Published in final edited form as:

J Evid Based Dent Pract. 2014 June ; 14 Suppl: 95–102. doi:10.1016/j.jebdp.2014.02.004.

Focus on Fluorides: Update on the Use of Fluoride for the Prevention of Dental Caries

Clifton M. Carey, BA, MS, PhD [Professor]

University of Colorado, School of Dental Medicine

Abstract

Declarative Title: Improving the efficacy of fluoride therapies reduces dental caries and lowers fluoride exposure.

Background—Fluoride is delivered to the teeth systemically or topically to aid in the prevention of dental caries. Systemic fluoride from ingested sources is in blood serum and can be deposited only in teeth that are forming in children. Topical fluoride is from sources such as community water, processed foods, beverages, toothpastes, mouthrinses, gels, foams, and varnishes. The United States Centers for Disease Control and Prevention (CDC) and the American Dental Association (ADA) have proposed changes in their long standing recommendations for the amount of fluoride in community drinking water in response to concerns about an increasing incidence of dental fluorosis in children. Current research is focused on the development of strategies to improve fluoride efficacy. The purpose of this update is to inform the reader about new research and policies related to the use of fluoride for the prevention of dental caries.

Methods—Reviews of the current research and recent evidence based systematic reviews on the topics of fluoride are presented. Topics discussed include: updates on community water fluoridation research and policies; available fluoride in dentifrices; fluoride varnish compositions, use, and recommendations; and other fluoride containing dental products. This update provides insights into current research and discusses proposed policy changes for the use of fluoride for the prevention of dental caries.

Conclusions—The dental profession is adjusting their recommendations for fluoride use based on current observations of the halo effect and subsequent outcomes. The research community is focused on improving the efficacy of fluoride therapies thus reducing dental caries and lowering the amount of fluoride required for efficacy.

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Corresponding Author: Clifton Carey, PhD, University of Colorado, School of Dental Medicine, 12800 E. 19th Ave, MS 8310, Aurora, CO 80045, clifton.carey@ucdenver.edu.

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None

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Introduction

There is no question about the importance of fluoride for the prevention of dental caries as it is the first line of defense, along with education, for preventing the onset of caries. Fluoride is the only compound recognized by US Food and Drug Administration (FDA) for the prevention of dental caries; however, not all fluoride containing products are recognized by the FDA for caries protection. At this time fluoride for caries prevention comes primarily from fluoridated community water, toothpastes, and mouth rinses. The intake of water and processed beverages in the United States provides approximately 75% of a person's fluoride intake.¹

In the last couple of years there has been a significant reevaluation and proposed adjustment of public policies related to community water fluoridation. The proposed changes are based on current research into fluoride availability in the environment as well as the increasing incidence of very mild and mild fluorosis. There is also new research into the mechanisms of fluoride for anticaries efficacy which may lead to better prevention strategies. New and/or improved fluoride products are entering the marketplace at an increased rate; these products include: toothpastes, fluoride varnishes, fluoride containing whitening agents, and other fluoride containing cleaning products. For some, if not most of these new products, there is very little research to support their efficacy. This update presents new evidence, implications, and strategies related to fluoride use in community water fluoridation and for some fluoride based products for the prevention of dental caries.

Community Water Fluoridation

Community water fluoridation began 70 years ago and now approximately 72 % of the population of the United States has fluoridated water in their homes. In early 2011, after years of review and evaluation, the CDC, EPA, and the ADA proposed a modification to their recommendations for the amount of fluoride in drinking water to be 0.7 µg/mL (ppm) everywhere in the United States. The previous recommendations ranged from 0.7 ppm to 1.2 ppm fluoride and were climate dependent. Although the announcements of the proposed changes in the recommendations were released for public comment, a large number of municipalities immediately lowered the fluoride content of their water supply to 0.7 ppm. This means that although the proposed recommendations have not been officially adopted by the CDC or ADA, the populations of those communities are already receiving less fluoride than they did in the past. The municipal water providers are possibly putting their communities at risk for increased incidence of dental caries. It may take several years for any change in caries incidence to be noticed.

The new proposed and previous water fluoridation recommendations are based on calculations of total fluoride intake by children under the age of 8 because this is the population most vulnerable to develop fluorosis from systemic fluoride. In the 1950's the only source of fluoride for children was in the drinking water so the calculations about fluoride intake estimated the amount of water that children drank and set the recommendations accordingly. In the warmer southern regions the children drank more water; while in the colder northern regions children drank less water. Thus, until 2011 the CDC and the ADA recommended that the amount of fluoride in drinking water should range

from 0.7 ppm in warmer climates to 1.2 ppm in cooler climates. Reviews about the drinking habits of children have shown that due to air conditioning and other factors, children in all regions of the United States drink similar amounts of water and fluoridated beverages.

Studies have also shown that the fluoride intake of most children is supplemented from environmental sources. This fluoride from the environment, called the halo effect, includes sources such as processed foods and beverages, toothpaste, and to a small extent pesticides (Fig 1). The total fluoride intake for the youngest members of the population can often be higher than optimal which may lead to an increased incidence of very mild and mild fluorosis. Fluoride use in drinking water, dentifrice, and professional therapies has reduced caries incidence; however, indiscriminant use of fluoride has led to an increase of fluoride in the environment. The fluoride halo is thought to be the cause for the rapid increase in the rates of very mild and mild fluorosis (the lowest categories) over the last decade.²

Fluorosis occurs as a result of elevated amounts of fluoride during enamel formation before the tooth is erupted. The elevated fluoride may lead to defects in the enamel ranging from white specks or white striations to rough and pitted surfaces. Figure 2 shows examples of fluorosis from none, to very mild, and severe. Very mild fluorosis is often misdiagnosed and thus may be over reported because there are other conditions that appear similar. For instance, the use of antibiotics such as amoxicillin (in the β -lactam family of antibiotics which includes penicillins, amoxicillins and cephalosporins) during childhood causes white spots on the tooth that could easily be mistaken for, but are not due to fluoride.³ It is interesting to note that other antibiotics such as tetracycline also cause tooth discoloration which results in a dark colored stained striations that are easily distinguished from fluorosis. Since anterior permanent teeth develop in children under the age of 8, higher than optimal fluoride concentration exposure on a consistent basis can result in fluorosis. Fluorosis is due to fluoride deposited in the tooth as it is maturing, therefore the effects cannot be seen until the tooth erupts. Sources of fluoride during these early years can occur from ingestion of infant formula, drinking water that has higher than optimum levels of fluoride, fluoride toothpaste ingestion, or from inappropriately supervised fluoride supplements.

Powdered infant formula and infant formula concentrate are particularly important contributing sources for higher amounts of fluoride. Studies have shown that some brands contain sufficient amounts of fluoride that when mixed with optimally fluoridated water result in greater than optimal amounts of fluoride in the formula.⁴ The CDC and ADA have varied their recommendations about this in recent years. In 2006 the CDC and ADA recommended that low-fluoride water be used to reconstitute infant formula to guard against exposing the infant to excess amounts of fluoride. Recent evidence reviewed by the CDC “suggests that mixing powdered or liquid infant formula concentrate with fluoridated water on a regular basis may increase the chance of a child developing the faint, white markings of very mild or mild enamel fluorosis”.⁵ Due in part to the proposed lower recommended concentrations of fluoride in community water, the ADA and CDC now recommend that fluoridated water be used to prepare infant formula. However, they caution that if the child exclusively consumes infant formula reconstituted with fluoridated water, there may be an increased chance for mild dental fluorosis. To lessen this chance, the ADA and CDC now state that parents can use low-fluoride bottled water some of the time to mix infant

formula.^{4,5} Although this statement seems vague, the relevant variable for fluoride intake is the size of the infant. If the infant is small then less fluoride is needed and low fluoride bottled water could be used to reconstitute the infant formula for alternate meals. As the infant grows fewer feedings of infant formula made with low fluoride bottled water would be needed.

Over the last couple of years there has been a significant reevaluation and proposed adjustment of public policies related to community water fluoridation lead by the EPA and CDC. This reevaluation came about because recent census surveys on oral health have reported a substantial increase in very mild and mild fluorosis. These reported increases are interpreted to mean that increasing numbers of children are ingesting more than optimal amounts of fluoride. However, it is possible that the increase in reported fluorosis by dental professionals is partly due to confusion in the differential diagnosis of very mild and mild fluorosis versus early caries such as white spot lesions, or white spots resulting from use of amoxicillin.. Additionally, a new awareness of fluorosis has led to increased reporting when there was actually fluorosis in the past that was not reported. This observation is supported by the lack of similar increase in the incidence of greater degrees of fluorosis (moderate and severe) reported by dental professionals.² Nevertheless research shows that water drinking habits of the population have drastically changed over the last 70 years and fluoride availability in the environment (the halo effect) has increased; therefore, it is likely that there is an increase in very mild and mild fluorosis over the last decade in the US due to fluoride ingestion.

Figure 3 shows a chart adapted from data published by H. Trendly Dean (1942)^{6,7} to show the relationship between fluoride concentration in drinking water and incidence of fluorosis and decayed-missing-filled teeth (DMFT) in children. This chart is used to help understand the potential effects due to the change in fluoride concentration from 1 ppm to 0.7 ppm F. The x-axis of the Dean chart is modified to show the Equivalent Water Fluoride concentration which is defined as the sum of the community water fluoride content and the net impact of the halo effect. The red arrow originating from the reported percent of population affected by very mild dental fluorosis (approximately 40 %) is projected to the edge of the very mild fluorosis curve. The intersection of the arrow and this curve is at 1.8 ppm equivalent community water fluoride concentration. This concentration includes all of the sources for fluoride such as water consumption and the halo effect which contribute to the observed rate of mild fluorosis. Note that the intersection is at the steepest portion of the fluorosis curve so that a very small change in the equivalent fluoride exposure should lead to a large change in the fluorosis incidence. Thus, to reduce the very mild fluorosis incidence by about 50 % a reduction of only 0.3 ppm fluoride (from 1.8 ppm to 1.5 ppm) in the equivalent fluoride is needed as shown by the blue arrow. The caries experience curve (black curve) is nearly flat between these two points (1.8 ppm to 1.5 ppm) and thus this model predicts that there is little if any increased risk for caries with this change. Clearly, there are a number of assumptions inherent in using this model for setting the public policy. It is up to the dental profession to carefully monitor both caries and fluorosis incidence for the next 6 to 10 years as the effects of the change in drinking water fluoride may reduce the impact of the halo effect more greatly than anticipated. At this time, there are no plans for a

national surveillance program to assess caries or fluorosis incidence in children listed at the CDC.

Potentially Available Fluoride in Toothpaste

There are some recent studies where the amount of fluoride made available in the oral cavity during tooth brushing (approximately 2 minutes) was measured.⁸ It seems that in developing regions of the world there are toothpastes marketed that contain the total fluoride as indicated on the label but which do not release sufficient fluoride during use to prevent caries. This is due to the composition of the toothpaste which can render a significant amount of the fluoride unavailable. Our studies have found that the composition of the toothpaste is critical to the amount of fluoride that is potentially available. For instance, products that contain sodium fluoride (NaF) as the active ingredient also need to have sufficient detergent (typically sodium lauryl sulfate, SLS) to prevent the fluoride ions from reacting with the silica abrasives forming insoluble fluorosilicates. At this time the literature is not clear about possible side effects of SLS in toothpastes. SLS is thought to cause gingival inflammation and ulcers on the mucosal tissues in the mouth. A recent double blind crossover study in patients with recurrent aphthous stomatitis (RAS) followed clinical parameters including the number and duration of ulcers and pain found that use of the SLS-free toothpastes reduced ulcer-healing time and reduced pain. There was no difference the number of ulcers.⁹ Other active ingredients such as monofluorophosphate (MFP), stannous fluoride (SnF₂), or amine fluorides (not available in the United States) are also dependent on the abrasive, detergent, and other non-active ingredients combined in the toothpaste to present sufficient available fluoride for efficacy.

Currently, there is a large effort by the American National Standards Institute (ADA/ANSI) and the International Organization for Standardization (ISO) to develop reliable methods for the measurement of potentially available fluoride to include in national and international standards. The difficulty in achieving the analytical methods is related to the large variety of ingredients used in toothpaste products and the different forms of fluoride delivered during tooth brushing. There are three categories of fluoride from toothpaste during tooth brushing: free ionic fluoride which has the ability to react with tooth structure, interfere with microbial metabolism, absorb to the oral mucosa, and has anticaries efficacy; profluoride compounds that are delivered or precipitate in the oral cavity during brushing, release ionic fluoride over time, and contribute to anticaries efficacy; and unavailable fluoride compounds that do not release fluoride ions, are either spat out or swallowed, and have no anticaries efficacy. Monofluorophosphate is an example of a profluoride compound that is hydrolyzed to release ionic fluoride through salivary enzyme action. Therefore potentially available fluoride is the sum of the ionic fluoride and the profluoride compounds that are available during the 2-minute tooth brushing. A single analytical method to measure both total fluoride and potentially available fluoride in the same sample is highly desirable for standardization purposes. The method should be able to quantify the total fluoride content and be able to analyze both free fluoride ion as well as any profluoride fluoride compound that is deposited in the oral cavity during tooth brushing. Studies in our laboratory to develop a single method that can be used for all dentifrices are near completion. An important feature of this method

is that the total and potentially available fluoride can be determined from a single toothpaste slurry.

The amount and persistence of fluoride ion available in the oral cavity during brushing and after brushing is an important parameter for anticaries efficacy. New strategies are being tested where profluoride compounds, such as calcium fluoride, are precipitated during brushing, resulting in longer exposures to fluoride than what is achieved in tooth brushing alone. A new generation of toothpastes based on these strategies are anticipated that will optimize the precipitation of profluoride compounds into the oral cavity.¹⁰ One method is to flood the oral cavity with an abundance of soluble calcium ions in a non-fluoride rinse followed immediately by a fluoride toothpaste. This strategy has been shown to form calcium fluoride reservoirs that release fluoride over time such that the amount of fluoride in saliva at 1 hour after brushing is doubled in comparison to a NaF containing toothpaste at the same fluoride concentration.¹⁰ Figure 4 shows the salivary fluoride concentration 1 hour after several different combinations of fluoride and calcium applications by rinse or toothpaste. This strategy seems effective but has the difficulty of requiring two separate steps. Current research in our labs is developing a toothpaste that provides calcium ions and profluoride compounds. After approximately 30 seconds of brushing, ionic fluoride is released and then reacts with the calcium ions to form calcium fluoride reservoirs.

Fluoride Rinses

The new strategy being designed for toothpastes can also be applied for oral rinses. A new generation of fluoride rinses is anticipated that will contain soluble calcium salts that help retain fluoride in the oral cavity to be released over time.¹⁰ The concept of including soluble calcium in a pre-rinse prior to a fluoride rinse has been shown to increase the amount of fluoride in saliva nearly five-fold at 1 hour after rinsing, in comparison to a NaF containing rinse at the same fluoride concentration.¹¹ Figure 5 shows the overnight persistence of salivary fluoride after the calcium pre-rinse/fluoride rinse sequence. The calcium pre-rinse provides large amounts of calcium ions *in situ* which, when followed by a fluoride rinse, precipitates large amounts of calcium-fluoride reserves. These reserves dissolve into saliva over time such that the salivary fluoride concentration is more than quadruple that of a NaF rinse at the same fluoride concentration.¹⁰ It is conceivable that these new rinses and dentifrices may provide sufficient anticaries efficacy to the point that a children's toothpaste with a lower fluoride concentration could be developed. This would help lower the body burden of fluoride for children and may reduce the incidence of fluorosis.

The recent systematic review of topical fluoride for caries prevention presents recommendations in favor of the use of 0.09 percent fluoride (900 ppm F) mouth rinse at least weekly for children aged 6 to 18 years. The recommendation of at least weekly use for older than 18 years or for root caries prevention is based on 'Expert Opinion' because the scientific evidence is lacking.¹²

Fluoride Releasing Varnish

The ADA has recommended the use of fluoride releasing varnish (F-varnish) for caries prevention in young patients at moderate and high risk. There is strong clinical evidence that

indicates anticaries efficacy of F-varnish for high-risk populations.¹³ Recent studies have found that F-varnish has long lasting efficacy to prevent caries.¹⁴ However, it seems inconsistent that the FDA has not approved F-varnish for caries prevention. The reticence of the FDA to approve F-varnish is because clinical efficacy caries trials have been equivocal or at best product based. There is insufficient science demonstrating mechanism of action or identifying the significant compositional variables for anticaries activity. It is possible that non-fluoride components of the varnish products such as the varnish resin, flavoring, or other additives have anticaries efficacy or are synergistic with the fluoride in the product. Therefore the FDA does not have sufficient information to describe the requirements needed for fluoride varnish efficacy. Current studies have not demonstrated that anticaries efficacy is due to the fluoride content as opposed to some other component of the product. Nor have there been studies that demonstrate the mechanism of action to explain how a therapy that has duration of 2 to 24 hours can have anticaries effects for 6 months. This lack of information has hampered the use of F-varnish for community prevention programs. In spite of this there are community based programs that have clear success in reducing the amount of dental caries in children. A notable example is the ongoing program in Clark County, Kentucky (USA) under the private Clark County Dental Health Initiative, where the application of a calcium-phosphate containing F-varnish has reduced the caries incidence over five years from over 50 % to 11 % in a population of over 6000 elementary students.¹⁵ While this community health program is not a robust mechanistic study, the observations are impressive and important for the scientific community to witness.

There is a critical need to develop the scientific knowledge and mechanism of action to understand how F-varnishes can give 6 months of anticaries efficacy from a single application. The basic technology inherent in the F-varnish design is to apply a very high concentration of fluoride salt, usually at 50,000 ppm NaF (22,600 ppm F), in a resin varnish which will reside on the tooth surface for several hours. During the residence time, saliva bathes the varnish and dissolves the fluoride salt, allowing fluoride ions to diffuse out of the varnish and become absorbed into fluoride reservoirs within oral soft tissues, plaque, and teeth. Over time the fluoride ions are re-released from these reservoirs. The commonly recited mechanism presumes that abundant calcium ion is available and that large quantities of calcium-fluoride are precipitated on the tooth surface. The reservoirs then slowly dissolve, releasing fluoride ion, which in turn acts to protect the tooth.¹⁶ This oft-cited mechanism cannot explain the long period of efficacy because calcium fluoride precipitates are not long lasting reservoirs and are thought to be less important than fluoride uptake into enamel.¹⁷ Another possible mechanism of F-varnishes could be antibacterial; however, it has been reported that F-varnish did not affect the levels of *S. mutans* in saliva or dental plaque.¹⁶ Thus the primary cariostatic effect of F-varnish is probably due to the action of fluoride on the chemical stability of tooth mineral converting enamel to fluoroapatite which is much less susceptible to acid attack than enamel. Additionally, the NaF concentration in the F-varnish that yields optimal fluoride enamel uptake and anti-caries efficacy is unknown.

We have launched a systematic series of studies to establish the mechanism by which F-varnish affords long-term caries protection and to identify the optimal fluoride concentration for anticaries efficacy of the F-varnish. Our *in vitro* studies show that F-varnish saturates the

fluoride binding sites of enamel by flooding the tooth surface with high concentrations of fluoride ion for several hours. Our study also shows that very high concentrations of fluoride in contact with the tooth for extended time are required to overcome the slow rate of fluoride binding to enamel binding sites. Figure 6 shows the fluoride uptake into hydroxyapatite discs (a mineral model for tooth enamel) as a function of the fluoride concentration in F-varnish at three hours exposure. We measured both tightly bound fluoride, which gives long term protection by preventing dissolution and loosely bound fluoride, which gives short term protection by inducing surface stability and through antimicrobial mechanisms. Both the loosely bound and tightly bound F uptake into the hydroxyapatite disc is a non-linear function of NaF concentration in the varnish. The fluoride saturates the binding sites at 2.5 % NaF, thus the uptake does not increase above this concentration. In our study we have found that the number of fluoride binding sites on the hydroxyapatite disc is limited and there is an optimal NaF concentration at 2.5 % that saturates the binding sites. Saturation of fluoride binding sites gives maximal protection against demineralization.¹⁸

The ADA has performed several systematic reviews of the literature on F-varnish efficacy for caries protection and has concluded that there is sufficient evidence to recommend twice a year use of F-varnish for children who are at moderate and high caries risk. Application of F-varnish at six month intervals is recommended for caries prevention in permanent teeth. Children who are not at caries risk may not benefit from F-varnish applications; however, the risks from the therapy are negligible and the benefits have been judged to outweigh the risks. The most recent systematic review on topical fluoride indicates that the evidence favors F-varnish applications at least every three to six months for all children younger than 18 years of age.¹² This same review found that the evidence is lacking for use of F-varnish for adults 18 and older or for prevention of root caries, however, expert opinion is in favor of these uses to prevent caries.

Summary

Research has developed significant improvements in the use of fluoride in toothpaste and oral rinses, and insights into the mechanism for F-varnish efficacy. New systematic reviews of the literature have provided the basis for updated recommendations from the profession on how topical fluoride can be used to prevent caries. Finally, the adjustment of policy recommendations for community water fluoridation addresses changes in water drinking habits of children and the effects of the halo effect on fluoride exposure.

Abbreviations

ADA	American Dental Association
ADA/ANSI	American National Standards Institute
CDC	United States Health and Human Services Centers for Disease Control and Prevention
DMFT	Diseased, Missing or Filled Teeth
EPA	United States Environmental Protection Agency

ISO	International Organization of Standards
MFP	Monofluorophosphate
NaF	Sodium Fluoride
SLS	Sodium lauryl sulfate
SnF2	Stannous Fluoride

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Figure 1. Halo Effect Sources

Percentage source contribution to total daily fluoride intake: 90th Percentile Drinking Water Intakes for Consumers Only and a Fluoride Concentration of 0.87 mg/L. Image from Environmental Protection Agency. Fluoride: Exposure and Relative Source Contribution Analysis. 2010, page 99.¹⁹

Figure 2. Fluorosis – tooth hypomineralization resulting in a change in the appearance of teeth
Causes:

- Long term ingestions of higher than optimal levels of fluoride during tooth mineralization
- Use of antibiotics (amoxicillin) during childhood < 6 years of age
- Genetic predisposition

Images from Centers for Disease Control and Prevention. Community Water Fluoridation, Images of Fluorosis, http://www.cdc.gov/fluoridation/faqs/dental_fluorosis/.²⁰

Figure 3. Relationship between equivalent fluoride in water and fluorosis incidence and caries DMFT experience

The percent caries experience (DMFT) and fluorosis was reported for 12 to 14 year old children in 21 communities. The categories for fluorosis are: Normal, white; Questionable () yellow; Very Mild (□) cyan; Mild (◇) green; Moderate (▲) blue; and Severe (◆) red areas. The caries experience in permanent teeth is reported as diseased, missing, or filled teeth (●) heavy black curve. The red arrow shows the current incidence of very mild fluorosis, and the blue arrow shows the anticipated incidence of very mild fluorosis due to the reduction of community water fluoride concentration by 0.3 ppm F. Adapted from data published by Dean^{6,7}

Figure 4. Salivary fluoride concentration 1 hour after indicated fluoride and calcium therapies. This comparison of the salivary fluoride concentration after 1 hour is for the following rinses or toothpastes in singly or in combination.¹¹ The error bars are 95 % confidence intervals
The therapies are:

- None: no rinse baseline; n = 10
- C-R: 20 mL of 150 mmol/L calcium lactate 60-second rinse; n = 12
- F-R: 20 mL of 228 ppm (12 mmol/L) NaF 60-second rinse; n = 12
- F-R/C-R: 20 mL of 228 ppm NaF 60-second rinse followed by 20 mL of 150 mmol/L calcium lactate 60-second rinse; n = 12
- Fp/H₂O: 60-second brush with 1.5 g of 1100 ppm NaF toothpaste followed by a 10 second rinse with 10 mL H₂O; n = 12
- C-R/Fp/H₂O: 20 mL of 150 mmol/L calcium lactate 60-second rinse followed by a 60-second brush with 1.5 g of 1100 ppm NaF toothpaste and then followed by a 10 second rinse with 10 mL H₂O; n = 12
- Cp/F-R: 60-second brush with 1.5 g of 5.6 % (w/w) calcium glycerophosphate toothpaste followed by a 20 mL of 228 ppm NaF 60-second rinse; n = 11
- C-R/F-R: 20 mL of 150 mmol/L calcium lactate 60-second rinse followed by a 20 mL of 228 ppm NaF 60-second rinse n = 12.

Figure 5. Comparison of fluoride concentrations in overnight salivary samples after a calcium pre-rinse or a fluoride rinse

Fluoride concentration in saliva samples obtained overnight after 60-second 20 mL rinse as follows: Baseline distilled water (H₂O), 228 ppm fluoride (F-R Lo), 912 ppm fluoride (F-R Hi), or 150 mmol/L calcium lactate pre-rinse immediately followed by a 228 ppm fluoride rinse.

All fluoride was from sodium fluoride. The error bars are standard errors (N = 12) statistical differences ($p < 0.05$, Holm-Sidak pairwise multiple comparison test) are indicated by the letters. Data from Vogel et al (2008) ²¹

Figure 6. Fluoride uptake into hydroxyapatite after 3 hours exposure to F-varnishes of varying concentration of sodium fluoride.¹⁸