes are a highly effective means of caries control, every effort must be made to ensure the availability of affordable fluoride toothpastes for use in developing countries. As the use of fluoride toothpastes is a public health measure, it would be in the interest of countries to exempt them from the duties and taxation applied to cosmetics.
13. Fluoride toothpaste tubes should carry advice that, for children under 6 years of age, brushing should be supervised to minimize swallowing and only a very small amount (less than 5 mm or 'pea' sized

amount or smear (0.25g)) should be placed on the brush or chewing-stick. The caries-preventive effectiveness of toothpastes with lower levels of fluoride, manufactured especially for use by children is less well established.

14. In low-fluoride communities, school-based brushing or fluoride mouthrinsing programmes can be recommended, but their adoption should be based on the cost of implementation and the caries status of the community. Fluoride mouthrinsing is not recommended in young children.
15. Further research on the effectiveness of fluoride in improving the dental health of adults is recommended.

Annexe 1. Worldwide totals for populations with artificially and naturally fluoridated water

The estimated worldwide total of people supplied with artificially fluoridated water as at April 2011 is 369,226,000 in 25 countries, including the United Kingdom, the United States, Canada, Brazil, Chile, Argentina, Peru, Panama, Guyana, Guatemala, Republic of Ireland, Spain, Serbia, Australia, New Zealand, Fiji, Malaysia, Singapore, Vietnam, Brunei, China (Special Administrative Region of Hong Kong), Papua New Guinea, Republic of Korea (South Korea), Israel and Libya. See Table 1.

Natural fluoridation in the 25 countries operating artificial fluoridation schemes

In the 25 countries with artificially fluoridated water there are an estimated 18,061,000 million people drinking naturally fluoridated water at or around the optimal level. That brings the total in these 25 countries consuming optimally fluoridated water to around 387,287,000 million.

Other countries with natural fluoridation

In addition, there are a further 27 countries with naturally fluoridated water supplied to an estimated 239,903,000 million people. However, it should be stressed that, in many instances, the naturally occurring fluoride level is in excess of the optimum – for example, in China, India, Argentina, Tanzania, Zambia and Zimbabwe.

Total worldwide population drinking optimally fluoridated water

General estimates for the number of people around the world whose water supplies contain naturally fluoridated water at the optimum level for oral health are around 50 million. This means that, when the numbers of people with artificially (369.2 million) and naturally fluoridated water supplies (50 million) at the optimum level are added together, the total is around 437.2 million.

Table 1. Estimated numbers of people supplied with artificially fluoridated water around the world

<i>Country</i>	<i>Estimated number of people receiving artificially fluoridated water</i>	<i>% of total population (based on 2009/10 population estimates)</i>
Argentina	3,100,00	8%
Australia ¹	17,600,00	79%
Brazil ²	73,200,000	38%
Brunei ³	375,000	92%
Canada ⁴	14,260,000	42%
Chile ⁵	11,000,000	64%
China (Special Administrative Region of Hong Kong)	6,968,000	100%
Fiji	300,000	35%
Guatemala	1,800,000	13%
Guyana	45,000	6%
Republic of Ireland ⁶	3,250,000	73%
Israel ⁷	5,272,000	69%
Libya	400,000	7%
Malaysia ⁸	20,700,000	73%
New Zealand ⁹	2,330,000	53%
Panama	510,000	15%
Papua New Guinea	102,000	2%
Peru	500,000	2%
Serbia	300,000	4%
Singapore	5,080,000	100%
Republic of Korea (South Korea) ¹⁰	2,820,000	6%
Spain ¹¹	4,250,000	9%
United Kingdom ¹²	5,797,000	9%
United States ¹³	185,767,000	60%
Vietnam ¹⁴	3,500,000	4%
Total	369,226,000	

Notes on sources of information:

Unless otherwise stated, the figures given are based on pre-2003 data.

1. Sources for Australia include:

Queensland Government, 2008: *Timetable for water fluoridation in Queensland*.

Centre for Oral Health Strategy, New South Wales Government (2011): *Support for water fluoridation in New South Wales – June 2011 update*.

Department of Health, Victorian Government, Australia (2010): *Water fluoridation – community information*.

2. Sources for Brazil include:

Brazilian Institute of Geography and Statistics, (2008): *Communities with fluoridated public water supplies*.

Pucca Junior, G.A, Costa J.F., Chagas, L. and Sivistre, R.M. (2009): Oral health policies in Brazil. *Brazilian Oral Research*, 23, suppl 1.

Narvai PC (2000): Dental caries and fluorine – A 20th century relationship. *Ciencia and Saude Coletiva* 5, 381-392.

3. Sources for Brunei include:

Cheong, M., Department of Dental Services, Ministry of Health, Negara Brunei Darussalam (2011): *Effective Uses of Fluorides in Brunei Darussalam*. Paper presented at a WHO/FDI/IADR scientific workshop, Thailand, March 2011.

4. Sources for Canada include:

Community Dental Health Services Research Unit (2007): *Provincial and territorial estimates for community water fluoridation coverage in 2007*. Toronto: Faculty of Dentistry, University of Toronto.

Rabb-Waytowich, D. (2009): Water fluoridation in Canada – past and present. *Journal of the Canadian Dental Association*, 75, 451-454.

5. Sources for Chile include:

Ministry of Health, Chile (2011): *Fluoridation of drinking water*. www.redsalud.gov.cl/noticias/noticias.php?id_n=201

6. Sources for the Republic of Ireland include:

An evaluation of the delivery and monitoring of water fluoridation in Ireland. Commissioned by the Irish Department of Health and Children from the Department of Public and Child Dental Health, Dublin Dental School and Hospital, Trinity College, Dublin.

7. Sources for Israel include:

Ministry of Health, Israel, July 2011

8. Sources for Malaysia include:

Statement from the Malaysian Health Ministry (Oct. 2010): Published in the Star online, 31 Dec. 2010.

Dato' Dr Norain bt Abu Talib, Principal Director of Oral Health, Malaysian Ministry of Health, and Prof. Ishak Abdul Rashak, Dept. of Community Dentistry, University of Malaysia, Kuala Lumpur. (2011): *Effective use of fluorides in Malaysia*. Paper presented at a WHO/FDI/IADR scientific workshop in Thailand, Mar. 2011.

9. Sources for New Zealand include:

Ministry of Health, New Zealand (2010): *Drinking water for New Zealand – fluoridated supplies at 8th March 2010*.

Ministry of Health, New Zealand (2010): *Drinking water for New Zealand – treatment plants for fluoride*.

10. Sources for the Republic of Korea (South Korea) include:

Jin, B.H. and Lee, S.G., Dept. of Preventive and Social Dentistry, Seoul National University, and Paik, D.I., Korean Dental Assoc..(2011): *Public use of fluoride for the prevention of dental caries in Korea*. Paper presented at a WHO/FDI/IADR scientific workshop in Thailand, Mar. 2011.

11. Sources for Spain include:

Sala, E.C. and Garcia, P.B. (2005): *Preventive and community dentistry – principles, methods and applications*. Masson SA, Barcelona.

12. Sources for the United Kingdom include:

British Fluoridation Society (2012): Survey of localities in England with water fluoridation schemes. See *One in a Million* at www.bfsweb.org.

13. Sources for the United States include:

US Centers for Disease Control and Prevention (2008): *2008 Water Fluoridation Statistics* at www.cdc.gov/fluoridation/statistics/2008stats.htm

US Centers for Disease Control and Prevention (2008): *Morbidity and Mortality Weekly Report*, 11th July 2008/57(27); 737-741, *Populations receiving optimally fluoridated drinking water – United States, 1992-2006*.

14. Sources for Vietnam include:

Trinh Dinh Hai and Nguyen Thi Hong Minh, National Hospital of Odonto-Stomatology, Vietnam (2011): *The Public Use of Fluoride for Caries Prevention in Vietnam*. Paper presented at a WHO/FDI/IADR scientific workshop in Thailand, Mar. 2011.

Prepared by Paul Castle based on, *One in a million - the facts about water fluoridation*, 3rd edn. Manchester: British Fluoridation Society, 2012.

Annexe 2. Worldwide use of fluoridated salt - Availability of fluoridated domestic salt by region, programme status and market share

Region	Country	Approx. country population	F-Salt Potential % of population	Programme scope	Market Share
Africa					
	Madagascar	18,000,000		Partially available	
Americas					
	Belize	333,200		Partially available	
	Bolivia	10,000,000		Partial coverage	
	Colombia	46,406,000		National programme	
	Costa Rica	4,608,000		National programme	
	Cuba	11,000,000	100	National programme	100
	Dominican Republic	10,000,000		National programme	
	Ecuador	14,307,000		National programme	
	El Salvador	5,744,113		Baseline studies	
	Grenada	110,000		Baseline studies	
	Guatemala	13,276,517		Baseline studies	
	Honduras	8,000,000		Baseline studies	
	Jamaica	2,800,000	100	National programme	98
	Mexico	112,000,000		National programme (with exceptions ¹)	
	Paraguay	6,300,000		Not started	
	Peru	29,500,000		National programme	
	Trinidad and Tobago	1,317,714		Available	
	Uruguay	3,494,382	96	National programme (with exceptions ¹)	
	Venezuela	29,105,632		National programme (with exceptions ¹)	
Caribbean Countries and Islands				Available - Programme not identified	
Europe ²					
	Armenia	3,262,200		Available	
	Austria	8,414,638		National programme	
	Belarus	9,490,000		National programme	
	Belgium	11,007,020		Available	
	Czech Republic	10,535,811		National programme	
	France	65,821,885		National programme	
	Germany	81,799,600		National programme	
	Greece	10,787,690		Available	
	Greenland	56,615		Available	
	Hungary	10,198,315		Available	
	Poland	38,186,860		Trial - Available	
	Romania	21,904,551		Available	
	Slovenia	2,048,951		Available	
	Spain	46,030,109		Potasas, Navarra (status unknown)	
	Switzerland	7,866,500		National programme	
	Turkey	73,722,988		In process (status unknown)	
Eastern Mediterranean					
	Iran	74,700,000		EU approved	
	Lebanon	4,224,000		Available	
South East Asia					
	Nepal	29,331,000		Baseline studies	
Western Pacific					
	Cambodia	14,805,358		In process	
	China, Wuhan city	9,785,392		Trial	
	Laos	6,800,000		In process	
	Philippines	94,013,200		Interest	
	Vietnam	90,549,390		In process	

¹with exceptions - relates to populations with adequate fluoride from other sources; ² EU has approved the addition of both Potassium fluoride and Sodium fluoride to salt for caries prevention; Table prepared by Professor Andrew Rugg-Gunn

Annexe 3. Worldwide use of fluoridated milk

	UK	The Russian Federation	Chile	Thailand
Year programme started	1993	1994	1994	2000
Number of participating children	4,000	29,000	175,000	1,410,300
Age (years) of participating children	3-11	3-7	6-14	3-12
Daily dosage (mgF)	0.8	0.5	0.85	0.5

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References

- American Dental Association Council on Scientific Affairs (2014): Fluoride toothpaste use for young children. *Journal of the American Dental Association* **145**, 190-191.
- American Water Works Association (2004): *Water fluoridation principles and practices: Manual of water supply practices - M4* 5th edn. Denver, CO: AWWA.
- Australian Government, National Health and Medical Research Council. (2007): A Systematic Review of the Efficacy and Safety of Water Fluoridation. www.nhmrc.gov.au/publications/synopses/eh41syn.htm
- Australian Research Centre for Population Oral Health, ARCPPOH (2012): *Fluoride review guidelines outcomes of fluoride consensus workshop 2012*. www.adelaide.edu.au/arcposh/dperu/fluoride/ARCPPOH_FluorideOct2014.pdf
- Australian Research Centre for Population Oral Health, Dental School, University of Adelaide, South Australia (2006): The use of fluorides in Australia; guidelines. *Australian Dental Journal* **51**, 195-199.
- Baez, R.J. (2001): *Epidemiological surveillance system for salt fluoridation programs in the region of the Americas, Proceedings of the eighth world salt symposium, volume II*, page 1239. Editor: Geertman, R.M. Amsterdam: Elsevier Science B.V.
- Baez, R.J., Marthaler, T.M., Baez, M.X. and Warpeha R.A. (2010): Urinary fluoride levels in Jamaican children in 2008, after 21 years of salt fluoridation. *Schweiz Monatsschr Zahnmed* **120**, 21-28
- Baker, I.A., Elwood, P.C., Hughes, J., Jones, M., Moore, F. and Sweetnam, P.M. (1980): A randomised controlled trial of the effect of the provision of free school milk on the growth of children. *Journal of Epidemiology and Community Health*, **34**, 31-34.
- Bánóczy, J., Petersen, P.E. and Rugg-Gunn, A.J. (2009): *Milk fluoridation for the prevention of dental caries*. Geneva: WHO.
- Bánóczy, J., Rugg-Gunn, A.J. and Woodward, M. (2013): Milk fluoridation for the prevention of dental caries. *Acta Medica Academica* **42**, 156-167.
- Bánóczy, J. and Rugg-Gunn, A.J. (2009): Clinical Studies. Ch.2 In: Bánóczy, J., Petersen, P.E. and Rugg-Gunn, A.J. eds, *Milk fluoridation for the prevention of dental caries*. Geneva: WHO.
- Bassin, E.B., Wypij, D., Davis, R.B. and Mittleman, M.A. (2006): Age-specific fluoride exposure in drinking water and osteosarcoma (Unites States). *Cancer Causes Control* **17**, 421-428.
- Berg, J., Gerweck, C., Hujoel, P., King, R., Krol, D., Kumar, J., Levy, S., Pollick, H., Whitford, G., Strock, S. and Aravamudan, K. (2011): Evidence-based clinical recommendations regarding fluoride intake from reconstituted infant formula and enamel fluorosis. *Journal of the American Dental Association* **142**, 79-87.
- Berta, L., Silva, D.D. and Sousa, M.L.R. (2009): Dental caries and tooth loss in adults in a Brazilian Southeastern State. *Journal of Applied Oral Science* **17**, 392-396.
- Blakey, K., Feltbower, R.G., Parslow, R.C., James, P.W., Gómez Pozo, B., Stiller, C., Vincent, T.J., Norman, P., McKinney, P.A., Murphy, M.F., Craft, A.W. and McNally, R.J. (2014): 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* **43**, 224-234.
- Boruff, C.S. (1934): Removal of fluorides from drinking waters. *Industrial and Engineering Chemistry*, **25**, 69-71.
- Bratthall, D., Hansel-Petersson, G. and Sundberg, H. (1996): Reasons for the caries decline: what do the experts believe? *European Journal of Oral Sciences* **104**, 416-422.
- British Fluoridation Society. (2012): *One in a million - the facts about water fluoridation*, 3rd edn. www.bfsweb.org/onemillion/onemillion.htm

- Buzalaf, M. A. R., Pessan, J. P., Honoria, H. M. and ten Cate, J.M. (2011): Mechanism of action of fluoride for caries control. *Monographs in Oral Science* **22**, 97-114.
- Buzalaf, M.A.R. (ed) (2011): Fluoride and the Oral Environment. In: *Monograph in Oral Science* **22**. Basel: Karger.
- Buzalaf, M.A.R. and Levy, S.M. (2011): Fluoride intake of children: considerations for dental caries and dental fluorosis. In: Fluoride and the Oral Environment. *Monograph in Oral Science* **22**, 1-19.
- Buzalaf, M.A.R. and Whitford, G.M. (2011): Fluoride Metabolism. In: Buzalaf, M.A.R. ed., Fluoride and the Oral Environment. *Monograph in Oral Science* **22**, 20-36.
- Buzalaf, M.A.R., Pessan, J.P., Honorio, H.M. and tenCate, J.M. (2011): Mechanisms of action of fluoride for caries control. In: 'Fluoride and the oral environment'. ed Buzalaf, M.A.R. *Monograph in Oral Science* **22** Basel, Karger.
- Cangetti, M.G., Milia, E. and Lingström, P. (2013): A systematic review on fluoridated food in caries prevention. *Acta Odontologica Scandinavica* **71**, 381-387.
- Camargo, J.A. (2003): Fluoride toxicity to aquatic organisms: a review. *Chemosphere* **50**, 251-264.
- Carvalho, D.M., Salazar, M., Oliveira, B.H., and Coutinho, E.S. (2010): Fluoride varnishes and decrease in caries incidence in preschool children: a systematic review. *Revista Brasileira de Epidemiologia* **13**, 139-149.
- Centers for Disease Control and Prevention (2001): Recommendations for using fluoride to prevent and control dental caries in the United States. *MMWR Recommendations and Reports* **50**, 1-42.
- Chankanka, O., Levy, S.M., Warren, J. J. and Chalmers, J.M. (2010): A literature review of aesthetic perceptions of dental fluorosis and relationships with psychosocial aspects/oral health-related quality of life. *Community Dentistry and Oral Epidemiology* **38**, 97-109.
- Chong, L.Y., Clarkson, J.E., Dobbryn-Ross L. and Bhakta S. (2014): Slow-release fluoride devices for the control of dental decay. *Cochrane Database of Systematic Reviews* 2014 Issue **11**. CD005101.
- Cochran, J.A., Ketley, C.E., Duckworth, R.M., van Loveren, C., Holbrook, W.P., Seppa, L., Sanches, L., Polychronopoulou, A. and O'Mullane, D.M. (2004): Development of a standardized method for comparing fluoride ingested from toothpaste by 1.5-3.5-year-old children in seven European countries. Part 2: Ingestion results. *Community Dentistry and Oral Epidemiology* **32** (Suppl 1), 47-53.
- Comber, H., Deady, S., Montgomery, E. and Gavin, A. (2011): Drinking water fluoridation and osteosarcoma incidence on the island of Ireland. *Cancer Causes Control* **22**, 919-924.
- Coop, C., Fitzgerald, A.C., Whyman, R.A., Lethaby, A., Beatson, E., Caddie, C., Drummond, B.K., Hegan, B., Jennings, D., Koopu, P.I., Lee, J.M. and Thomson, W.M. (2009): Summary of guidance for the use of fluorides. *New Zealand Dental Journal* **105**, 135-137.
- Dean, H.T. (1936): Chronic endemic dental fluorosis (mottled enamel). *Journal of the American Medical Association* **107**, 1269-1272.
- Dean, H.T. (1942): The investigation of physiological effects by the epidemiological method. In: *Fluorine and dental health*, Moulton, R.F. ed., pp23-31. Washington, DC: American Association for the Advancement of Science.
- Do, L.G. and Spencer, A.J. (2007): Risk-benefit balance in the use of fluoride among young children. *Journal of Dental Research* **86**, 723-728.
- dos Santos, V.E., de Vascócelos, F.M., Ribeiro A.G. and Rosenblatt A. (2012): Paradigm shift in the effective treatment of caries in school children at risk. *International Dental Journal* **62**, 47-51.
- Douglass, C.W. and Joshipuri, K. (2006): Caution needed in fluoride and osteocarcinoma study. *Cancer Causes Control* **17**, 481-482.
- Downer, M. (2007): Editorial: The STROBE initiative and its implications for dental public health research. *Community Dental Health* **24**, 194-197.
- Drinking Water Inspectorate. (2005): *Code of practice on technical aspects of fluoridation of water supplies 2005*. London: Drinking Water Inspectorate.
- Edgar, W.M. (2009): Basic science studies. In: Bánóczy, J., Petersen, P.E. and Rugg-Gunn, A.J. eds., *Milk fluoridation for the prevention of dental caries*, Ch.3. Geneva: WHO.
- Espelid, I. (2009): Caries preventive effect of fluoride in milk, salt and tablets: a literature review. *European Archives of Paediatric Dentistry* **10**, 149-156.
- EU Regulations (2009): <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1925:20091221:EN:PDF>
- European Academy of Paediatric Dentistry (2009): Guidelines on the use of fluoride in children: an EAPD policy document. *European Archives of Paediatric Dentistry* **10**, 129-135.
- European Commission (2004): European Union System for the Evaluation of Substances (EUSES). <http://ecb.jrc.ec.europa.eu/euses>
- European Food Safety Authority NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies (2013): Scientific opinion on Dietary Reference Values for fluoride. *EFSA Journal* **11**, 3332, 46pp. www.efsa.europa.eu/efsajournal.
- Fawell, J., Bailey, K., Chilton, J., Dahi, E., Fewtrell, L. and Magara, Y (2006): *Fluoride in drinking water*. London: IWA/WHO.
- FDI Commission (2002): Mouthrinses and dental caries. *International Dental Journal* **52**, 337-345.
- Forum on Fluoridation (2002): *Forum on Fluoridation 2002*. Dublin: Irish Government Stationery Office. <http://health.gov.ie/blog/publications/report-of-the-forum-on-fluoridation>
- Gibson, G., Jurasic, M.M. and Wehler, C.J. (2011): Supplemental fluoride use for moderate and high caries risk adults: a systematic review. *Journal of Public Health Dentistry* **71**, 171-184.
- Gillespie, G.M. and Baez, R. (2005): Development of salt fluoridation in the Americas. *Schweiz Monatsschr Zahnmed* **115**, 663-669.
- Goldman, A.S., Yee, R., Holmgren, C.J. and Benzan, H. (2008): Global affordability of fluoride toothpaste. *Global Health* **4**, 7.
- Gordon, S.L. and Corbin, S.B. (1992): Summary of workshop on drinking water fluoride influence on hip fracture on bone health. *Osteoporosis International* **2**, 109-117.
- Götzfried, F. (2006): Legal aspects of fluoride in salt, particularly within the EU. *Schweiz Monatsschr Zahnmed* **116**, 371-375.
- Griffin, S.O., Jones, K. and Tomar, S.L. (2001): An economic evaluation of community water fluoridation. *Journal of Public Health Dentistry* **61**, 78-86.
- Griffin, S.O., Regnier, E., Griffin, P.M. and Huntley, V. (2007): Effectiveness of fluorides in preventing caries in adults. *Journal of Dental Research* **86**, 410-415.
- Groeneveld, A., Van Eck, A.A. and Backer Dirks, O. (1990): Fluoride in caries prevention: is the effect pre- or post- eruptive? *Journal of Dental Research* **69** Spec No:751-5, 820-823.
- Hardwick, J., Teasdale, J. and Bloodworth, G. (1982): Caries increments over 4 years in children aged 12 at the start of water fluoridation. *British Dental Journal* **153**, 217-222.
- Health Canada (2010): *Fluoride and Human Health*. www.hc-sc.gc.ca/hl-vs/fyh-vsv/environ/fluor-eng.php#child
- Health Canada (2010): *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Fluoride*. Ottawa: Health Canada.
- Hillier, S., Cooper, C., Kellinray, S., Russell, G., Huges, H. and Coggan, D. (2000): Fluoride in drinking water and risk of hip fracture in the UK: a case-control study. *Lancet* **355**, 265-269.
- Ho, T.W.M., Wong, T.C. and Lo, E.C.M. (2011): Water fluoridation in Hong Kong. In: *The Workshop on 'Effective Use of Fluoride in Asia'*. Phang-Nga, Thailand, March 22-24, p82-85.
- Hopcraft, M.S., Yapp, K.E., Mahoney, G. and Morgan, M.V. (2009): Dental caries experience in young Australian Army recruits 2008. *Australian Dental Journal* **54**, 316-322.
- Hujoel, P. P., Zina, L. G., Moimaz, S. A. and Cunha-Cruz, J. (2009): Infant formula and enamel fluorosis: a systematic review. *Journal of the American Dental Association* **140**, 841-854.

- Iheozor-Ejiobar, Z., Worthington H.V., Walsh, T., O'Malley, L., Clarkson, J. E., Macey, R., Alam, R., Tugwell, P., Welch, V. and Glenny, A.M.(2015): Water fluoridation for the prevention of dental caries (Review). *The Cochrane Library*, Issue 6. <http://www.thecochranelibrary.com>
- International Programme on Chemical Safety (2002): *Environmental Health Criteria 227 Fluorides*. Geneva: World Health Organization.
- Ismail, A.I. and Hasson, H. (2008): Fluoride supplements, dental caries and fluorosis: a systematic review. *Journal of the American Dental Association* **139**, 1457-1468.
- Jones, S., Burt, B.A., Petersen, P.E. and Lennon, M.A. (2005): The effective use of fluorides in public health. *Bulletin of the World Health Organization* **83**, 670-676.
- Kim, F.M., Hayes, C., Williams, P.L., Whitford, G.M., Joshipura, K.J., Hoover, R.N. and Douglass, C.W. (2011): An assessment of bone fluoride and osteosarcoma. *Journal of Dental Research* **90**, 1171-1176.
- Knox, E.G. (1985): *Fluoridation of water and cancer: a review of the epidemiological evidence*. London: HMSO.
- Komiyama, K., Kimoto, K., Taura, K. and Sakai, O. (2014): National survey on school-based fluoride mouth-rinsing programme in Japan: regional spread conditions from pre-school to junior high school in 2010. *International Dental Journal* **64**, 127-137.
- Levine, R. (2004): *Millions saved-proven successes in global health*. Center for Global Development, Washington DC, Case 16, 137-140.
- Levy, S.M., Broffitt, B., Marshall, T.A., Eichenberger-Gilmore, J.M. and Warren, J.J. (2010): Associations between fluorosis of permanent incisors and fluoride intake from infant formula, other dietary sources and dentifrice during early childhood. *Journal of the American Dental Association* **141**, 1190-1201.
- Lippert, F (2013): An introduction to toothpaste - its purpose, history and ingredients. *Monographs in Oral Science* **23**, 1-14.
- Mahoney, G. and Slade, G.D. (2008): Lifetime fluoridation exposure and dental caries experience in a military population. *Community Dentistry and Oral Epidemiology* **36**, 485-492.
- Malinowska, E., Inkielewicz, I., Czarnowski, W. and Szefer, P. (2008): Assessment of fluoride concentration and daily intake by human from tea and herbal infusions. *Food and Chemical Toxicology* **46**, 1055-1061.
- Marinho, V., Higgins, J., Logan, S. and Sheiham, A. (2003a): Fluoride toothpastes for preventing dental caries in children and adolescents. *Cochrane Database of Systematic Reviews* 2003. Issue **1**, CD002278.
- Marinho, V., Higgins, J., Logan, S., and Sheiham, A. (2002): Fluoride gels for preventing dental caries in children and adolescents. *The Cochrane Database of Systematic Reviews* Issue **1**, CD002280.
- Marinho, V., Higgins, J., Logan, S., and Sheiham, A. (2003c): Fluoride mouthrinses for preventing dental caries in children and adolescents. *The Cochrane Database of Systematic Reviews* 2003, Issue **3**, CD002284.
- Marinho, V., Higgins, J., Logan, S., Sheiham, A. (2003b): Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents. *Cochrane Database of Systematic Review* 2003 Issue **4**, CD002782.
- Marinho, V.C., Worthington, H.V., Walsh T. and Clarkson, J.E. (2013): Fluoride varnishes for preventing dental caries in children and adolescents. *Cochrane Database of Systematic Reviews* 2013 Issue **7**, CD002279.
- Marinho, V.C.C., Higgins, J.P.T., Sheiham, A. and Logan, S. (2004): Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. *The Cochrane Database of Systematic Reviews* Issue **1**, CD002781.
- Marinho, R., Fajardo, J. and Morgan, M. (2011): Economic evaluation of dental caries prevention programs using milk and its products as the vehicle for fluorides: cost versus benefits. In: *Nutrients, dietary supplements, and nutraceuticals: cost analysis versus clinical benefit*, Ch.11; Watson, R.R., Gerald, J.K. and Preedy, V.R. eds. New York: Springer Science.
- Marinho, R., Morgan, M., Weitz, A. and Villa, A. (2007): The cost-effectiveness of adding fluorides to milk-products distributed by the National Food Supplement Program (PNAC) in rural areas of Chile. *Community Dental Health*, **24**, 75-81.
- Marinho, R., Villa, A., Weitz, A. and Guerrero, S. (2003): Prevalence of fluorosis in children aged 6-9 years old who participated in a milk fluoridation programme in Codegua, Chile. *Community Dental Health* **20**, 143-149.
- Marthaler, T.M. (2005): Overview of salt fluoridation in Switzerland since 1955, a short history. *Schweiz Monatsschr Zahnmed* **115**, 651-655.
- Marthaler, T.M. and Petersen, P.E. (2005): Salt fluoridation – an alternative in automatic prevention of dental caries. *International Dental Journal* **55**, 351-358
- McDonagh, M.S., Whiting, P.F., Wilson P.M., Sutton, A.J., Chestnutt, I., Cooper, J., Misso, K., Bradley, M., Treasure, E. and Kleijnen, J. (2000): Systematic review of water fluoridation. *British Medical Journal* **321**, 855-859.
- McGrady, M.G., Ellwood, R.P., Maguire, A. Goodwin, M. and Boothman, N. (2012): 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* **12**, 1122.
- McLaughlin, E.J., Sleeper, R.B., McNatty, D. and Raeli, C.L. (2006): Management of age-related osteoporosis and prevention of associated fractures. *Journal of Therapeutics and Clinical Risk Management* **2**, 281-295.
- Medical Research Council (2002): *Working Group report: Water fluoridation and health*. London : MRC.
- Menghini, G.D., Marthaler, T.M., Steiner, M. and Bandi, A. (1991): [Caries prevalence and gingival inflammation in conscripts in 1985: effect of preventive programmes.] *Schweizer Monatsschrift fur Zahnmedizin*, **101**, 1119-1126.
- Merika, K., HefitArthur, F., and Preshaw, P.M. (2006): Comparison of two topical treatments for dentine sensitivity. *European Journal of Prosthodontics and Restorative Dentistry* **14**, 38-41.
- Milgrom, P., Taves, D. M., Kim, A. S., Watson, G. E. and Horst, J. A. (2014): Pharmacokinetics of fluoride in toddlers after application of 5% sodium fluoride dental varnish. *The Journal of Pediatrics* **134**: e870-874.
- Min, L., Zhu, L., Zhang, B.X. and Petersen P.E. (2007): Changing use and knowledge of fluoride toothpaste by schoolchildren, parents and schoolteachers in Beijing, China. *International Dental Journal* **57**, 187-194.
- Moyer, V.A. on behalf of the US Preventive Services Task Force (2014): Prevention of dental caries in children from birth through age 5 years: US Preventive Services Task Force recommendation statement. *The Journal of Pediatrics* **133**, 1102-1111.
- Murray, J.J., Rugg-Gunn, A.G. and Jenkins, G.N. (1991): *Fluorides in Caries Prevention* 3rd edn. London: Butterworth-Heinemann , pp86-87.
- Näsman, P., Ekstrand, J., Granath, F., Ekblom, A. and Forell, C.M. (2013): Estimated drinking water fluoride exposure and risk of hip fracture: A cohort study. *Journal of Dental Research* **92**, 1029-1034.
- National Academy of Sciences Report (2006): *Fluoride in drinking water: A scientific review of EPA's standards*. Washington: National Academies Press. www.nap.edu/catalog/11571.html
- National Board of Health and Welfare (Socialstyrelsen) Sweden. (2011): *National guidelines for adult dental care in 2011: Scientific basis*. www.socialstyrelsen.se/SiteCollectionDocuments/nr-vuxentandvard-rekommendationsoversikt-karies.pdf

- National Health and Medical Research Council (2007): *A systematic review of the efficacy and safety of fluoridation*. Canberra: Australian Government.
- National Toxicology Program (NTP), (1990): *Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Fluoride (CAS No. 7681-49-4) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies), Technical Report 393*. Research Triangle Park, NC: NIH Publ. No 91-2848. U.S. Department of Health and Human Services, Public Health Services, National Institutes of Health
- Neidell, M., Herzog, K. and Glied S. (2010): The association between community water fluoridation and adult tooth loss. *American Journal of Public Health* **100**, 1980-1985.
- O'Mullane, D., James, P., Whelton H. and Parnell, C. (2012): Methodological issues in oral health research: intervention studies. *Community Dentistry and Oral Epidemiology* **40**(Suppl 1), 15-20.
- Okunseri, C., Szabo, A., Jackson, S., Pajewski, N. M., and Garcia, R.J. (2009): Increased children's access to fluoride varnish treatment by involving medical care providers: Effect of a medicaid policy change. *Health Services Research*, **44**, 1144-1156.
- Osterman, J.W. (1990): Evaluating the impact of municipal water fluoridation on the aquatic environment. *American Journal of Public Health*, **80**, 1230-1235.
- Parnell, C. and O'Mullane D. (2013): After-brush rinsing protocols, frequency of toothpaste use: fluoride and other active ingredients. *Monographs in Oral Science* **23**, 140-153.
- Pessan, J.P. and Buzalaf, M.A.R. (2011): Historical and recent biological markers of exposure to fluoride. In, Fluoride and the Oral Environment *Monograph in Oral Science* **22**, 52-65. Basel, Karger.
- Pessan, J.P. and Buzalaf, M.A.R. (2011): *Historical and recent biological markers of exposure to fluoride*. In, Buzalaf, M.A.R. ed., Fluoride and the Oral Environment. *Monograph in Oral Science* **22**, 52-65.
- Pessan, J.P., Tumba, K.J., and Buzalaf, M.A. (2011): Topical use of fluorides for caries control. *Monographs in Oral Science* **22**, 115-132.
- Petersen, P.E., Kwan, S., Zhu, L., Zhang, B.X. and Bian J.Y. (2008): Effective use of fluorides in the People's Republic of China: a model for WHO Mega Country initiatives. *Community Dental Health* **25** (Suppl 1), 257-267.
- Petersen, P.E. (2004): Challenges to improvement of oral health in the 21st century-the approach of the WHO Global Oral Health Programme. *International Dental Journal* **54**, 329-343.
- Petersen, P.E. (2008): World Health Organization global policy for improvement of oral health – World Health Assembly 2007. *International Dental Journal* **58**, 115-121.
- Petersen, P.E. and Baez R.J. (2013): *Oral Health Surveys Basic Methods 5th ed*. Geneva: World Health Organization.
- Petersen, P.E. and Kwan, S. (2004): Evaluation of community-based oral health promotion and oral disease prevention-WHO recommendations for improved evidence in public health practice. *Community Dental Health* **21** (Suppl), 319-329.
- Petersen, P.E. and Lennon, M.A. (2004): Effective use of fluorides for the prevention of dental caries in the 21st century: The WHO approach. *Community Dentistry and Oral Epidemiology* **32**, 319-321.
- Petersen, P.E. and Phantumvanit, P. (2012): Perspectives in the effective use of fluoride in Asia. *Journal of Dental Research* **91**, 119-121.
- Petersen, P.E., Hunsrisakul, J., Thearmontree, A., Pithpornchaiyakul, S., Hintao, J., Jürgeisen N. and Ellwood, R.P. (2015): School-based intervention for improving the oral health of children in southern Thailand. *Community Dental Health* **32**, 44-50.
- Petersen, P.E., Kwan, K. and Ogawa, H. (2015): Long term evaluation of the clinical effectiveness of community milk fluoridation in Bulgaria. *Community Dental Health* **32**, 1-5.
- Petersson, L.G., Magnusson, K., Hakestam, U., Baigi, A. and Twetman, S. (2011): Reversal of primary root caries lesions after daily intake of milk supplemented with fluoride and probiotic lactobacilli in older adults. *Acta Odontologica Scandinavica* **69**, 321-327.
- Petersson, L., Twetman, S., Dahlgren, H., Norlund, A., Holm, A.K., Nordenram, G., Lagerlof, F., Soder, B., Kallestal, C., Mejare, I., Axelsson, S. and Lingstrom P. (2004): Professional fluoride varnish treatment for caries control: a systematic review of clinical trials. *Acta Odontologica Scandinavica* **62**, 170-176.
- Phipps, K.R., Orwall, E.S., Mason, J.D. and Cauley, J.A. (2000): Community water fluoridation, bone mineral density and fractures: prospective study of effects in older women. *British Medical Journal* **321**, 860-864.
- Poulsen, S. (2009): Fluoride-containing gels, mouth rinses and varnishes: an update of evidence of efficacy. *European Archives of Paediatric Dentistry* **10**, 157-161.
- Public Health England, PHE (2014): *Delivering Better Oral Health - an evidence-based toolkit for prevention*. 3rd Edn. London: PHE.
- Public Health England: *Water fluoridation – health monitoring report for England 2014*. Public Health England. London.
- Ritter, A.V., de L. Dias, W., Miguez, P., Caplan, D.J. and Swift, E.J. Jr. (2006): Treating cervical dentin hypersensitivity with fluoride varnish: a randomized clinical study. *Journal of the American Dental Association* **137**, 1013-1020.
- Rosenblatt, A., Stamford, T.C. and Niederman, R. (2009): Silver diamine fluoride: a caries "silver-fluoride bullet". *Journal of Dental Research* **88**, 116-125.
- Royal Society of New Zealand and the Office of the Prime Minister's Chief Science Advisor (2014): Health effects of water fluoridation: A review of the scientific evidence. <http://www.royalsociety.org.nz/expert-advice/papers/yr2014/health-effects-of-water-fluoridation>
- Royal Society of New Zealand and the Office of the Prime Minister's Chief Science Advisor (2014): *Health effects of water fluoridation – a review of the scientific evidence*. Wellington: Royal Society of New Zealand. http://assets.royalsociety.org.nz/media/2014/08/Health-effects-of-water-fluoridation_Aug_2014_corrected_Jan_2015.pdf
- Rozier, R.G., Adair, S., Graham, F., Iafolla, T., Kingman, A., Kohn, W., Krol, D., Levy, S., Pollick, H., Whitford, G., Strock, S., Frantsve-Hawley, J., Aravamudhan, K. and Meyer, D.M. (2010): Evidence-based clinical recommendations on the prescription of dietary fluoride supplements for caries prevention: a report of the American Dental Association Council on Scientific Affairs. *Journal of the American Dental Association* **141**, 1480-1489.
- Rugg-Gunn, A.J. and Do, L. (2012): Effectiveness of water fluoridation in caries prevention. *Community Dentistry and Oral Epidemiology*, **40**, suppl 2, 55-64.
- Rugg-Gunn, A.J., Hackett, A.F., Appleton, D.R., Eastoe, J.E., Dowthwaite, L. and Wright, W.G. (1987): The water intake of 405 Northumbrian adolescents aged 12-14 years. *British Dental Journal* **162**, 335-340.
- Rugg-Gunn, A.J., Villa, A.E. and Buzalaf, M.A.R. (2011): Contemporary biological markers of exposure to fluoride. In, Buzalaf, M.A.R. ed., Fluoride and the Oral Environment. *Monograph in Oral Science* **22**, 37-51. Basel, Karger.
- Rugg-Gunn, A.J., Spencer, A.J., Whelton, H.P., Jones, C., Beal, J.F., Castle, P., Cooney, P.V., Johnson, J., Kelly, M.P., Lennon, M.A., McGinley, J., Morris, J., O'Mullane, D., Sgan-Cohen, H.D., Sharma, P.P., Thomson, W.M., Woodward, S.M. and Zusman, S.P. (2016). Critique of the review of 'Water fluoridation for the prevention of dental caries' published by the Cochrane Collaboration in 2015. *British Dental Journal*, in press.
- Scientific Committee on Health and Environmental Risks (SCHER) (2011): *Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water*. EU Brussels: EU.

- Scottish Intercollegiate Guidelines Network (2014): *SIGN 138: Dental Interventions to prevent caries in children*. www.sign.ac.uk/guidelines/fulltext/138/index.html.
- Singh, K.A. and Spencer, A.J. (2004): Relative effects of pre- and post-eruption water fluoride on caries experience by surface type of permanent first molars. *Community Dentistry and Oral Epidemiology* 32, 435-446.
- Singh, K.A., Spencer, A.J. and Brennan, D.S. (2007): Effects of water fluoride exposure at crown completion and maturation on caries of permanent first molars. *Caries Research*, 41, 34-42.
- Sutton, N., Kiersey, R., Farragher, L. and Long, J. (2015): *Health effects of water fluoridation*. Health Research Board, Dublin, Ireland.
- Toumba, K. J., Al-Ibrahim, N.S. and Curzon, M.E. (2009): A review of slow-release fluoride devices. *European Archives of Paediatric Dentistry* 10, 175-182.
- Truman, B., Gooch, B., Sulaimana, I., Gift, H., Horowitz, A., Evans, C., Griffin, S. and Carande-Kulis, V. (2002): Reviews of evidence on interventions to prevent dental caries, oral and pharyngeal cancers, and sports-related craniofacial injuries, and recommendations on selected interventions to prevent dental caries, oral and pharyngeal cancers, and sports-related craniofacial injuries *American Journal of Preventive Medicine* 23, 16-54.
- Twetman, S. (2009): Caries prevention with fluoride toothpaste in children: an update. *European Archives of Paediatric Dentistry* 10, 162-167.
- Twetman, S., Axelsson, S., Dahlgren, H., Holm, A.K., Källestål, C., Lagerlöf, F., Lingstrom, P., Mejare, I., Nordenram, G., Norlund, A., Petersson, L.G., and Soder, B. (2003): Caries-preventive effect of fluoride toothpaste: a systematic review. *Acta Odontologica Scandinavica* 61, 347-355.
- Twetman, S., Petersson, L., Axelsson, S., Dahlgren, H., Holm, A.K., Källestål, C., Lagerlöf, F., Lingstrom P., Mejare I, Nordenram G, Norlund A, Soder B. (2004): Caries preventive effect of sodium fluoride mouthrinses: a systematic review of controlled clinical trials. *Acta Odontologica Scandinavica* 62, 223-230.
- Villa, A., Anabalon, M., Zohouri, F.V., Maguire, A., Franco, A.M. and Rugg-Gunn, A.J. (2010): Relationships between fluoride intake, urinary fluoride excretion and fluoride retention in children and adults: An analysis of available data. *Caries Research* 44, 60-68.
- Villa, A.E. (2009a): The addition of fluoride to milk. In: *Milk fluoridation for the prevention of dental caries*, Ch.4; Bánóczy, J., Petersen, P.E. and Rugg-Gunn, A.J. eds. Geneva: WHO.
- Villa, A.E. (2009b): Evaluating fluoride exposure in milk fluoridation programmes. In: *Milk fluoridation for the prevention of dental caries*, Ch.6; Bánóczy, J., Petersen, P.E. and Rugg-Gunn, A.J., eds. Geneva: WHO.
- von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C. and Vandenbroucke J.P. (2008): Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Journal of Clinical Epidemiology* 61, 344-349.
- Walls, R., Zohoori V., Teasdale L., Landes D., Steen I.N., Moynihan P.J., Lloyd J., Omid N. and Maguire A. (2012): Compliance with school F-milk and non-F milk intake in 3 to 4 and 6 to 7 year old children. *Community Dental Health* 29, 188-192.
- Walsh, T., Worthington, H.V., Glenny, A.M., Appelbe, P., Marinho, V.C. and Shi, X. (2010): Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD007868.
- Warpeha, R., Beltran-Aguilar, E. and Baez, R. (2001): Methodological and biological factors explaining the reduction of dental caries in Jamaican school children between 1984 and 1995. *Pan American Journal of Public Health* 10, 37-44.
- Waterhouse, C., Taves, D. and Munzer, A. (1980): Serum inorganic fluoride: changes related to previous fluoride intake, renal function and bone resorption. *Clinical Science* 58, 145-152.
- Weyant, R.J., Tracy S.L., Anselmo, T., Beltrán-Aguilar, E. D., Donly, K.J., Frese, W.A., Hujoel, P.P., Lafolla, T., Kohn, W., Kumar, J., Levy, S.M., Tinanoff, N., Wright, J.T., Zero, D., Aravamudhan, K., Frantsve-Hawley, J. and Meyer, D.M. (2013): Topical fluoride for caries prevention. *Journal of the American Dental Association* 144, 1279-1291.
- Whelton, H., Crowley, E., O'Mullane, D., Woods, N., McGrath, C., Kelleher, V., Guiney, H. and Byrtek, M. (2007): *Oral Health of Irish Adults 2000-2002*. Dublin, Brunswick Press Ltd.
- Whitford, G.M. (2005): Fluoride metabolism when added to salt. *Schweiz Monatsschr Zahnmed* 115, 675-678.
- Whitford, G.M., Adair, S.M., McKnight Hanes, C.M., Perdue, E.C. and Russell, C.M. (1995): Enamel uptake and patient exposure to fluoride: comparison of APF gel and foam. *Pediatric Dentistry* 17, 199-203.
- WHO (2010): *Inadequate or excess fluoride: a major public health concern*. Geneva: World Health Organization.
- WHO (2014): *Basic methods for assessment of renal fluoride excretion in community prevention programmes for oral health*. Geneva: World Health Organization
- Wong, M.C., Glenny, A.M., Tsang, B.W., Lo, E.C., Worthington, H.V. and Marinho, V.C. (2010): Topical fluoride as a cause of dental fluorosis in children. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD007693. DOI: 10.1002/14651858.CD007693.pub2.
- Wong, M.C.M., Clarkson, J., Glenny, A.M., Lo, E.C.M., Marinho, V.C., Tsang, B.W.K., Walsh, T. and Worthington, H.V. (2011): Cochrane Reviews on the benefits/risks of fluoride toothpastes. *Journal of Dental Research* 90, 573-579.
- Woodward, S.M. (2009): The implementation of community based programmes. In: *Milk fluoridation for the prevention of dental caries*, Ch.5; Bánóczy, J., Petersen, P.E. and Rugg-Gunn, A.J., eds. Geneva: WHO.
- World Health Organization (2005): *Nutrients in Drinking Water: Water, Sanitation and Health Protection and the Human Environment*. Geneva: WHO.
- World Health Organization (2007): *Oral Health: action plan for promotion and integrated disease prevention*. Resolution WHA 60.17 May 2007, Geneva: WHO.
- Wright, J.T., Hanson, N., Ristic, H., Whall, C.W., Estrich, C.G. and Zentz, R.R. (2014): Fluoride toothpaste efficacy and safety in children younger than 6 years: a systematic review. *Journal of the American Dental Association* 145, 182-189.
- Yengopal, V., Chikte, U.M.E., Mickenautsch, S., Oliveira, L.B. and Bhayat, A. (2010): Salt fluoridation: a meta-analysis of its efficacy for caries prevention. *South African Dental Journal* 65, 60-67.
- Yeung, C.A., Chong, L.Y. and Glenny, A.M. (2015): Fluoridated milk for preventing dental caries. *Cochrane Database of Systematic Reviews* 2015 8, CD003876.
- Zohouri, F.V. and Rugg-Gunn, A.J. (2000): Total fluoride intake and urinary excretion in 4-year-old Iranian children residing in low-fluoride areas. *British Journal of Nutrition* 83, 15-25.
- Zohouri, F.V., Rugg-Gunn, A.J., Fletcher, E.S., Hackett, A.F., Moynihan, P.J., Mathers, J.C. and Adamson, A.J. (2004): Changes in water intake of Northumbrian adolescents 1980 to 2000. *British Dental Journal* 196, 547-552.