Topical Review Article

Journal of Evidence-Based Complementary & Alternative Medicine
17(1) 28-32

DOI: 10.1177/2156587211428076
http://cam.sagepub.com

Fluoride: Its Metabolism, Toxicity, and Role in Dental Health

E. Angeles Martínez-Mier, DDS, PhD[1]

Abstract

Fluoride is a naturally occurring element with multiple implications for human health. This review discusses its metabolism and toxicity, along with the current understanding of the mechanism of action of fluoride and its role as a safe and effective agent in the prevention of dental caries. The relationship between excessive fluoride intake during periods of dental enamel formation and the development of dental fluorosis is also reviewed.

Keywords

fluoride, dental caries, dental fluorosis

Received September 29, 2011. Accepted for publication September 29, 2011.

Fluorine is an electronegative, naturally occurring element and is the 13th most abundant on earth. The range of fluorine-containing compounds is extensive since fluorine is capable of reacting with all the elements except helium and neon. The reduced form of fluorine (or its anion) is designated as fluoride both when present as an ion and when bonded to other elements. Fluorides are naturally occurring and are found in all water sources in small but traceable amounts.

Absorption, Distribution, Secretion, and Excretion of Fluoride

Fluoride-containing compounds are extremely diverse. For that reason it is not possible to generalize on their metabolism, which depends on their reactivity and structure, solubility, and ability to release fluoride ions. The ionic form of fluoride, which can be either generated within the body by the biochemical modification of the different fluoride-containing compounds or ingested directly, is metabolized by the body in a simple manner (see Figure 1 for a schematic of fluoride metabolism).

Fluoride mostly enters the body via the gastrointestinal tract and is absorbed quickly in the stomach without the need of specialized enzymatic systems.[1] It crosses epithelia in the form of undissociated acid (hydrogen fluoride). The diffusibility of hydrogen fluoride explains the physiological behavior of fluoride. At low pH (<3.5), the more undissociated form hydrogen fluoride predominates, whereas at higher pH the ionized form dominates.[2] Recent studies have indicated that in addition to crossing the stomach as undissociated acid, the majority of fluoride absorption occurs in the small intestine and is not pH dependent. Evidence suggests that there are several pH gradient-dependent, carrier-mediated mechanisms for fluoride transport in the intestine.[3-5]

The rate of fluoride absorption from the stomach is directly related to the acidity of its contents.[6] However, several other factors influence the rate of absorption, including the solubility of the ingested fluoride compound. More soluble compounds such as sodium fluoride (NaF) and hydrogen fluoride would result in faster absorptions, whereas less soluble fluoride compounds, such as calcium fluoride (CaF_2) and magnesium fluoride (MgF_2), would slow absorption.[7]

As soon as fluoride is absorbed, plasma fluoride levels increase (at 10 minutes), reaching peak levels at 60 minutes. A return to basal levels is achieved within 11 to 15 hours.[1] It is well documented that there are 2 forms of fluoride in plasma. One fraction is designated as ionic fluoride and the second is designated nonionic or bound fluoride, composed of lipid-soluble organic fluoro-compounds. The biological significance of the nonionic fraction is not well understood.[7]

Once fluoride reaches plasma, it is rapidly deposited in the skeleton or excreted via the kidneys. Fluoride skeletal uptake is also modified by factors such as the activity of bone modeling and remodeling and age.[8] The degree of fluoride retained in the

[1] Indiana University, Indianapolis, IN, USA

Corresponding Author:
E. Angeles Martínez-Mier, DDS, PhD, Department of Preventive and Community Dentistry, Oral Health Research Institute, Indiana University School of Dentistry, 415 Lansing Street, Indianapolis, IN 46202, USA
Email: esmartin@iupui.edu

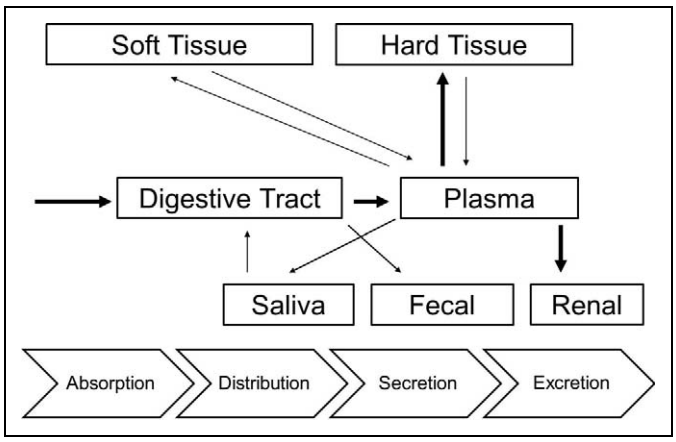

Figure 1. Flowchart of fluoride metabolism

skeleton is inversely proportional to the age of the individual. In subjects with no previous exposure to fluoride, the amount of fluoride absorbed increases until saturation is reached.[9] In bone, fluoride can be deposited in the adsorbed layers, the crystal structures, or the bone matrix. Once fluoride is incorporated and when bone saturation is approached, the fluoride can be slowly removed. Previous observations after removal of fluoride from community waters have shown that the half-life for loss of fluoride for adults is 120 weeks, whereas it is 70 weeks for children.[10]

Fluoride is secreted in saliva; salivary levels increase as plasma levels increase. Although salivary levels are only within the range of 0.01 to 0.06 ppm for individuals exposed to fluoride, they are of critical importance for the role of fluoride as a preventive agent for dental caries.[11] The fluoride that is not stored in bone is excreted mainly via the kidneys, with a minimal quantity excreted through feces. Both urinary flow and pH are involved in regulating renal clearance of fluoride from plasma.[1] The proportion of ingested fluoride that is excreted in the urine (fractional urinary fluoride excretion) is also influenced by age and demonstrates clear and distinct nocturnal and diurnal patterns.[3,4] In adults and children, the fractional urinary excretion, just like fluoride absorption, is influenced by pH and other factors. Diets with a high proportion of vegetable and fruit intake lead to urinary pH on the alkaline side, whereas protein-rich diets lead to acidification of urine. These changes in urinary pH in turn modify the fractional urinary fluoride excretion. Multiple studies have calculated fractional urinary fluoride excretion values for adults and children, with more recent studies calculating fractional urinary fluoride excretion for young healthy adults to be in the range of 78%.

Sources of Fluoride Ingestion and Exposure

The different sources that contribute to fluoride intake and exposure can be classified as follows: (*a*) *systemic/planned*—fluoridated milk, water, or salt, fluoride supplements; (*b*) *systemic/incidental*—dentifrice ingestion, fluoride rinse ingestion, environmental pollution, ingestion of Teflon coatings on pans; exposure to food/soil/pesticides, prescription drugs, smoking; (*c*) *topical/planned*—professionally applied gels and varnishes, toothpaste, or home use rinses and gel; and (*d*) *topical/incidental*—alginate impression materials. Longitudinal studies by Levy et al[12] have identified the following as major sources of fluoride intake: milk derivatives, water, fish and seafood, chicken, and toothpaste and other oral products containing fluoride. However, their results demonstrated that intake levels at early ages present wide ranges due to variations in consumption and the diversity of products available. Milk formulas mixed with drinking water can increase the amount of fluoride and therefore the risk of dental fluorosis. The ingestion of fluoridated toothpaste in children younger than age 6 years has also been strongly associated with increased fluoride intake.[13,14]

Fluoride Toxicity

Ingested in excessive quantities, fluoride can be toxic. The American Dental Association has recommended that no more than 120 mg fluoride (264 mg sodium fluoride) be dispensed at any one time.[15] Statistics kept by the American Association of Poison Control Centers indicate that of all reported cases of fluoride intoxication, 68% were related to fluoride dentifrice ingestion, 17% to fluoride mouth rinses, and 15% to fluoride supplements. Children younger than 6 years of age account for more than 80% of reports of suspected overingestion.[16,17] The minimum dose that could cause toxic signs and symptoms, including death, and that should trigger immediate therapeutic intervention and hospitalization for fluoride intoxication has been set at 5 mg/kg body weight. The lethal dose of fluoride has been set at 15 mg/kg (the literature reports lethal doses between 7 and 16 mg/kg body weight). Death has occurred in infants with as little as 250 mg.[1]

Common signs and symptoms of acute fluoride toxicity include nausea, vomiting, and a drop in blood calcium, causing local or general signs of muscle tetany. Signs also include abdominal cramping and pain and increasing hypocalcaemia and hyperkalemia, leading coma, convulsions, and cardiac arrhythmias. Generally, death from excessive fluoride ingestion will occur within 4 hours; if the individual survives for 24 hours, the prognosis is guarded to good.[18]

The toxic effects of fluoride are mainly due to 4 different actions: (*a*) burning the tissues (it forms hydrofluoric acid when it comes in contact with moisture, which has a corrosive action), (*b*) impeding nerve function (through its affinity for calcium, which is needed for nerve function), (*c*) cellular poisoning (through the inhibition of enzyme systems), and (*d*) impeding cardiac function (by causing an electrolyte imbalance leading to hyperkalemia).[18]

Fluorides and Dental Caries Prevention

Fluoride is widely recognized for reducing the prevalence of dental caries. Dental caries is a site-specific, multifactorial disease. Numerous biological factors for each individual influence

the development of caries on a tooth surface. The development of caries on a specific site is the result of that site's individual dental plaque composition and metabolism, which is influenced by biological determinants, including saliva, diet, and possibly genetic factors.[19]

Over time, acids are produced as a result of dental plaque metabolism. Those acids interact with the surface dental enamel, removing minerals or demineralizing it. In turn those acids are neutralized by other ions and proteins present in the oral environment, with a resulting increase in the pH of the environment surrounding the dental enamel. This creates the conditions for minerals to return to dental tissues to remineralize it. During normal physiological conditions, deviations from these remineralizing conditions are brief and sparse. However, when the conditions that favor demineralization are frequent, the net result is a loss of mineral from the tooth surface and the development of dental caries.[19]

Although dental caries is multifactorial and complex, it is preventable.[19] Results of numerous studies have shown that fluoride decreases the incidence of dental caries and slows or reverses the progression of existing lesions by decreasing the rate of dental enamel demineralization and enhancing the rate of enamel remineralization.[20-24] Current understanding of the mechanism of action of fluoride indicates that its major effect is topical and that this depends on fluoride being present in the dental plaque/enamel interface in adequate amounts during caries formation and reversal.[25] A secondary mechanism for fluoride is exerted through its influence on dental plaque bacterial metabolism. However, the relative importance of the direct effects of fluoride on bacterial metabolism is still debated.[26] Finally, it is recognized that there is some minor incorporation of fluoride into the enamel crystals prior to tooth eruption, which could increase resistance to solubility in acids.[26]

The current understanding of the mechanism of action for caries prevention by fluoride indicates that fluoride mostly acts topically, and not systemically; therefore, fluoride exerts its preventive effects through an individual's life span, not just when teeth are forming. Topical forms of exposure to fluoride in the United States include toothpaste, rinse, and gel use, as well as professionally applied gels and varnishes. Fluoride in toothpaste has been determined to be the most effective use of fluoride in controlling caries.[27] Systemic sources of fluoride (such as intake of fluoridated water) also have a place in public health, resulting in more widespread exposure to fluoride. The systemic fluoride is secreted into the oral cavity via saliva, where it can affect caries formation topically. Water fluoridation is considered one of the top 10 greatest public health achievements in the United States during the past century. Addition of fluoride to public water supplies at 0.7 ppm has particular benefits for population groups that do not have access to topical fluorides or regular dental care.[22,23]

The precise "optimal" oral intake of fluoride to provide effective protection against dental caries has not been determined.[13,14,28] In 1997, the United States Institute of Medicine published age-specific recommendations for total dietary intake of fluoride. These recommendations list the tolerable upper intake, defined as a level unlikely to pose risk for adverse effects in almost all persons. For children aged 12 years and younger, 0.05 to 0.07 mg/kg of body weight has been accepted as optimum amount of total daily intake of fluoride, while total daily intake should not exceed 0.10 mg/kg of body weight to avoid an undesirable degree of fluorosis.[29]

Fluorides and Dental Fluorosis

Dental fluorosis is a hypomineralization of dental enamel that occurs as a result of excessive fluoride ingestion during tooth formation.[30-32] It has been suggested that for dental fluorosis to appear, an excessive amount of fluoride has to be present in the environment of the developing enamel during a critical period of greater susceptibility (or "window of susceptibility") for that given surface.[33] Based on the results of an epidemiological study done in Hong Kong, China, in which investigators were able to determine precise periods of excessive fluoride intake for groups of children because fluoride levels in the water were adjusted downwards, a window of susceptibility was estimated for the central maxillary incisors.[33-35] More recent studies have estimated the window of susceptibility to cover the first 2 years of life.[36,37]

The effects of ingested fluoride on dental enamel during its formation are well documented. Most of the studies that have documented these effects have been conducted in communities where the water sources are fluoridated. At 1 ppm in the water supply, early signs of fluorosis are visible on the enamel surface as opacities. As the dose increases, the severity of the signs increases until at approximately 10 ppm the porosity of the enamel is compromised and large pieces of enamel are fractured after eruption.

At the cellular level, dental fluorosis development depends on the levels of fluoride in the extracellular fluid that surround the developing dental enamel.[38,39] These levels of fluoride are determined by the plasma concentration, which in turn is a function of daily intake of fluoride.[40] There is evidence suggesting that the effects of fluoride are cumulative and depend mostly, but not entirely, on the amount and duration of exposure.[35,41] The exact tissue concentrations at which fluoride begins to exert its effects have not yet been determined. Tissue fluoride concentrations have been reported differently in published studies, and in many cases not even reported. Different studies have described measuring fluoride concentrations in culture media, tissues, or plasma, and in many animal studies, only the fluoride content of the water administered to animals is included in the explanation of the experiment. Differences in methodological designs make it extremely difficult to compare results from various studies and to extrapolate them to the effects on human dental enamel development in vivo. Experimental results suggest that a linear relationship exists between increasing fluoride doses and their effects on dental tissue. However, a clear-cut direct relationship between amount of fluoride ingested and severity of dental fluorosis has not been proven; rather, fluorosis development has a demonstrated genetic component.[41]

Several epidemiological studies have indicated that there are additional factors that modify the development of dental fluorosis independently of the amount of fluoride ingested. A relationship could exist between higher prevalence and severity of dental fluorosis and residence at high altitude, even when suboptimal concentrations of fluoride are ingested. Other factors, such as malnutrition and systemic disease that affect the physiological state of individuals, have been described to modify fluorosis development. Finally, the use of prescription drugs that may affect the acid–base balance in the body has been reported to increase the risk of developing dental fluorosis.[42-45]

Conclusion

Fluoride is a naturally occurring element with multiple implications for human health. Its metabolism and toxicity have been extensively studied. However, there are still gaps in knowledge that need to be addressed. Current understanding of the mechanism of action and toxicity of fluoride leads to conclusions that at appropriate levels, fluoride has been established as a safe and effective agent in the prevention of dental caries throughout an individual's lifespan. However, a positive relationship has also been established between excessive fluoride intake during periods of enamel formation and the development of dental fluorosis.

Acknowledgments

The author wishes to acknowledge Mr Andres Mantilla for his assistance in manuscript preparation.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

This study is exempt from oversight by human subjects research protection as there were no human subjects involved.

References

1. Whitford GM. *The Metabolism and Toxicity of Fluoride*. 2nd ed. Basel, Switzerland: Karger; 1996.
2. Whitford GM. Effects of plasma fluoride and dietary calcium concentrations on GI absorption and secretion of fluoride in the rat. *Calcif Tissue Int*. 1994;54:421-425.
3. Villa A, Cabezas L, Anabalón M, Rugg-Gunn A. The fractional urinary fluoride excretion of adults consuming naturally and artificially fluoridated water and the influence of water hardness: a randomized trial. *Community Dent Health.* 2009;26:132-137.
4. Villa A, Anabalon M, Zohouri V, Maguire A, Franco AM, Rugg-Gunn A. Relationships between fluoride intake, urinary fluoride excretion and fluoride retention in children and adults; an analysis of available data. *Caries Res*, 2010;44:60-68.
5. Villa A, Rosenkranz C, Garrido A. Fluoride absorption from disodium and calcium monofluorophosphates from the gastrointestinal tract of rats. *Res Commun Chem Pathol Pharmacol*. 1993;81:53-67.
6. Whitford GM, Pashley DH. Fluoride absorption: the influence of gastric acidity. *Calcif Tissue Int.* 1984;36:302-307.
7. Ekstrand J, Ehrnebo M. The relationship between plasma fluoride, urinary excretion rate and urine fluoride concentration in man. *J Occup Med*. 1983;25:745-748.
8. Dunipace AJ, Brizendine EJ, Zhang W, et al. Effect of aging on animal response to chronic fluoride exposure. *J Dent Res.* 1995;74:358-368.
9. Hodge HC, Smith FA, Gedali L. Excretion of fluorides. *WHO Monograph.* 1960;141-161.
10. Likins RC, McClure FJ, Steere AC. Urinary excretion of fluoride following defluoridation of water supply. *Public Health Rep.* 1952;71:217-220.
11. Ingram GS, Agalamanyi EA, Higham SM. Caries and fluoride processes. *J Dent.* 2005;33:187-191.
12. Levy SM, Kiritsy M, Warren JJ. Sources of fluoride intake in children. *J Public Health Dent*. 1995;55:39-52.
13. Levy SM, Zavash Zarei M. Evaluation of fluoride exposures in children. *ASDC J Dent Child.* 1991;58:467-473.
14. Levy SM. Review of fluoride exposures and ingestion. *Community Dent Oral Epidemiol.* 1994;22:173-180.
15. Bayless JM, Tinanoff N. Diagnosis and treatment of acute fluoride toxicity. *J Am Dent Assoc.* 1985;110:209-211.
16. Shulman JD, Wells LM. Acute ethanol toxicity from ingesting mouthwash in children younger than 6-years of age. *Pediatr Dent.* 1997;19:404-408.
17. Shulman JD, Wells LM. Acute fluoride toxicity from ingesting home-use dental products in children, birth to 6 years of age. *J Public Health Dent.* 1997;57:150-158.
18. Norman HO, Arden CG. *Water Fluoridation in Primary Preventive Dentistry.* 3rd ed. Stamford, CT: Appleton & Lange; 1991.
19. Thylstrup A, Fejerskov O. *Textbook of Clinical Cariology.* 2nd ed. Copenhagen, Denmark: Munksgaard; 1994.
20. Centers for Disease Control and Prevention. Ten great public health achievements—United States, 1900-1999. *MMWR Morb Mortal Wkly Rep.* 2000;48:241-243.
21. Bratthall D, Hänsel Petersson G, Sundberg H. Reasons for the caries decline: what do the experts believe? *Eur J Oral Sci.* 1996;104:416-422.
22. Public Health Service Committee to Coordinate Environmental Health and Related Programs. *Review of Fluoride: Benefits and Risk*. Washington, DC: US Department of Health and Human Services, Public Health Service; 1991.
23. Murray JJ. Efficacy of preventive agents for dental caries. Systemic fluorides: water fluoridation. *Caries Res.* 1993;27(suppl 1):2-8.
24. Margolis HC, Moreno EC. Physicochemical perspectives on the cariostatic mechanisms of systemic and topical fluorides. *J Dent Res.* 1990;69(special issue):606-613.
25. Hamilton IR. Biochemical effects of fluoride on oral bacteria. *J Dent Res.* 1990;69(special issue):660-667.
26. Featherstone JDB. Discussion of session II: Fluoride and the caries process. In: Proceedings of a Joint IADR/ORCA

International Symposium on Fluorides: Mechanisms of Action and Recommendations for Use, 1989. *J Dent Res.* 1990;69(special issue):634-636.
27. Marinho VCC, Higgins JPT, Logan S, Sheiham. A. Fluoride toothpastes for preventing dental caries in children and adolescents. Cochrane Oral Health Group. *Cochrane Database Syst Rev.* 2009;(1):CD002278.
28. Levy SM, Guha-Chowdhury N. Total fluoride intake and implications for dietary fluoride supplements. *J Public Health Dent*. 1999;56:211-223.
29. Institute of Medicine. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board. *DRI Dietary Reference Intake for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: National Academies Press; 1997.
30. Fejerskov O, Larsen MJ, Richards A, Baelum V. Dental tissue effects of fluoride. *Adv Dent Res.* 1994;8:15-31.
31. Fejerskov O, Stephen KW, Richards A, Speirs R. Combined effect of systemic and topical fluoride treatments on human deciduous teeth-case studies. *Caries Res*. 1987;21:452-459.
32. Richards A, Kragstrup J, Josephsen K, Fejerskov O. Dental fluorosis developed in postsecretory enamel. *J Den Res*. 1986;65:1406-1409.
33. Evans RW, Darvell BW. Refining the estimate of the critical period for susceptibility to enamel fluorosis in human maxillary central incisors. *J Public Health Dent.* 1995;55: 238-249.
34. Evans RW, Stamm JW. An epidemiological estimate of the critical period during which human maxillary central incisors are more susceptible to fluorosis. *J Public Health Dent*. 1991;51:251-259.
35. Evans RW, Stamm JW. Dental fluorosis following downward adjustment of fluoride in drinking water. *J Public Health Dent.* 1991;51:91-98.
36. Hong L, Levy SM, Warren JJ, Broffitt B, Cavanaugh J. Fluoride intake levels in relation to fluorosis development in permanent maxillary central incisors and first molars. *Caries Res.* 2006;40:494-500.
37. Hong L, Levy SM, Broffitt B, et al. Timing of fluoride intake in relation to development of fluorosis on maxillary central incisors. *Community Dent Oral Epidemiol.* 2006;34:299-309.
38. Fejerskov O, Thylstrup A, Larsen MJ. Clinical and structural features and possible pathogenic mechanisms of dental fluorosis. *Scand J Dent Res*. 1977;85:510-534.
39. Arends J, ten Cate JM. Tooth enamel remineralization. *J Crystal Growth.* 1981;53:135-147.
40. Featherstone JD, Glena R, Shariati M, Shields CP. Dependence of in vitro demineralization of apatite and remineralization of dental enamel on fluoride concentrations. *J Dent Res*. 1990;69:620-625.
41. Everett ET, McHenry MA, Reynolds N, et al. Dental fluorosis: variability among different inbred mouse strains. *J Dent Res*. 2002;81:794-798.
42. Manji F, Boelum V, Fejerskov O. Fluoride, altitude, and dental fluorosis. *Caries Res.* 1986;20:473-480.
43. Martínez-Mier EA, Soto-Rojas AE, Ureña-Cirett JL, Katz BP, Stookey GK, Dunipace A. Dental fluorosis and altitude: a preliminary study. *Oral Health Prev Dent.* 2004;2:39-48.
44. Angmar-Månsson B, Whitford GM. Enamel fluorosis related to plasma F levels in the rat. *Caries Res*. 1984;18:25-32.
45. Yoder KM, Mabelya L, Robison VA, Dunipace AJ, Brizendine EJ, Stookey GK. Severe dental fluorosis in a Tanzanian population consuming water with negligible fluoride concentration. *Community Dent Oral Epidemiol*. 1998;26:382-393.