A-Z Fundamentals of Dentifrice: Oral Health Benefits in a Tube

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Conflict of Interest Disclosure Statement

- Beth Jordan is a current employee of Procter & Gamble.

Short Description – Fundamentals of Dentifrice

This course will focus on the most common dentifrice ingredients and the oral health benefits they provide. Upon completion of the course, participants will understand not only the fundamentals of dentifrice ingredients, but also key regulatory aspects of the dentifrice market and the role of the ADA Seal program in credentialing consumer dentifrices.

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Overview

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Learning Objectives

Upon completion of this course, the dental professional should be able to:

- Help dental professionals talk to their patients from a position of knowledge about the variety of fluoride dentifrices available in the current marketplace.
- Understand the history and development of modern-day dentifrices.
- Understand the evolution and combination of different benefits in the dentifrice marketplace.
- Describe the FDA Monograph system.
- Compare the Monograph system with a New Drug Application (NDA).
- Differentiate between claims for therapeutic and cosmetic benefits.
- Describe the American Dental Association (ADA) Seal of Acceptance program.
- Explain fluoride's mechanism of action and understand key differences of common dentifrice actives.
- List common therapeutic benefits vs cosmetic benefits.
- Compare nerve desensitizing and dentin tubule occluding agents and describe the agents Mechanism of Action to treat dentinal hypersensitivity.
- Help the dental professional understand the connection between modern lifestyle (diet), new emerging issues such as dental erosion and appropriate therapies to help them guide their patients.
- Name the dentifrice ingredients used to control calculus, stain and bad breath; explain how these agents function.
- Describe the role of non-therapeutic dentifrice ingredients used to improve esthetics and stability.
- Explain compatibility concerns manufacturers face when formulating a dentifrice.

Glossary

bioavailability – The degree to which a drug or substance is available to the target tissue following administration.

buffer – Chemical system that confers resistance to a change in the pH of a solution

(e.g., saliva) when hydrogen ions (H+) are added or removed.

carbohydrate – Important energy source for the body; a complex molecule made up of one or more simple sugars.

calculus – Calcified plaque: a hard, yellowish deposit on the teeth, consisting of organic secretions and food particles deposited in various salts, such as calcium carbonate; also called tartar.

caries – The process of dental decay, beginning with the earliest initiation of tooth demineralization and culminating with the collapse (cavitation) of a specific tooth surface. Dental caries is an infectious disease caused by the complex interaction of certain plaque bacteria with carbohydrates (i.e., sugars), resulting in the generation of acids that can attack and damage both enamel and dentin.

cariogenic – Contributing to the production of caries.

chelate – Action of certain chemical compounds whereby they form several noncovalent bonds to a single metal ion (e.g., Ca^{2+}), sequestering it and preventing it from reacting with its surroundings.

chromogen – Substance that can be converted to a pigment or dye.

compound – In chemistry, a substance that consists of two or more chemical elements in union.

covalent – In chemistry, a chemical bond formed by the sharing of one or more electrons, especially pairs of electrons, between atoms.

crevicular – A fluid produced by epithelium of the gingival crevice; it contains immunoglobulins and has antimicrobial properties.

dental erosion – Irreversible loss of tooth structure resulting from strong acids of non-bacterial origin (e.g. dietary, gastric).

enzyme – Protein that catalyzes, or facilitates, biochemical reactions.

extrinsic stain – Tooth stain on the exterior surface of the tooth that can be removed through routine cleaning procedures. It is generally composed of dietary chromogenic molecules and metal ions which become bound within the salivary pellicle layer that coats exposed tooth surfaces.

gingivitis – Inflammation of the gums that often manifests as bleeding during brushing and flossing; mildest form of periodontal disease that is reversible.

heme – A complex red organic pigment containing iron and other atoms to which oxygen binds.

halitosis – The condition of having stale or foul-smelling breath.

hydrophobic – Water-resisting; refers to a chemical entity that repels water and prefers oily environments.

ions – Atoms or molecules that carry either a positive or a negative electric charge in a solution. For example, sodium chloride (NaCl, common table salt) in water dissociates into Na+ and Cl– ions.

intrinsic stain – Staining caused by the presence of pigment within the enamel or dentine. Intrinsic stain can often be mediated through bleaching procedures.

lysis – The destruction or dissolution of a cell or molecule, generally through the action of a specific agent.

metabolize – The process through which food is broken down to release energy.

molecule – Chemical entity that consists of two or more atoms that have chemically combined to form a single species.

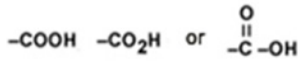
NaF – Sodium fluoride.

New drug application (NDA) – Application

requesting FDA approval to market a new drug, drug formulation, or dose.

noncavitated lesion – Demineralized, subsurface carious lesion without evidence of discontinuity or break in the enamel surface (sometimes called an early lesion, incipient lesion, or white spot lesion).

organic acids – Acid containing at least one carbon atom; also called a carboxylic acid; written chemically as:



Over-the-counter (OTC) – Drug products that are generally recognized as safe and effective and are available without a prescription; in oral care, many dentifrices and some rinses are OTC products.

OTC Monograph – A document published by the US FDA that includes lists of ingredients that have proven effectiveness and safety for a particular health concern, as well as information about dosing, drug formulations and labeling.

patency – State or quality of being open, expanded, or unblocked.

pharmacology – Study of a drug's origin, chemistry, effects, and uses.

plaque – An organized community of many different microorganisms that forms itself into a biofilm and is found on the surface of the tongue and all hard surfaces in the oral cavity. Dental plaque is present in all people and can vary from being comprised of totally healthy microorganisms (commensals) to being very harmful (pathogenic), predisposing the patient to dental caries or periodontal diseases. Note: Dental plaque is not food debris, nor does it contain food debris. Dental plaque can only be completely removed by mechanical means, such as toothbrushing or prophylaxis.

SHMP – Sodium hexametaphosphate

SMFP – Sodium monofluorophosphate.

SnF_2 – Stannous fluoride.

subgingival – Located beneath the free margin of gingival tissue.

supragingival – Located on a portion of the tooth that is not surrounded by gingival tissue.

surfactant – compounds such as detergents, emulsifiers, and foaming agents that provide cleaning or help mix substances that prefer to separate (like oil and water). Surfactants typically have a hydrophilic, polar head that interacts with water and a hydrophobic, nonpolar tail that avoids water.

tartar – Calcified plaque: a hard, yellowish deposit on the teeth, consisting of organic secretions and food particles deposited in various salts, such as calcium carbonate; also called calculus.

toxicology – Study of the unwanted and often adverse effects of substances.

Introduction

The majority of patients use dentifrice in their daily hygiene routine. As such, it is a cost-effective and convenient vehicle to deliver ingredients that provide therapeutic benefits, cosmetic benefits, or both. Classification of dentifrice ingredients into these key benefit categories affects how products are regulated as well as the types of claims that can be made about a product. Products providing therapeutic benefits are regulated by the US Food and Drug Administration (FDA). The first clinically proven therapeutic ingredient to be included in dentifrices was fluoride. Since this first therapeutic advancement in the dentifrice market, other ingredients have been formulated into dentifrices to provide benefits, such as plaque and gingivitis reduction, enamel erosion protection, antihypersensitivity benefits, extrinsic whitening, calculus protection and reducing halitosis (bad breath). These ingredients and their mechanisms of action are described in detail in this course, along with ingredients that provide stability and esthetic benefits to a dentifrice formulation.

Dentifrice Market Fundamentals

The use of dentifrice as part of normal daily hygiene practices in the United States is widespread. In fact, there are so many dentifrice options in the oral care aisle today it can be overwhelming. Patients often choose based on marketed benefit, cost, or turn to dental professionals for a product recommendation that will meet their specific oral care needs. Given the wide array of benefits delivered today, it is imperative that dental professionals proactively teach patients what specific product (Rx or OTC) will deliver their desired therapeutic or cosmetic outcomes.

It can be helpful for the dental professional to understand the regulatory environment and the process used by the ADA that guides product claims as this dictates how a product comes to market. However, in the end, the therapeutic benefit to the patient will depend upon professionals discussing home care options with patients and prescribing their use, whether OTC or Rx.

The first dentifrice ingredient clinically proven to provide a health benefit was fluoride, which can be delivered from one of several different fluoride-based **compounds** (three are allowed for use in the US under the US monograph system). Over time, dentifrices evolved to provide multiple therapeutic and cosmetic benefits. This course describes the most common dentifrice ingredients used for therapeutic benefits (caries, plaque/gingivitis, hypersensitivity and enamel erosion) as well as cosmetic ones (calculus, whitening, and bad breath), and it provides their mechanisms of action (MoA) and perspectives on how the market evolved to deliver multiple benefits in dentifrice formulations.

History: Tooth Cleaning

The concoctions used to clean the mouth, decrease malodor and treat the gums in early writings often were more detrimental than preventive. For example, in the writings of Pliny (23-79 C.E.) several remedies are mentioned: burnt nitre (potassium nitrate) to restore whiteness; goat's milk to sweeten the breath; burnt stag's horn and ashes of various animals for strengthening the gums, etc.[1] Many different remedies have been proposed for improving the conditions found in the oral environment, and one may even go so far as to call these unpleasant concoctions the first dentifrices. Two basic components of oral hygiene have passed the test of time and, although modified and improved, have their roots in ancient times.

These components are both the bristle toothbrush and the dentifrice used in conjunction with the brush. Primitive cleaning sticks of different types still exist today and are the cleaning tool of choice in some cultures; although the modern-day brush has evolved into a skillfully designed multi-tufted product and further into electric rechargeable toothbrushes which outperform their manual counterparts. The "toothbrush" continues to be improved in ways that enhance both function and performance, as do dentifrice formulations. Improved gum cleaning, coupled with excellent safety profiles for these dentifrice products, makes them important developments for efficiently delivering fluoride, as well as other key ingredients. Dentifrices have also changed dramatically from the predominantly acid concoctions of the past to more basic or neutral products. This was the result of the acceptance of Miller's acidogenic theory of caries formation which helped promote the change moving away from acidic formulations.[2]

Description of the US Monograph System

In the United States, the Food and Drug Administration (FDA) regulates therapeutic agents to ensure product safety and efficacy. Drugs can enter the market by one of two regulatory pathways. The most common pathway for **Over-the-counter (OTC)** drugs is under the **OTC Monograph** system. There are three monographs that regulate OTC dentifrices.

In 1962, an amendment was passed to the US Federal Food, Drug, and Cosmetics Act (FD&C) requiring that marketed drug products not only had to be safe, but they also had to be effective. At that time, hundreds of thousands of OTC drugs were on the market, and time and resources were too limited to ensure that all these OTC drugs complied with the new regulations. To ease the approval of OTC

therapies considered safe by virtue of their extensive historical use, the monograph drug review mechanism was instituted in 1972. Under this process, the FDA convened committees to review safety and efficacy data submitted for therapeutic ingredients in the OTC market. The end result of the process is a published document that lists certain therapeutic ingredients (referred to as active ingredients) and the requirements for marketing products that contain those active ingredients. These requirements include a number of parameters, including the intended use, drug dosage or concentration, dosage forms, allowable combinations with other drugs, required labeling, and any special packaging or testing requirements.[3]

There are several classes of monographed OTC drugs for oral use, including anticaries agents, tooth desensitizers, oral antiseptics, anesthetics, and analgesics. Therapeutic dentifrices are regulated by three separate monographs: Anticaries, Antiplaque-Antigingivitis, and Tooth Desensitizer (Table 1).

One factor that differentiates OTC fluoride dentifrices from prescription fluoride dentifrices is the amount of fluoride they contain as a therapeutic ingredient. Fluoride is a known anticaries ingredient, but it can be toxic if excessive levels are ingested. Although dentifrices are not intended to be ingested, there is enough safety concern to warrant stricter regulations for higher dose products. Most OTC fluoride dentifrices contain 1000–1500 parts per million (ppm) of fluoride and are considered conventional fluoride dentifrices. The maximum allowable fluoride in a monographed OTC dentifrice is 1500 ppm for a sodium monofluorophosphate (**SMFP**) dentifrice and 1150 ppm for sodium fluoride (**NaF**) and stannous fluoride (**SnF2**) dentifrices. Some prescription-strength fluoride dentifrices contain as much as 5000 ppm of sodium fluoride. Because this level of fluoride is not allowed in an OTC product under the anticaries monograph, these types of products must be prescribed by a dentist.[4,5]

Monograph vs. New Drug Application (NDA) for Marketing Approval

The second pathway is through a **New drug application (NDA)**, which is used for new drug products that fall outside the range of ingredients already included in the OTC Monograph system, as above. NDAs for dentifrices are uncommon and require the manufacturer to demonstrate that the product is safe and effective through comprehensive

Table 1. Oral Care Monographs: Dentifrices are Regulated with Three Separate Monographs.

Monograph	Current Status*	Example Indication	Example Ingredients and Products
Anticaries	FM	Prevents cavities	Sodium fluoride (Aquafresh Extreme Clean) Sodium monofluorophosphate (Colgate Cavity Protection) Stannous fluoride (Crest Pro-Health)
Tooth Desensitizer	TFM	Helps reduce sensitivity	Potassium nitrate (Sensodyne) Stannous fluoride (Crest Pro-Health)
Antiplaque-Antigingivitis	ANPR	Prevents plaque and gingivitis	Stannous fluoride (Crest Pro-Health)

* FM–Final Monograph; TFM–Tentative Final Monograph; ANPR–Advanced Notice of Proposed Rulemaking

clinical testing. Examples include extensive data packages (e.g., clinical efficacy, pharmacology and toxicology data) which must be submitted for FDA review to establish the drug's safety and efficacy to receive approval to market as therapeutic. Important characteristics of NDA versus monographed drugs are presented in Table 2.[6]

If a product contains an ingredient or drug not included in the monograph, it must be approved through the NDA process. Even if the drug is included in the monograph but is being used at a different dose, a new indication, or in combination with another drug (dual-active product) not specified in the monograph, the product is subject to NDA approval. For example, triclosan is an antibacterial ingredient that is not included in the Antiplaque-Antigingivitis Monograph and therefore underwent NDA approval. Despite their differences, both NDAs and monographs for OTC medicines have very similar standards for safety and efficacy.[6]

Claims for Therapeutic vs. Cosmetic Benefits

The US Federal Food Drug & Cosmetic Act defines a cosmetic as an article intended to be applied to the human body to cleanse, beautify, promote attractiveness, or alter the appearance. In contrast, a therapeutic drug is defined as an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or article intended to affect the structure or any function of the body. Manufacturer claims for therapeutic vs. cosmetic benefits thus are required to follow these definitions.[3] Dentifrices contain ingredients that help reduce caries, **plaque**, gingivitis, hypersensitivity, **dental erosion**, **calculus (anti-tarter)**, stain, and **halitosis**. Some ingredients provide a therapeutic benefit, while other ingredients or additives contribute to the cosmetic benefits or physical properties of the dentifrice.

If an ingredient is not included in an OTC monograph or is not approved under an NDA, it is not considered a drug, and therapeutic benefit claims cannot be made for it. Many

Table 2. NDA and Monograph Pathways: Key Regulatory Differences in These Processes Are Highlighted.

NDA	Monograph
Product specific.	Active ingredient specific.
Process seeks FDA premarket approval.	FDA premarket approval not required if monograph conditions met.
Product changes may require additional FDA approval.	Changes within monograph conditions require no FDA approval.
Labeling is unique to approved drug product.	Labeling is the same for all similar products.
Possible marketing exclusivity.	No marketing exclusivity: monograph is open to everyone.

nontherapeutic ingredients are described later in this course.[3,5]

Credentialing- The ADA Seal Program

While not a regulatory body, the American Dental Association (ADA) as the leading US dental professional association takes a vested interest in informing the public on the safety and efficacy of oral care products. They do this primarily through their Seal of Acceptance program, which began in 1930. The ADA Seal of Acceptance is a registered certification mark of the American Dental Association as assigned by the Council on Scientific Affairs where manufactures may submit safety and efficacy data for review.

This can be a powerful product endorsement in both professionals' and consumers' minds, as both of these groups have come to trust the ADA for providing guidance on the safety and efficacy of products. According to a 2017 survey conducted by the ADA, 3 out of 4 dentists recommend products with the seal to their patients. 69% of caregivers are more likely to look for the ADA seal, agreeing that the seal simplifies purchasing decisions in the dental aisle.[9]

In order to obtain the ADA Seal, manufacturers are required to submit data in accordance with published ADA guidelines for confirmation of each benefit for which the Seal of Acceptance is desired. For some benefits, these requirements include the submission of at least two well controlled clinical studies confirming efficacy, with the clinical trials run according to established ADA protocols. For benefits where clinical studies are not required, the ADA has established a series of specific laboratory tests that must be followed to confirm product effectiveness. For a product that wishes to claim multiple benefits, each benefit must be confirmed according to the required guidelines; thus, the overall investment (both clinical and laboratory) to obtain the ADA Seal is considerably higher for a product that is able to claim multiple benefits, compared to a product that claims a single benefit. The ADA Seal is usually awarded for a 5-year period, after which the company must seek renewal. If a dentifrice formulation changes, the manufacturer must submit a new application for the modified product.[5,6,7,8] Through this standardized, scientific review process, the Council decides whether to award its Seal of Acceptance to the product.

Click here for more information about the "*ADA Seal of Acceptance Program & Products*" requirements and products that carry the ADA Seal.

Figure 1. Examples of the ADA Acceptance Seal on Products.

Fluoride History

Early efforts to incorporate fluoride into dental preparations as well as research towards understanding the fluoride content of teeth gave conflicting results. A phenomenon called "Brown Stain", associated with too much fluoride ingestion, was thought to be "typical caries" in a paper presented in 1904 before the German Society for Surgery.[10] Mckay and Black investigated what had been termed Colorado Brown Stain as early as 1916. They found that this stain was present in other communities and associated it with the communal water supply, although they were not certain of the cause.[10] These and other findings led the United States Public Health Service to do extensive epidemiological surveys to study both dental caries and dental fluorosis in the late 1930s.[11] When it was confirmed that fluoride intake from water was associated with the prevalence of dental fluorosis as well as a reduction in dental caries, many delivery systems and strategies

were investigated to optimize the benefit of fluorides at the community level as well as the individual level.

In 1937, a dental preparation claiming to prevent decay was not favorably looked upon by the American Dental Association's (ADA) Council on Dental Therapeutics. The possibility of toxicity, conditions of usage and absorption questions led to the ADA's conclusion that "The use of fluoride in dentifrices is unscientific and irrational, and therefore should not be permitted."[6] At that time, dental problems were considered to be a personal matter. The finding that the single greatest reason for rejecting people from the military in World War II was a result of poor oral health changed this sentiment. Very quickly, oral health became a national security issue and was recognized as a public health problem. Studies in which the water supply of cities was artificially fluoridated were done in order to determine potential effectiveness of such a measure. Initial studies were placed in Grand Rapids, MI in 1945, with Muskegon, MI acting as the control city. Other sister city studies work also begun around that same time. The overall results demonstrated a significant reduction in dental caries without cosmetically displeasing dental fluorosis, when the fluoride concentration in the local water supply was maintained at about 1 ppm.[10]

In 2021, researchers in Canada published a study about the effect of stopping water fluoridation on children's dental caries in the cities of Calgary, where fluoridation began in 1991 and stopped in 2011, and Edmonton, which has fluoridated its water since 1967. After testing children some 7 to 8 years after Calgary stopped fluoridating its water, researchers said the prevalence of caries was significantly higher there than in Edmonton, "[pointing] to the need for universal, publicly funded prevention activities—including, but not limited to, fluoridation."[12]

Successfully formulating a fluoride dentifrice that was efficacious against caries was a significant oral health breakthrough because fluoride is incompatible with many ingredients or additives. In 1950, The Procter & Gamble Company formed a joint research project team headed by Dr. Joseph Muhler at Indiana University to develop and test a new dentifrice with fluoride. Results from a clinical study of this dentifrice indicated that children ages six to 16 showed an average 49% reduction in cavities, and adults showed tooth decay reduction to almost the same degree.[17,18] Interestingly, a market survey in 1958 showed the response to a therapeutic dentifrice had had little effect on market shares. It wasn't until Crest was granted the American Dental Association (ADA) Seal of Acceptance that it was able to set itself apart from all other toothpastes. A total of over 40 clinical trials had been conducted with the original stannous fluoride that have verified its efficacy. The combined importance of ADA acceptance plus no comparable therapeutic rival gave the Crest brand a chance to become a market leader. Following the success of this study, Crest® with Fluoristan® dentifrice launched into a number of test markets in 1955, followed by national expansion in January 1956. In 1960, and again in 1964, the American Dental Association confirmed that Crest effectively prevents tooth decay, reporting that "Crest has been shown to be an effective anticavity dentifrice that can be of significant value when used in a conscientiously applied program of oral hygiene and regular professional care" in granting its Seal of Acceptance (Figure 2).[19,20]

In 1969, Colgate received endorsement for a therapeutic dentifrice. This shifted the category of toothpastes from delivering merely cosmetic benefits to those focused on more therapeutic benefits, and the entire market began to evolve. In 1976, the American Chemical Society recognized Crest® with Fluoristan® as one of the 100 greatest discoveries of the previous 100 years.[21]

Figure 2. Original Crest toothpaste, with the ADA Seal of Acceptance.

One of the basic tenants of dentifrice is to contribute to cleaning efficacy. The desire to find more effective dentifrices with high compatibility between the fluoride active and different abrasive systems spurred continued research in the development of therapeutic dentifrices. After the success achieved with SnF_2 dentifrices, sodium monofluorophosphate (SMFP, Na_2FPO_3) (Figure 3) new dentifrices were eventually introduced with compatible abrasive systems, and the combinations demonstrated positive caries benefits in most clinical studies. The search for a more stable formulation capable of providing even greater anticaries effectiveness also led to the introduction of a sodium fluoride (NaF) formulation, which eventually replaced the original stannous fluoride (SnF_2) active ingredient. This new product used the advertising phrase of "Fluoristat®" and combined NaF with a silica abrasive system that proved more effective against caries than the earlier "Fluoristan®" formulation. This change in active agents occurred in 1981, after silica abrasive systems were developed that were compatible with most of the active agents found in dentifrices.[37] All of the fluoride actives have been shown to be successful, to some extent, in preventing dental caries when used in a regular program of oral hygiene. The highly competitive toothpaste market has been a factor in the research development of the chemistry to deliver a more effective product as well as improving flavor and increasing worldwide usage. This has been a great benefit to public dental health, as evidenced by the decline in the prevalence of dental caries over the past several decades in most developed countries.[38]

The predominance of NaF and SMFP (Na_2FPO_3) as the active agents in most toothpastes during this time also led to the inevitable question "**Are all fluoride dentifrices the same?**" This question was addressed by Stookey in 1985 after a review of over 140 articles on fluoride dentifrices.[39] It was found that a number of dentifrices with various active ingredients (NaF, SnF_2, AmF and Na_2FPO_3) and abrasive system combinations provided significant cariostatic benefits.

The major fluoride sources approved for use in the US are stannous fluoride (SnF_2), sodium fluoride (NaF) and sodium monofluorophosphate (Na_2FPO_3). During use, NaF and SnF_2 dissociate to provide the free fluoride ion and the companion cation. The Sn cation may have some interactions on its own, although the primary effects on caries are generally associated with the fluoride component. For Na_2FPO_3, the fluoride source is in a different chemical form and requires enzymatic hydrolysis to cleave the covalent bond between the phosphate molecule and fluoride yielding slower fluoride release. Studies of SMFP have shown it is compatible with a broader range of dentifrice abrasives, but it may differ in its mode of action from the fluoride ion.

In 1999, the US Center for Disease Control (CDC) issued a statement that water fluoridation is one of the 10 most important public health measures of the 20th century.[7] Fluoride's presence in low concentration and high frequency is more effective at preventing caries than high levels of fluoride used in low frequency. Because water fluoridation is not available in many countries,

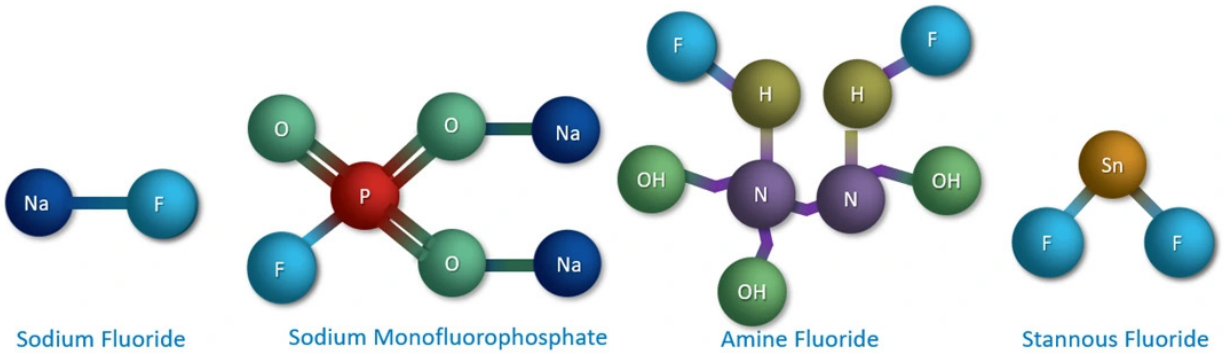


Figure 3. Fluoride is the active ingredient in most dentifrices that is providing caries therapeutic benefits. The carrier fluoride molecule varies.

dentifrice is considered to be one of the most important sources of fluoride globally.[8] Common environmental sources of fluoride are depicted in (Figure 4).[4,15,16]

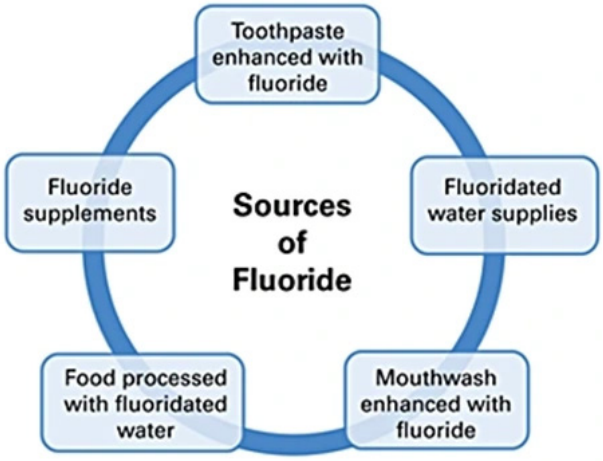


Figure 4. Fluoride Sources. There are several common environmental sources of fluoride, including fluoridated drinking water and oral health care products.

While the popularity of non-fluoridated or fluoride alternatives toothpastes are on the rise, there are none that have demonstrated the breadth of clinical efficacy for caries prevention as Fluoride has, otherwise the FDA and other regulatory bodies would recognize them as therapeutic.

Although fluoride dentifrices and improved oral health have greatly benefited the population by reducing caries incidence, surveys showed a continued high prevalence of gingivitis and gingival recession among adults.[49] The desire to treat both caries and gingivitis, coupled with the changing patterns in oral health and the recognition of the importance of oral health in relation to systemic disease, led to extensive research by the Procter & Gamble laboratories and the "return" to stannous fluoride as an active ingredient. This required the development of a stabilized formulation that would provide sufficient stannous fluoride activity to provide the anti-gingivitis inflammatory benefit and sufficient reserves of the active fluoride to provide a caries benefit. The stabilization system developed used sodium gluconate as a chelating agent to protect SnF_2 from hydrolysis. Stannous chloride was also included as an antioxidant to protect SnF_2 from oxidation and as a stannous reservoir to reduce the SnF_2 loss onto the abrasive. The broad range of beneficial aspects of stannous fluoride, such as dentin desensitization, root surface reactivity, plaque and gingivitis benefits as well as its anticaries effectiveness strongly suggested that this unique active could be the basis for many future improvements in dentifrice formulations.[42-52] Thus, the active agents most readily available in the US market once again included SnF_2 as well as NaF and Na_2FPO_3.

Another product innovation that helped shape the market for years came from the public's desire for whiter teeth. Whitening agents were available in the dental office but not in the drugstore as an over-the-counter product. One of the first claims was the removal of extrinsic stains by existing tartar control agents. These formulas were optimized and tested for stain removal as well as tartar control. Intrinsic stains normally required the use of peroxides or carbamides which have the ability to bleach the teeth and increase "whiteness." Crest Whitestrips marked the advent of consumer applied whitening agents and allowed the individual to brighten their smile at home.[40] Dentifrice manufacturers were also aware of this public interest in a cosmetic benefit of oral health products and improved formulations for stain removal, stain prevention, tartar reduction, and whitening all became available in the marketplace. This cosmetic benefit has been a continuing focus in oral care product development since the late 1990s. The whitening effect encompasses the original cleaning function of dentifrices, such as tartar and stain removal, but may also include intrinsic stain removal agents.

As oral care products continue to evolve, we can expect to see even more interesting combinations and approaches in the future, with each iteration intended to deliver either enhanced performance or an increased number of overall oral care benefits. While some of these future products may come from unique combinations of ingredients currently in use, others may include ingredients that are completely new to oral care products. In addition, according to monograph, a product can't have 2 ingredients for the same therapeutic benefit (e.g., no fluoride combinations for caries prevention).

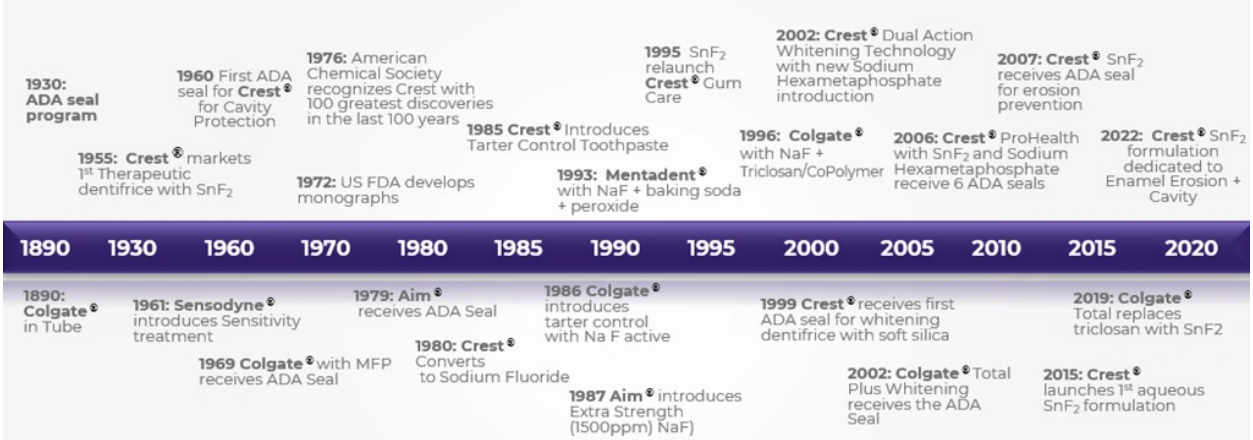


Figure 5. Timeline evolution of commercially available dentifrice

Therapeutic Ingredients:

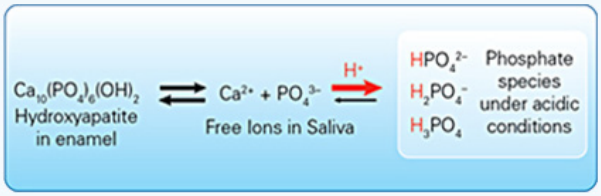
The following sections will explain the mechanism of action of fluoride, and common fluoride actives used in dentifrices marketed in the U.S. will be described.

Caries Process and Fluoride's Mechanism of Action

Dental caries is an infectious disease caused by the complex interaction of cariogenic (caries-causing) bacteria with carbohydrates (i.e., sugars) on the tooth surface over time. Cariogenic bacteria metabolize carbohydrates for energy and produce organic acids as byproducts. The acids lower the pH in the plaque biofilm.[22]

The hydroxyapatite of tooth enamel is primarily composed of phosphate ions (PO_4^{3-}) and calcium ions (Ca^{2+}). Under normal conditions, there is a stable equilibrium between the calcium and phosphate ions in saliva and the crystalline hydroxyapatite that comprises 96% of tooth enamel. When the pH drops below a critical level (approximately 5.5 for enamel, and 6.2 for dentin), it causes the dissolution of tooth mineral (hydroxyapatite) in a process called demineralization.
When the natural buffer capacity of saliva elevates pH, minerals are reincorporated into the tooth through the process of remineralization.[22-24]

Point of Interest: When the pH on the tooth surface becomes acidic, phosphate in oral fluids combines with hydrogen ions (H+) to form hydrogen phosphate species (see below.) Under these conditions, phosphate is "pulled" from tooth enamel to restore phosphate levels in the saliva, and the hydroxyapatite dissolves. As pH returns to normal, the calcium and phosphate in saliva can recrystallize into the hydroxyapatite, remineralizing the enamel.



Caries is simply the result of a series of demineralization/remineralization cycles where, over time, demineralization conditions prevail. The caries process can be affected in several ways. One of the most effective methods to prevent caries is by promoting remineralization and slowing down demineralization. This can be accomplished with fluoride therapy.[4,15,25]

When fluoride is present in oral fluids (i.e., saliva), fluorapatite, rather than hydroxyapatite, forms during the remineralization process. Fluoride ions (F-) replace hydroxyl groups (OH–)

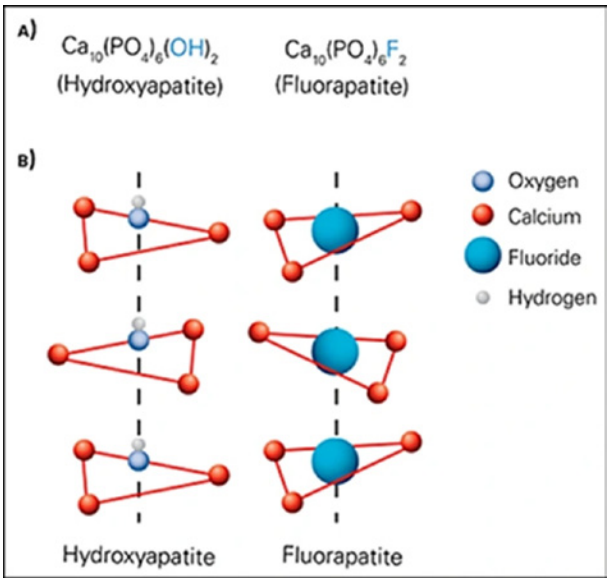


Figure 6. Fluorapatite Formation.
(A) Fluoride ions (F–) replace hydroxyl groups (OH–) in hydroxyapatite to form fluorapatite in the tooth enamel. (B) A portion of the apatite crystal lattice is depicted showing the replacement of hydroxide for fluoride

Adapted from: Posner, 1985.[26]

in the formation of the apatite crystal lattice (Figure 6). In fact, the presence of fluoride increases the rate of remineralization.

Fluorapatite is inherently less soluble than hydroxyapatite, even under acidic conditions. When hydroxyapatite dissolves under cariogenic (acidic) conditions, if fluoride is present, then fluorapatite will form. Because fluorapatite is less soluble than hydroxyapatite, it is also more resistant to subsequent demineralization when acid challenged (Figure 7).

Under cariogenic conditions, carbohydrates are converted to acids by bacteria in the plaque biofilm. When the pH drops below 5.5, the biofilm fluid becomes undersaturated with phosphate ion and enamel dissolves to restore balance. When fluoride (F–) is present, fluorapatite is incorporated into demineralized enamel and subsequent demineralization is inhibited. Under pH conditions 4, the fluoride is unavailable for remineralization.

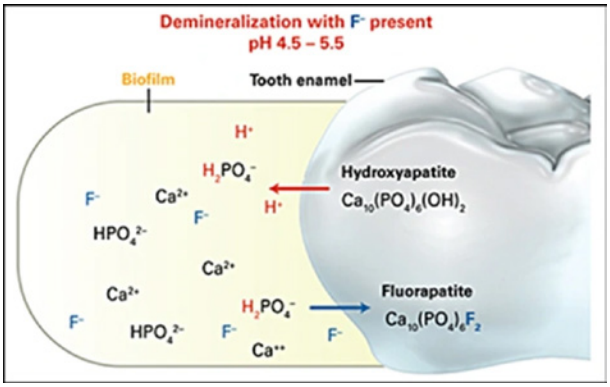


Figure 7. Fluoride Reactivity.

Adapted from: Posner, 1985.[19]

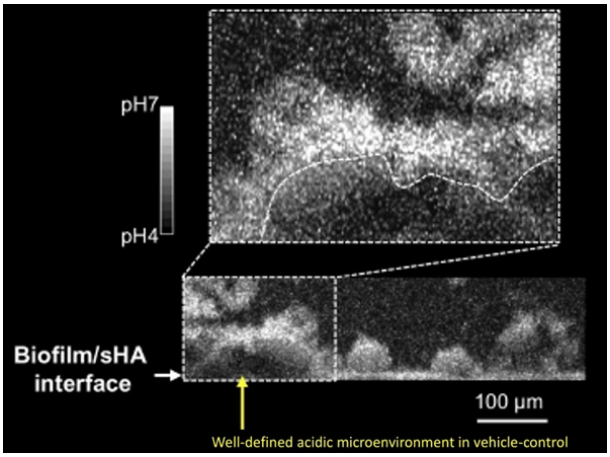


FIGURE 8. pH mapping image reveals acid pocket underneath the biofilm on the tooth surface despite exposure to pH 7 buffer.

Caries is a sub-surface phenomenon. With fluoride treatment, a noncavitated lesion can be remineralized with fluorapatite and have greater resistance to subsequent demineralization than hydroxyapatite (Figure 9). Even when available at very low concentrations, fluoride is effective as an anticaries agent.[4,25,27]

Common Fluorides

Fluoride can be delivered from several different fluoride molecules. The three most popular sources of fluoride globally, which are all accepted by the US FDA as clinically effective, are (figure 3):

- stannous fluoride (SnF_2)
- sodium fluoride (NaF)
- sodium monofluorophosphate (Na_2PO_3F)

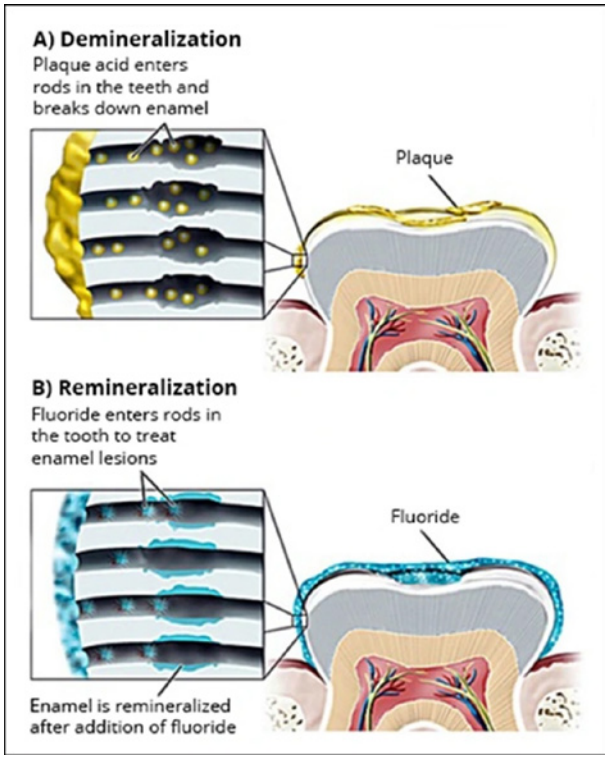


Figure 9. Demineralization/Remineralization.
(A) Plaque acids cause a demineralized, sub-surface lesion. (B) Fluoride treatments remineralize the lesion with a more acid resistant fluorapatite mineral.

The efficacy of fluoride as a caries preventive agent depends largely on its concentration and availability in the oral fluids to affect the demineralization/remineralization balance. Over the years, hundreds of clinical studies have been conducted to test the efficacy of fluoride dentifrices in caries prevention. In general, across all fluoride types, these studies show approximately a 25% reduction in caries over a nonfluoridated control dentifrice.[28]

1. **Stannous fluoride.** Stannous fluoride (SnF_2; also called tin fluoride) is highly reactive, and the challenge was finding an abrasive system that had low enough reactivity with fluoride to maintain the **bioavailability** of the fluoride. The formulation included 0.454% stannous fluoride and the abrasive calcium pyrophosphate was marketed as Crest® with Fluoristan®. While stannous fluoride also has the potential to deliver benefits related to the antibacterial properties of the ingredient, this early formulation only delivered an anticaries benefit based on the action of fluoride. In the 1990s, manufacturers developed methods to stabilize stannous fluoride formulations that deliver the antibacterial benefit of the ingredient as well.[29,30]

Video 1. Demineralization/Remineralization with Fluoride.
Video Does Not Contain Sound or Voiceover.
Click on image to view video online.

2. **Sodium fluoride.** Sodium fluoride (NaF) is a fluoride salt commonly used in dentifrices and oral rinses. Sodium fluoride delivers a highly reactive fluoride ion; therefore, formulation chemistry with a compatible abrasive is critically important for achieving the anticaries benefit. The earliest fluoride dentifrices, formulated with NaF and calcium abrasives, provided essentially no anticaries efficacy.[31,32] In the early 1980s, silica abrasives that were compatible with sodium fluoride became available and allowed dentifrices with NaF to be developed; these formulas were tested and proven to be clinically effective against caries.[33,34]

3. **Sodium monofluorophosphate.** Sodium monofluorophosphate (SMFP) was introduced into Colgate's first fluoridated dentifrice and allowed this brand to obtain the ADA Seal of Acceptance for cavity protection in 1968 (Figure 10).[35] Unlike sodium fluoride, SMFP is not an ionic fluoride salt, but rather a **covalently** bound compound that requires enzymatic activation by a salivary **enzyme** (alkaline phosphatase) to release bioavailable fluoride (Figure 10).[36] Because of this lower reactivity, SMFP is compatible with more abrasives than other fluoride sources.[35]

Antiplaque/Antigingivitis

Adding antibacterial action to dentifrice to reduce plaque and gingivitis was a major therapeutic breakthrough. SnF_2 is the only ADA recognized dentifrice ingredient that has the potential to kill or inhibit bacteria that cause plaque and gingivitis. With the evolving evidence linking oral health to other systemic conditions via chronic inflammation it is of utmost importance to help patients resolve gingivitis. While mechanical removal is foundational, the use of a highly bioavailable stannous fluoride dentifrice can reduce gingivitis by 51% relative to regular fluoride toothpastes in three months.[146]

Figure 10. Colgate® with SMFP.

Stannous Fluoride

Stannous fluoride exerts antibacterial effects by two modes of action. First, stannous fluoride exerts a killing effect on bacteria (bactericidal action). This is probably due to non-specific interaction with the bacterial membrane that causes membrane disruption. The result is leakage of cellular components that leads to cell **lysis** and death.

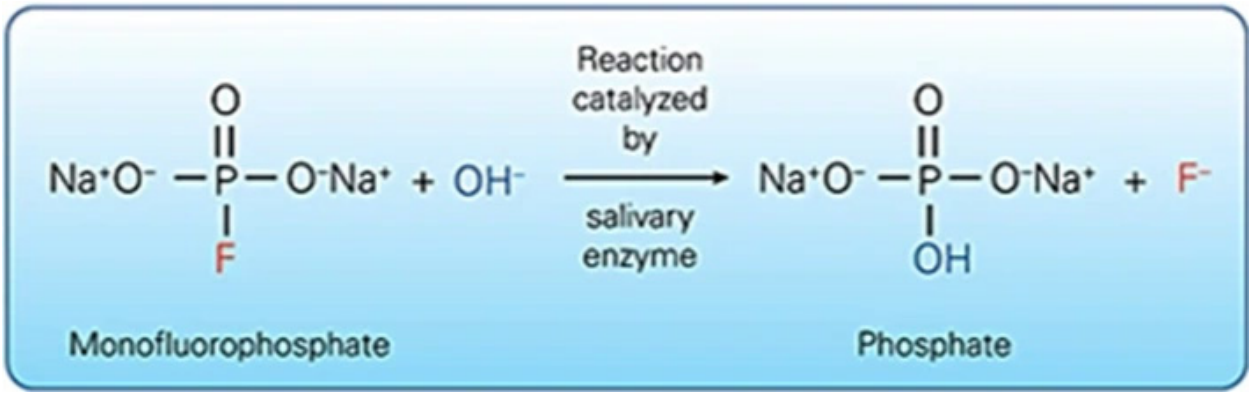


Figure 11. Enzymatic activation of SMFP.
The covalent bond of SMFP must be broken to release fluoride for bioavailability.

The second, and more important, mode of antibacterial activity is through stannous fluoride's inhibition of metabolic enzymes. The inhibition of metabolic activity affects bacteria in a number of ways, including:[58,59]

- reduction of bacterial growth
- prevention of bacterial adhesion to oral surfaces (e.g., enamel, exposed dentin)
- reduction in bacterial toxins that are recognized to boost the inflammatory response leading to gingivitis

Stannous fluoride's inhibitory effect on bacteria is related to its inhibition of bacterial glycolysis, an energy making process whereby metabolic enzymes break down carbohydrates. In addition, studies have demonstrated that stannous fluoride significantly reduces metabolic toxins produced by bacteria in plaque biofilm.[58,59] Stannous effects are further recognized to bind to bacterial toxins, preventing immune receptor signaling. Stannous is therefore important to rebalance the oral microbiome in favor of a healthier flora, not only reducing the amount of plaque but reducing plaque toxicity for both soft and hard tissue.[60,61]

One of the major breakthroughs in stannous fluoride formulation efforts was due to technology innovations that enabled the combination of both whitening and stabilization chemistries to provide highly effective stannous fluoride formulations that are not compromised by common esthetic negatives, such as poor taste or staining of earlier stannous fluoride products.[42,61,62]

Antihypersensitivity

Cervical dentinal hypersensitivity is a condition characterized by sharp pain associated with thermal, evaporative, tactile, osmotic or chemical stimuli. This condition depends on dentin exposure, as well as the patency of the dentinal tubules. It is widely accepted that dentinal hypersensitivity is a result of fluid movement within the dentinal tubules, which stimulates nerve endings in the pulp matrix.[63-68]

Tooth hypersensitivity is a condition that patients commonly report to their dental professional; thus, it is a segment of the dentifrice market heavily influenced by professional recommendations. It has been reported that up to 92% of the adult population suffers from this condition.[63-68]

Video 2. Progression of Gingivitis Induced by Bacteria.
Video Does Not Contain Sound or Voiceover.
Click on image to view video online.

Video 3. How an Antibacterial Agent Reduces Bacteria and Gingivitis (Inflammation).
Video Does Not Contain Sound or Voiceover.
Click on image to view video online.

Video 4. Fluid Movement in Tubules.
Video Does Not Contain Sound or Voiceover.
Click on image to view video online.

A segment of the fluoride dentifrice market has emerged that specifically addresses the needs of patients suffering from sensitive teeth. One of the first dentifrice products to enter this segment of the market was Sensodyne®, which was introduced in 1961. More recently, tooth sensitivity has become a very dynamic area, as several new products have entered the market with proprietary ingredients to treat dentinal hypersensitivity.

Dentinal hypersensitivity is generally treated in one of two ways.

1. Chemical desensitization of the tooth nerve endings (nerve depolarization).
2. Tubule occluding agents or barriers to reduce dentin permeability.

Antihypersensitivity treatments with these mechanisms are described on the following pages.

Nerve Depolarization Agents

To understand how a chemical desensitization agent works, one must first understand how a nerve cell transmits pain stimuli. Potassium (K+), sodium (Na+), and chloride (Cl–) ions are all involved in the electrical activity of nerve cells. When the nerve cell is at rest, the potassium ion concentration is higher on the inside of the cell than on the outside, while the sodium ion concentration is higher on the outside of the cell than on the inside (Figure 12). When the nerve cell is stimulated, these ions cross the nerve cell membrane through channels and move from an area of high concentration to an area of lower concentration (referred to as the concentration gradient). Thus, potassium ions flow from the inside to the outside of the cell and the sensation of pain is transmitted.

Upon stimulation of nerve cells, potassium and sodium ions follow their concentration gradient from high to low. Potassium ions leave the cell and sodium ions enter the cell. Potassium ion is a desensitization agent because it

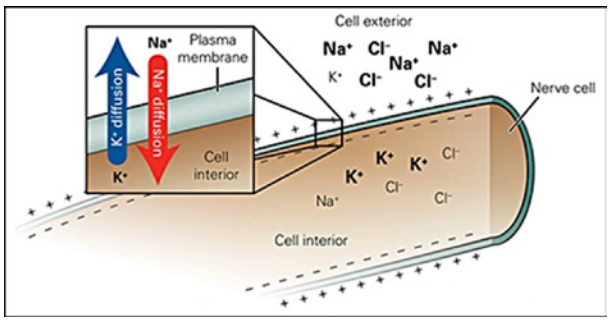


Figure 12. Basics of Nerve Activity.

diffuses through dentin tubules and increases the extracellular potassium concentration at the nerve ending, eliminating the potassium ion concentration gradient across the nerve cell membrane. Without this concentration gradient, the nerve cell will not depolarize and will not respond to stimuli; thus the sensation of pain will not be transmitted. Potassium ion can be delivered in a variety of salt forms (e.g., potassium nitrate, potassium citrate). The most common potassium salt used in sensitivity dentifrices is potassium nitrate (KNO_3).[66]

Video 5. How Nerve Depolarization Agents Work.
Video Does Not Contain Sound or Voiceover.
Click on image to view video online.

Tubule Blocking or Occluding Agents
Another strategy to treat/prevent dentinal hypersensitivity is to reduce the permeability of the dentin by occluding or blocking the exposed dentin tubules. This prevents stimuli from causing fluid flow in the tubules, thereby preventing the nerve endings inside the tooth from being stimulated.[68]

a. **General mechanism of action.** Several ingredients can be used to occlude or block the dentinal tubules. All of these agents have similar mechanisms of action, forming salt precipitates on the surface of the exposed dentin and inside the dentinal tubules. These precipitates effectively reduce or block the fluid flow in the tubules and exert a desensitization effect. Strontium chloride was the desensitizing ingredient used in the original Sensodyne® dentifrice, and it acted via this mechanism by forming strontium salt precipitates; however, it is rarely used anymore because of its strong metallic taste and incompatibility with fluoride.
b. **Tubule-occluding agents.** Other tubule-occluding agents new to the market include arginine at 8% with calcium carbonate (Pro-Argin™), strontium acetate, and calcium sodium phosphosilicate (Novamin®), Nano Hydroxyapatite (HAP), Stannous.

Arginine, found naturally in saliva, may help usher calcium to open tubules for incorporation of calcium phosphate into dentin. Calcium carbonate creates a basic environment, and calcium phosphate salts are less soluble at higher pH (more basic). The combination of high local calcium concentration at the dentin tubule at basic pH is designed to promote precipitation of calcium phosphate salts.[69]

Strontium acetate. Unlike the original strontium chloride, strontium acetate can be formulated into fluoride-containing dentifrices. Upon toothbrushing, strontium-based precipitates form to occlude dentinal tubules and build a resistant barrier over time.

Calcium sodium phosphosilicate (Novamin®). In saliva, Novamin® releases calcium and phosphate ions and raises the ph. Under these conditions, calcium phosphate salts precipitate from solution to not only block dentin tubules but also to form an insoluble calcium phosphate layer on the surface of enamel. [70,71]

Hydroxyapatite or *Nano HAP*: is a bioactive substance with components and structures resembling teeth which can occlude dentinal tubules.[73]

Video 6. Tubule Occlusion.
Video Does Not Contain Sound or Voiceover.
Click on image to view video online.

Stannous fluoride. Stannous fluoride, through hydrolysis and oxidation reactions, forms many insoluble metal salts that can precipitate in dentinal tubules and on the dentin surface (Video 6) to provide effective relief against hypersensitivity.[30,62,73] Stannous fluoride is the only fluoride delivering protection from caries[73] and plaque/gingivitis[46] as well as hypersensitivity[62,75] and dental erosion.[76-86]

Dental Erosion

One of the most challenging aspects of dentifrice development is to ensure that they continue to meet the changing needs of consumers. One example of this is the increased prevalence of dental erosion that has been reported on a global basis.[87] Most researchers believe that excessive consumption of acid-containing foods and beverages is a primary cause of this emerging issue.[88-90] Excessive ingestion of acid from any source can eventually overwhelm the pellicle coating on exposed tooth surfaces, the natural protective mechanism that is designed to protect teeth against damage due to acid intake.[91] Enamel erosion has become an important issue with the increased consumption of sports and energy drinks, soft drinks, and citric juices.[107] Dental professionals have been successful in steering consumers away from sugar laden beverages that can lead to caries. However, diet soft drinks, sports and energy drinks although better from a standpoint of sugar, contain essentially all of the acid contained in their sugared counterparts. From the standpoint of erosive potential, there is little to no difference between the two varieties of beverage.[93] All of these products have a pH below the critical level for dissolving dental enamel. In this context, the enamel erosion benefits of existing dentifrice ingredients has become more relevant. [108-110]

As a result of this drop in pH, teeth can become softened, and any abrasive action on these tooth surfaces while they are softened can result in permanent loss of the affected tooth mineral. Even the repetitive movement of the tongue over these acid-challenged surfaces has been noted as a potential source of abrasive activity.[92]

Since fluoride is well known for its ability to strengthen enamel, significant research has been done to determine whether or not fluoride is able to strengthen teeth to sufficiently protect them against erosive acid damage. Erosion is characterized by the dissolution and loss of mineral and removal of the tooth enamel surface under highly acidic conditions. When the localized pH drops below approximately 4.5, the pellicle cannot protect the enamel surface, and irreversible erosive damage can occur.

Many of these studies have found that fluoride, in general, does provide some level of benefit. However, there is an increasing body

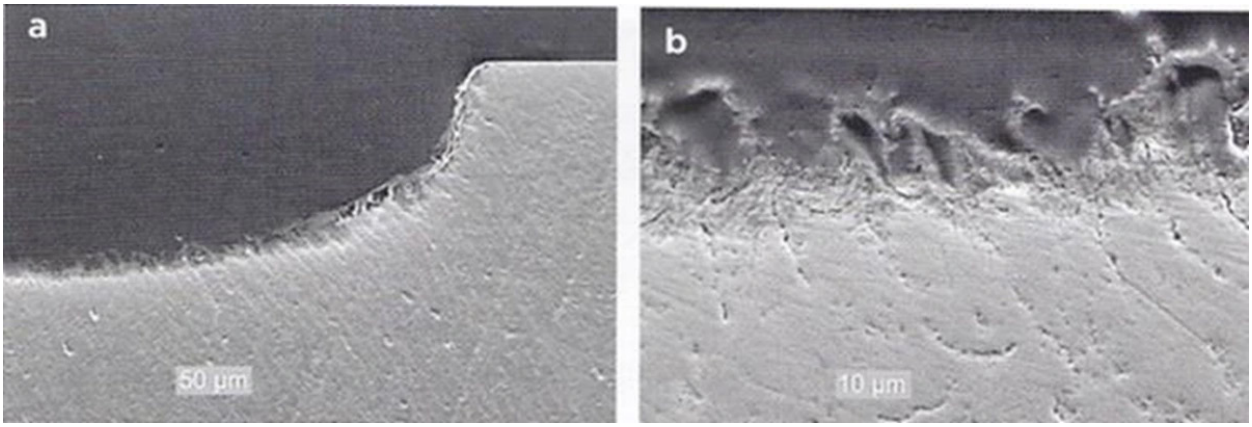


Figure 13. Surface Softening Leading to Tooth Erosion.

Credit: Lussi A, Schlueter N, Rakhmatullina E, Ganss C: Dental Erosion – An Overview with Emphasis on Chemical and Histopathological Aspects. Caries Res 2011;45(suppl 1):2-12. doi: 10.1159/000325915

of research that has demonstrated unique benefits attributable to stannous fluoride over all of the other fluoride sources used. Although all fluorides help form stronger mineral within the tooth structure after a caries challenge, under plaque, dental erosion primarily occurs on smooth surfaces of the teeth, in the absence of plaque. Thus, the type of acid challenge is much different than one that occurs during caries formation. The level of challenge and the concentration and volume of acid are generally much higher during an erosive acid challenge. Stannous fluoride is different from other fluorides in that it deposits, in addition to the caries preventative F- ion, an invisible, protective barrier layer onto exposed tooth surfaces that consists of stannous (tin) precipitates. This barrier layer is highly acid resistant and provides the tooth surface with an extra layer of protection against erosive acid challenges.

The first clinical trial that demonstrated the preventive benefits of a stabilized, SnF2 toothpaste (Crest PRO-HEALTH) against the initiation and progression of dental erosion was published in 2007.[95] A special issue of the *International Dental Journal* (2014) presented a range of studies that confirmed the erosive protective benefits of stabilized stannous fluoride dentifrice.[95-101] Interestingly, one study demonstrated the erosion protection potential of a stabilized SnF_2 dentifrice was significantly greater than that provided by some of the most popular prescription level (5000 ppm F) fluoride treatments available.[102] More recently, several additional human in situ clinical studies have demonstrated enhanced erosion protection benefits of stabilized stannous fluoride over other formulations tested.[103-106] Thus, formulations are now available that provide not only all of the major benefits generally attributable to toothpaste, but are also proven to provide a new benefit that meets the ever-changing needs of consumers by preventing the loss of mineral. A recent meta-analysis of Gluconate chelated stannous formulations demonstrated an 83% reduction in enamel surface loss vs sodium fluoride or arginine.[147]

While it is unlikely that dental professionals will be able to get consumers to stop drinking acid-containing beverages, it is comforting to know that therapies are available to help protect these consumers against things that are difficult for them to control. Stannous fluoride provides enhanced protection against the initiation and progression of dental erosion compared to other fluoride sources commonly used.

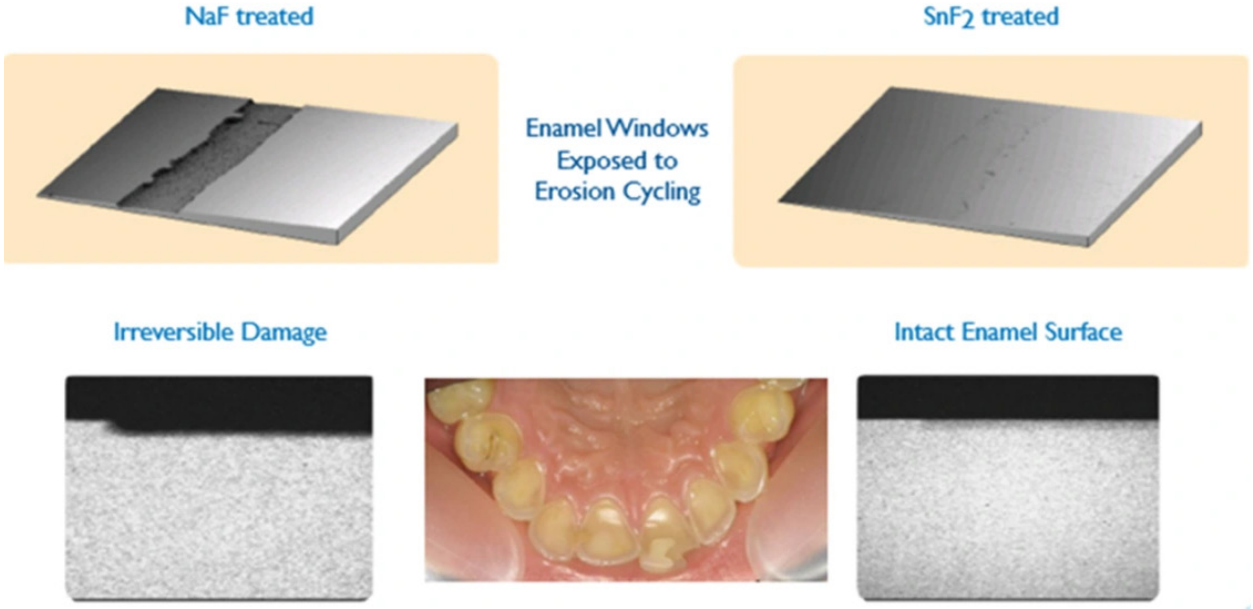


Figure 14. Testing the Erosion Prevention Effects of Different Fluoride Sources.

Cosmetic Benefits

While delivering fluoride for cavity protection was a major therapeutic advance in the dentifrice market, researchers saw an opportunity, over time, to expand the benefits offered by dentifrice. By the 1980s, additional innovations were having an impact. Agents were discovered that could provide protection against calculus and stain, and this opened an era where improved cosmetic benefits spurred the dentifrice market.

Calculus Control

Dental plaque calcifies when calcium phosphate begins depositing in it. Under normal conditions, the oral fluids are saturated with calcium and phosphate, which is important for maintaining sound enamel. However, this abundance of mineral ions also contributes to calculus formation on the tooth surface (i.e., calcification of plaque biofilm). The amount and type of calcium phosphate salts present vary greatly but include brushite, octacalcium phosphate (OCP), tricalcium phosphate (TCP) and apatite. While supragingival calculus forms from saliva, subgingival calculus forms either from saliva or crevicular fluid. Dental calculus that forms from crevicular fluid can contain heme and some breakdown products which make it pigmented. It is called serumnal calculus. Calculus forms most readily in areas which are adjacent to the openings of the salivary ducts, where the calcium phosphate in saliva is least stable. In populations with poor oral hygiene, supragingival calculus can be extensive and result in gingival recession. Calculus formation can be controlled by adding mineralization inhibitors to dentifrices and mouthrinse. The chemical agents used most often for calculus control in dentifrice are described briefly below.[111]

1. **Pyrophosphate**. Phosphate is a ubiquitous chemical group found in biological systems. As shown in (Figure 15), two phosphate groups combine chemically to form a molecule called pyrophosphate (P2O74-). Pyrophosphate occurs naturally in saliva and plays a role in inhibiting calculus formation. These molecules chelate calcium (Figure 16), slowing the rate of nucleation (crystal formation) and calcification of plaque. The pyrophosphate binds to calcium in a growing crystal, essentially slowing further crystal growth at that site and effectively decreasing calculus build-up (Figure 16). Original Crest© Tartar Control dentifrice contained 3.3% pyrophosphate. It was the first tartar control dentifrice introduced to the market, and the first tartar control dentifrice to receive the ADA Seal of Acceptance.[112-113]

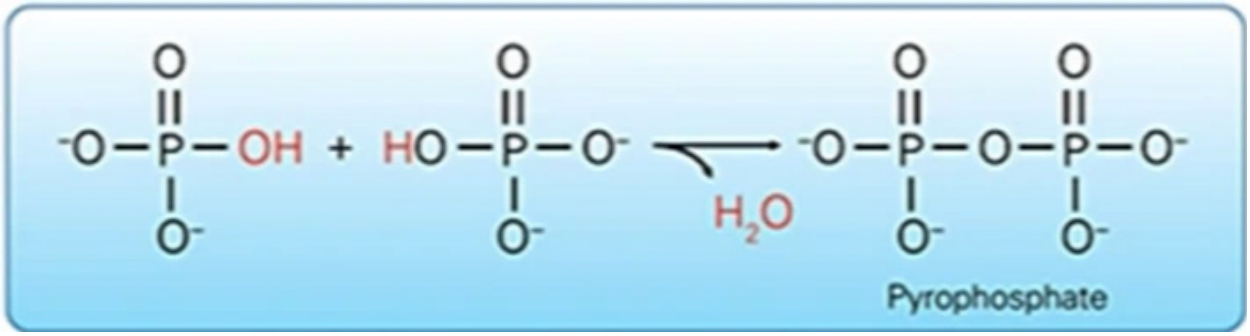


Figure 15. Pyrophosphate. Two phosphate groups combine to form pyrophosphate.

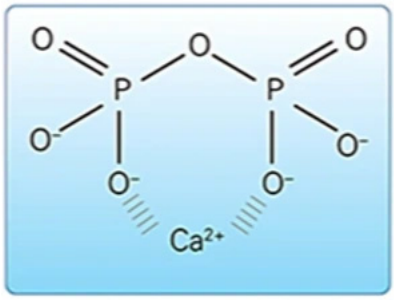


Figure 16. Pyrophosphate. Negatively charged pyrophosphate molecules bind (chelate) positively charged calcium ions.

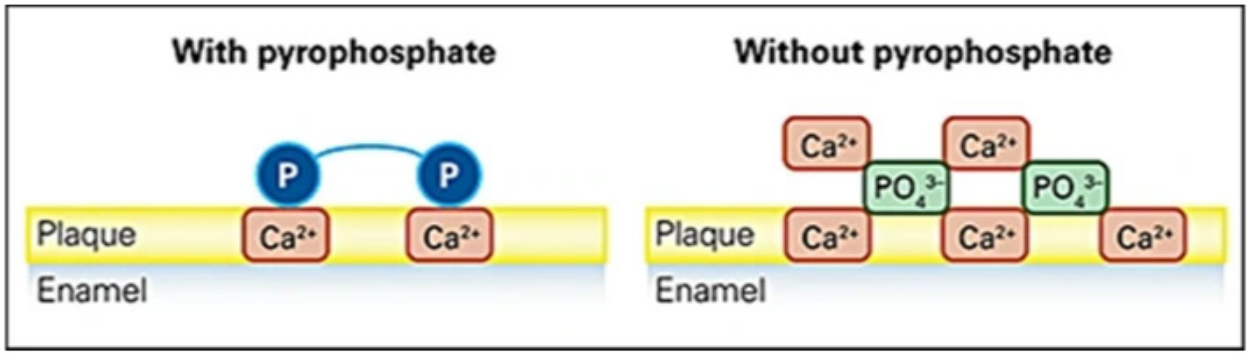


Figure 17.Anticalculus Action. Pyrophosphate inhibits calculus formation by inhibiting calcium phosphate deposition in plaque.

2. **Sodium hexametaphosphate (SHMP).** SHMP is a large polyphosphate molecule and has multiple calcium binding sites in one molecule. It is a very effective calculus inhibitor. Because it works only on the surface, it is sometimes called a calcium surface active builder. SHMP is susceptible to hydrolysis and must be formulated in a low water dentifrice to be stable (Figure 18).[114-115] SHMP particles will not dissolve in low-water formulations, so the SHMP particles may be perceived as "gritty." However, these particles are highly soluble in water and will begin dissolving immediately upon brushing without imparting abrasive action.

3. **Zinc.** Zinc salts (e.g., zinc citrate, zinc chloride, zinc lactate) are used in some tartar control dentifrices and oral rinses, and have been shown to be moderately effective at controlling calculus.[116] Positively charged zinc ions (Zn^{2+}) inhibit crystal growth by substituting for calcium in the crystal lattice of calcium phosphate. This interferes with the crystal formation and slows crystal growth. As a result, calculus formation is reduced.

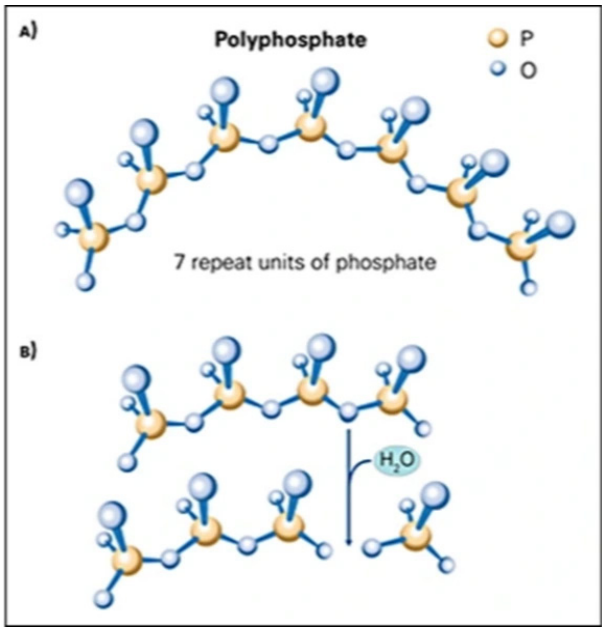


Figure 18. SHMP Hydrolysis. (A) SHMP is a polyphosphate created from a chain of repeating phosphate units. (B) The hydrolysis or breakdown of SHMP proceeds to single phosphate molecules, although many intermediate products are also produced.

Stain Control/Whitening Agents

Stain control and whitening are key benefits of modern dentifrices. These are accomplished via ingredients that target specific types of tooth stain. Stains can be classified as extrinsic (surface stains) or intrinsic (below the enamel surface), and their management is based primarily on that classification. Dentifrices primarily work against extrinsic stains. Bleaching products that contain hydrogen peroxide (i.e., whitening strips) or carbamide peroxide (i.e., dental office bleaching trays) and allow longer contact time with the dentition address intrinsic stains as well as extrinsic stains.[61,117]

Despite being extremely hard, the tooth's surface can be stained. Extrinsic (surface) stains can generally be relatively easily removed daily by proper tooth brushing with a dentifrice. If extrinsic stains are not frequently removed, they can firmly attach to the tooth surface, and may require a professional removal. Surface stains can be removed daily through either physical or chemical action, as described below.[61,118]

Video 7. Formation of calculus.
Video Does Not Contain Sound or Voiceover.
Click on image to view video online.

Video 8. Mechanism for calculus protection.
Video Does Not Contain Sound or Voiceover.
Click on image to view video online.

Physical action. Most dentifrices contain mild abrasives that help clean precipitated stain particles from the tooth surface, controlling surface stains with home care. While dentifrice abrasives are desirable to keep stains off teeth, they are also designed to not wear down the tooth enamel over time with repeated brushing.[117]

The abrasivity of dentifrice is measured in terms of Relative Dentin Abrasivity, or RDA. This rating was introduced in the early 1970s and is used by professional dental societies and boards of health to rate the abrasivity of commercial dentifrices.[117-119] RDA values are obtained in the laboratory by comparing the amount of tooth structure worn away by a

standardized tooth brushing protocol using any given dentifrice with that of a standard dentifrice. These laboratory values are not intended to replicate real life conditions or predict real world outcomes. Dentifrice with a low RDA value may or may not be less abrasive, also tends to remove less surface stain. The International Standards Organization (ISO) specification states that a dentifrice should not exceed an RDA of 250, which is considered safe for hard tissues for a lifetime of use. Although there is a wide range of RDA values for various dentifrices, there are no relative degrees of safety between 0 and 250. In other words, a dentifrice with an RDA of 200 is as safe as one with an RDA of 50 for daily usage for a lifetime. Having an effective abrasive system in a dentifrice is important for cleaning the teeth and removing extrinsic stain.[120] Fluoride ions are very reactive and can interact with common dentifrice abrasives, rendering the fluoride inactive for caries control. Also, many dentifrice abrasives have a very porous, negatively charged surface that can bind many dentifrice ingredients, lowering their bioavailability. For this reason, formulating dentifrices with the right abrasives is critical to achieving the desired benefits of other ingredients.

Chemical action. Polyphosphates, which are dentifrice ingredients used to control calculus, also target extrinsic stain. One of the most effective ingredients with this dual action is SHMP, which is used in several marketed dentifrices. SHMP controls stain with a chemical action. Stain molecules, or chromogens, are usually negatively charged molecules; they have an affinity for positively charged ions like calcium (Ca2+) that reside in the tooth enamel and cross-link pellicle proteins. SHMP is also negatively charged, with a strong affinity for calcium. SHMP can displace stain molecules from calcium binding sites. It binds to the tooth surface and integrates into the pellicle to prevent additional stain molecules from binding (Figure 19).[61,62,121]

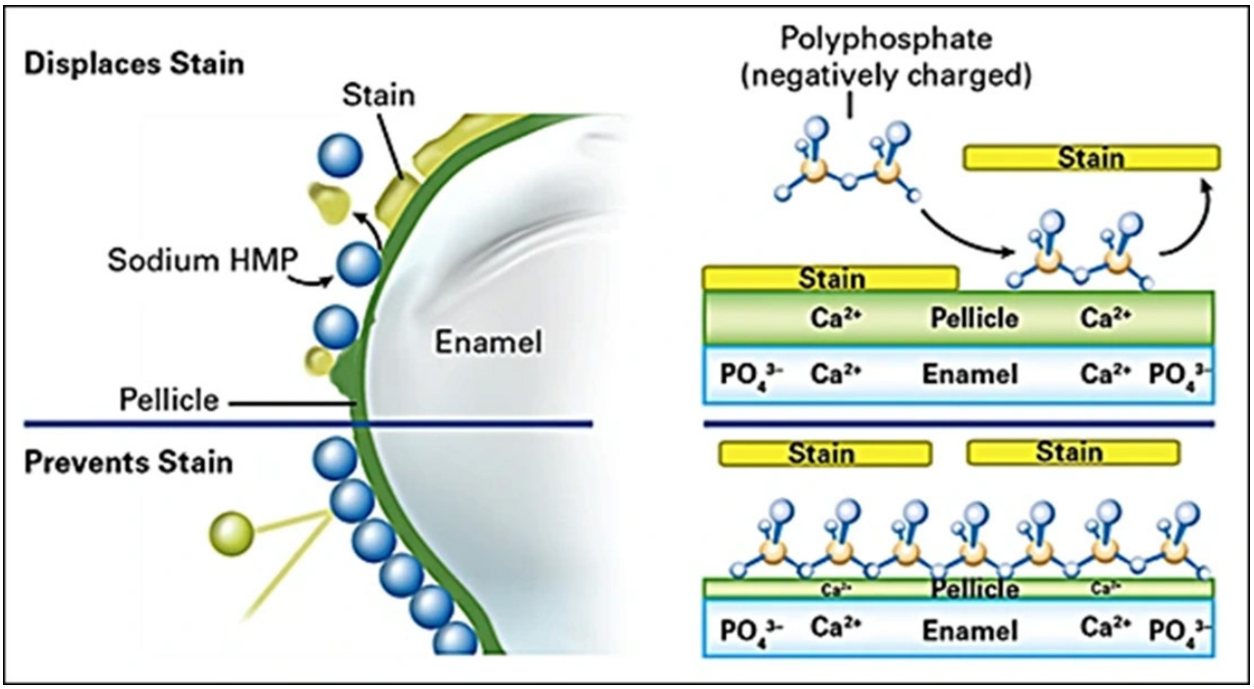


Figure 19. Stain Removal and Prevention.

Halitosis (Bad Breath)

Halitosis, otherwise known as fetor oris, oral malodor or simply bad breath, is universally considered to be a socially unacceptable condition.[122] Although prevalence estimates vary, the condition affects a significant portion of the population, with an estimated 20-30% of adults reported to suffer from chronic breath malodor.[123-128] Although a limited percentage of halitosis cases result from extraoral factors, such as diabetes, liver, kidney and other metabolic diseases,[129] the highest percentage of cases are the result of intraoral causes[130] and are characterized by the production of gaseous volatile sulfur compounds (VSCs) associated with unpleasant bad breath.[131,132] Hydrogen sulfide, methyl mercaptan and dimethyl sulfide are frequently cited as exhaled VSCs most commonly associated with unpleasant breath.[130,133]

Certain foods, especially ones like garlic and onions that contain pungent oils, can contribute to bad breath because the oils from these foods are eventually carried to your lungs and exhaled through your breath. Another source of bad breath can be individuals with sinus conditions who often have congested nasal passages and therefore need to breathe through their mouth. The drying effect of mouth breathing can create an environment that promotes bad breath. Additionally, sinus sufferers are likely to be taking antihistamines, a type of medicine that is known to create mouth dryness. Even people who don't have an ongoing problem with bad breath easily notice that their breath is least pleasant in the morning when they first wake up. During the night, a person's salivary flow is reduced when a person sleeps. Saliva flow helps maintain mouth moisture, and it helps cleanse debris, bacteria and bacterial by-products that cause bad breath every time we swallow. As that effect is reduced overnight when we sleep, the result can be stale breath in the morning; a condition that is similarly noticed by people whose mouth becomes dry after speaking for long periods of time. Smoking is also considered to be a major cause of bad breath.

In the majority of cases, bad breath is caused by the presence of oral bacteria and oral debris.[134] The bacteria and oral debris associated with breath malodor are largely found on the tongue as well as in subgingival and interproximal niches that are difficult to clean.[135-137] In the absence of regular, thorough brushing and flossing, bacteria can accumulate on the bits of food left between the teeth, in the mouth and on the tongue. Sulfur compounds released by these bacteria give breath an unpleasant smell; with halitosis occurring when the unpleasant odor is then expelled from the mouth when exhaling. In addition to halitosis being an undesirable condition to have, it clearly has the potential to make social situations particularly unbearable.

Oral inflammatory diseases such as gingivitis and periodontitis are also associated with halitosis; a result of bacteria hiding in diseased tissues, producing foul gases.[138-139] While meticulous oral hygiene in conjunction with scrupulous tongue brushing could theoretically help prevent persistent malodor, studies and surveys have shown that few adults regularly remove enough dental plaque through mechanical oral hygiene alone to alleviate the problem.[140,141] In most cases, good professional oral care combined with a daily regimen of oral hygiene, including interdental cleaning, deep tongue cleaning and optional use of efficacious oral care products specially formulated to combat the germs that can cause bad breath, will lead to improvement.

1. **Flavors to freshen breath**. Bad breath sufferers often seek out help in the form of commercial products marketed to freshen objectionable breath. While some of these products are able to deliver a brief masking of the halitosis, most do not have the potential to provide long-term benefits. They are designed simply to temporarily mask odors. Unfortunately, many are quickly washed away by the natural flow of saliva. Methods used to help reduce bad breath, such as mints, mouth sprays, mouthwash or gum, may only temporarily mask the odors created by the bacteria on the tongue. These methods, however, cannot cure bad breath because they do not remove the source of the bad breath.

2. **Antibacterial agents to reduce malodor**. Antibacterial approaches can provide substantially longer-term breath efficacy than that provided by odor masking agents.[142-144] As opposed to flavor agents that simply mask odor, antibacterial agents actually treat the source of the problem by targeting the malodor producing bacteria.

Zinc is a dentifrice ingredient that has been identified for its ability to target bacteria and help reduce volatile compounds responsible for bad breath.[143] Stannous fluoride, a well-studied antimicrobial agent with concurrent anticaries.[73] desensitizing,[62,74] dental erosion,[76,87] and anti-plaque and gingivitis benefits[59,74] has been found to be a particularly effective as a dentifrice ingredient compared to other approaches for its ability to provide both germ kill and breath protection.[144] One study found that when comparing SnF2 to Zinc plus arginine, the Zinc plus Arginine actually increased VSC and breath odor.[148]

Non-Therapeutic Dentifrice Ingredients Providing Stability or Esthetic Benefits

Dentifrices contain a number of ingredients that stabilize the product and/or provide esthetic benefits, in addition to the ingredients that provide therapeutic or cosmetic benefits. This section will review key dentifrice ingredients that provide stability and esthetic benefits. These nontherapeutic dentifrice components are called inactive ingredients, additives, or excipients and include binders, surfactants, buffering agents, humectants, preservatives, sweeteners, flavorings, and dyes (Figure 20). These components are essential to keep the dentifrice properly mixed with a smooth consistency, and they make the product palatable to the consumer. Three dentifrice ingredients (abrasive, humectants, and solvent) typically represent about 95% of the dentifrice ingredients.

Humectants

Humectants retain moisture so that the dentifrice does not dry out. Humectants function by binding and holding the solvent in the dentifrice. Water is the solvent used in most dentifrices. Humectants, such as glycerin and sorbitol, also inhibit bacterial growth and provide flowability to the dentifrice. Humectants and solvent combined represent approximately 75% of a typical dentifrice formulation.

Binders

Binders, also referred to as thickeners, provide texture and determine how "thick" or "runny" the dentifrice is. Binders are used for cohesiveness, to provide body, and to prevent ingredients from separating. Xanthan gum, carboxymethyl cellulose (CMC) carbomers, carrageenan, and synthetic cellulose are all commonly used dentifrice binders. Binders are usually large polymeric polar molecules that form strong interactions with water. These interactions change the consistency and flowability of the dentifrice. Without the binder, the toothpaste would separate into different phases, a liquid portion and a solid-like portion, and would have to be stirred before each use.

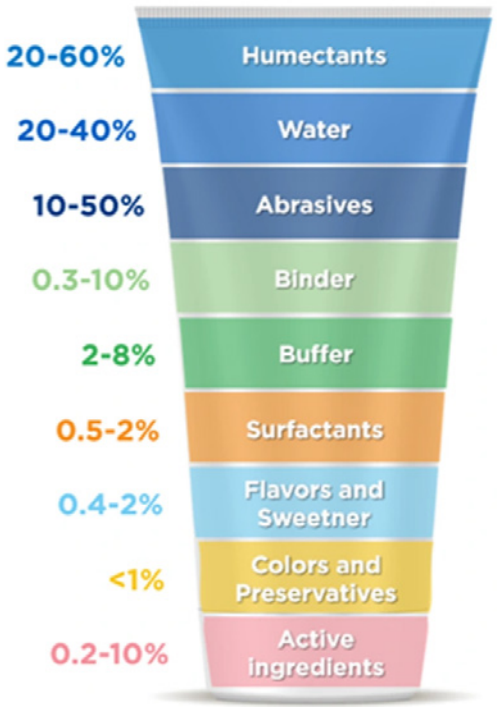


Figure 20. Representation of common dentifrice components.

Buffers
Manufacturers use buffers as part of their dentifrice formulation to keep the pH constant. This is important for the stability and effectiveness of a dentifrice. For example, pH can be an important factor in fluoride bioavailability; fluoride is more difficult to formulate at lower pH because of greater potential for interaction with common abrasives under acidic conditions. In some countries, regulations require dentifrice to be above a certain pH. Trisodium phosphate and sodium citrate are examples of dentifrice buffers. Pyrophosphates, which are used to control calculus formation, are also very effective buffers.

Flavors/Sweeteners
Flavoring agents and sweeteners are added to improve the dentifrice taste. This is a very important ingredient from a marketing standpoint, because consumers can have a strong preference for flavor. Most dentifrices have potent flavoring agents to mask the taste of some other ingredients that may have bitter or metallic tastes. Common flavoring agents and sweeteners include peppermint, saccharin, and xylitol.

Sweeteners used in dentifrices are all non-cariogenic; and thus, do not contribute to caries formation. Some dental professionals take special interest in knowing whether an oral care product contains xylitol because there are reports in the literature that it may provide a small anticaries benefit;[145] however, xylitol is not approved by the US FDA as a proven anticaries agent. In the US, products utilize the FDA approved drug actives [sodium fluoride, sodium monofluorophosphate or stannous fluoride] to provide anticaries benefits.

Surfactants
Surfactants (detergents) create the foaming commonly associated with dentifrices. They aid in the cleaning process by helping to loosen plaque and debris. Sodium lauryl sulfate (SLS) is the surfactant most commonly used, other popular surfactants are cocamidopropyl betaine and taurates. Without the surfactant in the toothpaste the flavor oil would not stay suspended in the product, causing oil separation from the product. Also, surfactants contribute to efficacy by distributing the therapeutic ingredient throughout the mouth as well as patient satisfaction for the mouth feel while using the product.

Colors/Visuals
Finally, coloring agents are added to provide dentifrice with pleasing colors. The opacity of a paste dentifrice comes from the addition of titanium dioxide. Dentifrices formulated without titanium dioxide result in the formation of a gel dentifrice, rather than an opaque paste. Mica is used to provide a sparkly appearance in some dentifrices, such as those marketed to children. A summary of dentifrice additives can be found in Table 3.

Conclusion
The FDA uses two mechanisms to regulate OTC drugs: drug monographs and NDAs. A drug monograph identifies active ingredients that are deemed to be safe and effective for a specific therapeutic need. Most OTC fluoride-containing dentifrices are regulated through the Anticaries, Antiplaque-Antigingivitis, and Tooth Desensitizer monographs. If a dentifrice contains a drug that is not included in a monograph, it must be approved through an NDA. Therapeutic dentifrices brought to market under one of these two regulatory pathways can make claims related to treating or preventing disease.

The ADA is a professional society that takes great interest in informing the public on the safety and efficacy of oral care products. This is done primarily by awarding its Seal of Acceptance. The ADA Seal of Acceptance program is a rigorous, voluntary process in which manufacturers can choose to participate for specific products.

Fluoride was the first therapeutic ingredient used in dentifrice. Fluoride helps prevent caries by enhancing remineralization and inhibiting demineralization. The three fluoride ingredients approved by the FDA for use in dentifrices are stannous fluoride (SnF_2), sodium fluoride (NaF), and sodium monofluorophosphate (Na_2PO_3F).

Since the introduction of early fluoride dentifrices, many other ingredients have been discovered and added to dentifrice to provide multiple additional benefits, including the following:

Table 3. Nontherapeutic Dentifrice Ingredients: Summarized Below are Common Dentifrice Ingredients and Their Functions.

	Examples	Functions
Humectants	Sorbitol, glycerin	Provide flowability Prevent dehydration Prevent microbial growth
Solvents	Water	Provide flowability Solvate polar ingredients Hydrate binders
Abrasives	Hydrated silica, alumina, calcium carbonate	Remove stains Increase viscosity
Surfactants	Sodium lauryl sulfate, cocamidopropyl betaine, poloxamer. Sodium Hexametaphosphate	Create foam Emulsify flavors Clean
Buffers	Trisodium phosphate, sodium hydroxide, sodium citrate	Maintain pH to maximize stability and maintain efficacy
Binders	Xanthan gum, carboxymethyl cellulose (CMC) carbomers, carrageenan	Provide structure and thickening.
Flavors and Sweeteners	Menthol, peppermint, spearmint, green tea, sodium saccharin	Mask taste of unpleasant ingredients Provide consumer acceptability
Emollients	Glycerin, Propylene Glycol	Retain moisture Soothing feel in mouth
Colors and Visuals	Titanium dioxide, dyes, pigments, mica	Enhance esthetics
Bleaches	Peroxide/Ca-Na Carbamide	Extrinsic Stain removal

- **Plaque/gingivitis/malodor reduction:** Plaque, gingivitis, and halitosis are caused by bacteria. Antibacterial-containing dentifrices can help prevent these conditions. Stannous fluoride is the only agent currently used in dentifrices sold in the U.S. that is recognized by the ADA as being effective for controlling plaque, gingivitis and malodor.

- **Antihypersensitivity:** Dentinal hypersensitivity can be treated by chemically depolarizing nerve endings in the tooth or by blocking dentinal tubules. Potassium nitrate is the most common nerve desensitizing agent. Stannous fluoride, arginine + calcium carbonate, strontium acetate, and calcium sodium phosphosilicate are tubule occluding agents used in newer antihypersensitivity dentifrices across the globe.

- **Erosive toothwear:** While Sodium Fluoride remineralizes and makes fluorapatite more resistant to moderate pH drops, Stannous fluoride deposits a protective layer to prevent loss of mineral in a lower pH acid challenge is the only ingredient recognized by the ADA to significantly prevent erosive toothwear.

- **Calculus control:** Polyphosphates, such as SHMP, are effective anticalculus agents. They chelate (bind) calcium and inhibit plaque calcification.

- **Stain removal/Whitening:** Stain removal or tooth whitening is achieved through chemical or physical action. Polyphosphates are good stain removal agents. They displace stain molecules that have attached to the tooth pellicle. Abrasives remove tooth stain through a physical action. Dentifrices with an RDA of 250 or lower are considered safe for everyday use.

Additional dentifrice ingredients include humectants, binders, buffers, flavors, sweeteners, and surfactants. These ingredients stabilize the product and create esthetic benefits for the consumer. They are needed to keep the dentifrice properly mixed with a palatable consistency. Not all dentifrice ingredients are compatible, however, so manufacturers must formulate the chemistry in a way that does not interfere with the bioavailability of the therapeutic ingredients. Creating a dentifrice that delivers important therapeutic and cosmetic benefits, while at the same time being acceptable to the consumer, requires the manufacturer to delicately balance the overall formulation. As noted throughout this course, a dentifrice is a very complex aggregate of chemicals with very specific functions. Not only do these ingredients have to be effective individually, they also have to be compatible with one another. All of these requirements demand very careful formulation and processing in order to be able to manufacture a high quality dentifrice.

This update has shown the market forces have continued to develop new and improved products for the consumer. The therapeutic dentifrices developed have been responsible for a large portion of the caries reduction in the industrialized world. What new oral care therapies await consumers of the future is open for speculation. Most importantly, research has continued to progress, identifying opportunities to deliver enhanced levels of benefit as well as confirmation of new benefits by focusing on key mechanistic aspects of the various active ingredients. We only have to wait to see what new systems may come to bear in this ever-changing marketplace. It will be interesting to see what the future of Oral Care will include!

Course Test Preview

To receive Continuing Education credit for this course, you must complete the online test. Please go to: *www.dentalcare.com/en-us/ce-courses/ce670/test*

1. The maximum allowable fluoride in a NaF-containing OTC dentifrice is _____ ppm.

A. 500
B. 1150
C. 2500
D. 5000

2. NDAs are typically used for which of the following?

A. All oral medications
B. Food supplements
C. New drug indications
D. New flavor formulations

3. The ADA Seal of Acceptance program is a required process to market a fluoride dentifrice in the US.

A. True
B. False, the ADA Seal of Acceptance program is a voluntary process to provide assurance to consumers of the safety and efficacy of a product.
C. False, the ADA Seal of Acceptance program is a voluntary program to monitor the efficacy of dentifrices.

4. Fluoride ingredients allowed by the FDA for use in US dentifrices include which of the following?

A. Stannous fluoride
B. Sodium fluoride
C. Sodium monofluorophosphate
D. Only B and C
E. A, B and C

5. Dental calculus control, tooth whitening and reduction of bad breath are considered by the FDA to be what type of benefits?

A. Therapeutic
B. Cosmetic
C. Either cosmetic or therapeutic, depending on the product.

6. The ISO standard specifies that dentifrices with an RDA of less than _____ are safe on hard tissues.

A. 100
B. 150
C. 250
D. 300

7. Which of the following is the more acid resistant form of tooth mineral?

A. Fluorapatite
B. Hydroxyapatite

8. Potassium nitrate is the most commonly used tubule-occluding agent used to treat dentinal hypersensitivity.

A. True
B. False

9. Dentifrice ingredients with antibacterial activity can help reduce all of the following EXCEPT _____.

A. gingivitis
B. intrinsic stain
C. oral malodor
D. plaque biofilm

10. Stannous fluoride is an antiplaque/antigingivitis agent.

A. True
B. False, stannous fluoride is a chemical whitening agent.
C. False, stannous fluoride is only effective as an anticaries agent.

11. What is the most common nerve depolarizing agent used in sensitivity dentifrice?

A. Amine fluoride
B. Potassium nitrate
C. Sodium hexametaphosphate
D. Strontium chloride

12. Humectants allow dentifrices to retain moisture.

A. True
B. False

13. Which fluoride active is unique in its ability to provide significantly greater levels of erosion protection compared to other fluoride sources?

A. Sodium fluoride
B. Sodium monofluorophosphate
C. Stannous fluoride

14. Antibacterial approaches can provide substantially longer-term breath efficacy than that provided by odor masking agents.

A. True
B. False

15. The active ingredient in the first dentifrice to receive the ADA Seal of Acceptance was _____.

A. sodium fluoride
B. sodium monofluorophosphate
C. stannous fluoride

16. The primary mechanism of action for fluoride includes _____.

A. promotion of remineralization
B. inhibition of demineralization
C. Both A and B
D. None of the above

17. Stannous fluoride adheres to the surface of tooth enamel and forms a protective layer that is able to shield enamel from the effects of erosive acids.

A. True
B. False

18. Stannous fluoride is the only fluoride that delivers anticaries, antiplaque/gingivitis, enamel protection and anti-hypersensitivity benefits from one ingredient.

A. True
B. False

19. Effective anticalculus agents work by binding calcium and inhibiting plaque calcification.

A. True
B. False

20. Halitosis, or bad breath, can be caused by which of the following?

A. Dry mouth
B. Bacteria
C. Oral debris
D. Oral diseases
E. All of the above

21. With fluoride treatment, a noncavitated lesion can be remineralized with fluorapatite and have greater resistance to subsequent demineralization than hydroxyapatite.

A. True
B. False

22. Which of the following is not a key therapeutic area for dentifrices?

A. Caries
B. Plaque/gingivitis
C. Hypersensitivity
D. Enamel erosion
E. Whitening

23. Without the binder, the toothpaste would separate into different phases, a liquid portion and a solid-like portion, and would have to be stirred before each use.

A. True
B. False

24. Which of the following ingredient(s) reduce(s) plaque and gingivitis?

A. Stannous fluoride
B. Potassium nitrate
C. Hydrated silica
D. A and C
E. A and B

References

1. Griffiths BM. Dentifrices--an item of historical interest. N Z Dent J. 1966 Oct;62(290):296-301
2. Miller WD. The Micro-Organisms of the Human Mouth. Basel, Switzerland. S. Karger. 1973. doi:10.1002/jobm.19740140117. Accessed July 8, 2023.
3. US Federal Food, Drug, & Cosmetic Act (FFDCA). 2018 Mar 29. Accessed June 17, 2023.
4. Tenuta LM, Cury JA. Fluoride: its role in dentistry. Braz Oral Res. 2010;24 Suppl 1:9-17. doi:10.1590/s1806-83242010000500003.
5. US FDA. Monograph System. Data Standards Manual (monographs). 2018 Feb 27. Accessed June 17, 2023.
6. US Food & Drug Administration (FDA). Accessed June 17, 2023.
7. American Dental Association (ADA). Seal of Acceptance Program. Accessed June 17, 2023.
8. American Dental Association (ADA). Requirements for Product Acceptance. Accessed June 17, 2023.
9. ADA Seal Brochure 2022
10. Newbrun E. Water fluoridation and dietary fluoride - Fluorides and Dental Caries, 2nd ed. Ernest Newbrun (Ed). Springfield, IL. CC Thomas. 1975. 31-45.
11. Dean HT, McKay FS, Elvone E. Mottled Enamel Survey of Bauxite, ARK., 10 Years After a Change in the Common Water Supply. Public Health Reports. 1896-1970;53(39):1736-1748. doi:10.2307/4582669.
12. https://adanews.ada.org/ada-news/2021/august/community-water-fluoridation-prevents-caries/ Accessed Sept 2023
13. Ten Great Public Health Achievements - United States, 1900-1999, CDC Morbidity and Mortality Weekly Report 1999 Apr 02;48(12):241-243. Accessed June 17, 2023.
14. Bratthall D, Hänsel-Petersson G, Sundberg H. Reasons for the caries decline: what do the experts believe?. Eur J Oral Sci. 1996;104(4 (Pt 2)):416-432. doi:10.1111/j.1600-0722.1996.tb00104.x.
15. Tenuta LM, Zamataro CB, Del Bel Cury AA, Tabchoury CP, Cury JA. Mechanism of fluoride dentifrice effect on enamel demineralization. Caries Res. 2009;43(4):278-285. doi:10.1159/000217860.
16. Cury JA, do Amaral RC, Tenuta LM, Del Bel Cury AA, Tabchoury CP. Low-fluoride toothpaste and deciduous enamel demineralization under biofilm accumulation and sucrose exposure. Eur J Oral Sci. 2010;118(4):370-375. doi:10.1111/j.1600-0722.2010.00745.x.
17. Muhler JC, Radike AW, Nebergall WH, Day HG. The effect of a stannous fluoride-containing dentrifice on caries reduction in children. J Dent Res. 1954;33(5):606-612 doi:10.1177/00220345455540330050401.
18. Muhler JC, Radike AW. Effect of a dentifrice containing stannous fluoride on dental caries in adults. II. Results at the end of two years of unsupervised use. J Am Dent Assoc. 1957;55(2):196-198. doi:10.14219/jada.archive.1957.0157.
19. American Dental Association, Council on Dental Therapeutics: Evaluation of Crest toothpaste. JADA. 1960 Aug;61(2):272-275.
20. Chace R, American Dental Association. Reclassification of Crest toothpaste; Council on Dental Therapeutics. J Am Dent Assoc. 1964;69:195-196.
21. Chronology of important chemical and related events since 1876. Chemical and Engineering News April 6th, 1976: 91-92.
22. Featherstone JD. The caries balance: the basis for caries management by risk assessment. Oral Health Prev Dent. 2004;2 Suppl 1:259-264.
23. Fejerskov O. Concepts of dental caries and their consequences for understanding the disease. Community Dent Oral Epidemiol. 1997;25(1):5-12. doi:10.1111/j.1600-0528.1997.tb00894.x.
24. Silverstone LM. Laboratory studies on the demineralization and remineralization of human enamel in relation to caries mechanisms. Aust Dent J. 1980;25(3):163-168. doi:10.1111/j.1834-7819.1980.tb03707.x.
25. Cury JA, Tenuta LM. Enamel remineralization: controlling the caries disease or treating early caries lesions?. Braz Oral Res. 2009;23 Suppl 1:23-30. doi:10.1590/s1806-83242009000500005.

26. Posner AS. The mineral of bone. Clin Orthop Relat Res. 1985;(200):87-99.
27. Dijkman A, Huizinga E, Ruben J, Arends J. Remineralization of human enamel in situ after 3 months: the effect of not brushing versus the effect of an F dentifrice and an F-free dentifrice. Caries Res. 1990;24(4):263-266. doi:10.1159/000261280.
28. Clarkson JE, Ellwood RP, Chandler RE. A comprehensive summary of fluoride dentifrice caries clinical trials. Am J Dent. 1993;6 Spec No:S59-S106.
29. White DJ. A "return" to stannous fluoride dentifrices. J Clin Dent. 1995;6 Spec No:29-36.
30. Baig A, He T. A novel dentifrice technology for advanced oral health protection: A review of technical and clinical data. Compend Contin Educ Dent. 2005;26(9 Suppl 1):4-11.
31. BIBBY BG. Fluoride mouthwashes, fluoride dentifrices, and other uses of fluorides in control of caries. J Dent Res. 1948;27(3):367-375. doi:10.1177/00220345480270031301.
32. Stookey GK. Are all fluoride dentifrices the same? In: Wei SHY Clinical uses of fluoride. Lea & Febiger 1985, Philadelphia.
33. Zacherl WA. A three-year clinical caries evaluation of the effect of a sodium fluoride-silica abrasive dentifrice. Pharmacol Ther Dent. 1981;6(1-2):1-7.
34. Beiswanger BB, Gish CW, Mallatt ME. A three-year study of the effect of a sodium fluoride-silica abrasive dentifrice on dental caries. Pharmacol Ther Dent. 1981;6(1-2):9-16.
35. Colgate Cavity Protection Information. Colgate-Cavity-Protection-Toothpaste/specifics. Accessed June 17, 2023.
36. Shellis RP, Duckworth RM. Studies on the cariostatic mechanisms of fluoride. Int Dent J. 1994;44(3 Suppl 1):263-273.
37. Zacherl WA. A three-year clinical caries evaluation of the effect of a sodium fluoride-silica abrasive dentifrice. Pharmacol Ther Dent. 1981;6(1-2):1-7.
38. Hargreaves JA, Thompson GW, Wagg BJ. Changes in caries prevalence of Isle of Lewis children between 1971 and 1981. Caries Res. 1983;17(6):554-559. doi:10.1159/000260717.
39. Stookey GK. Are all fluoride dentifrices the same? - Clinical Uses of Fluorides (Current Problems in Clinical Dentistry). Stephen H.Y. Wei (Ed). London. 1986. 105-131.
40. Gerlach RW, Gibb RD, Sagel PA. A randomized clinical trial comparing a novel 5.3% hydrogen peroxide whitening strip to 10%, 15%, and 20% carbamide peroxide tray-based bleaching systems. Compend Contin Educ Dent Suppl. 2000 Jun;(29):S22-28.
41. White DJ. A new and improved "dual action" whitening dentifrice technology--sodium hexametaphosphate. J Clin Dent. 2002;13(1):1-5.
42. White DJ. A "return" to stannous fluoride dentifrices. J Clin Dent. 1995;6 Spec No:29-36.
43. Tinanoff N. Progress regarding the use of stannous fluoride in clinical dentistry. J Clin Dent. 1995;6 Spec No:37-40.
44. Robinson PJ. Gingivitis: a prelude to periodontitis? J Clin Dent. 1995;6 Spec No:41-45.
45. Beiswanger BB, Doyle PM, Jackson RD, et al. The clinical effect of dentifrices containing stabilized stannous fluoride on plaque formation and gingivitis--a six-month study with ad libitum brushing. J Clin Dent. 1995;6 Spec No:46-53.
46. Perlich MA, Bacca LA, Bollmer BW, et al. The clinical effect of a stabilized stannous fluoride dentifrice on plaque formation, gingivitis and gingival bleeding: a six-month study. J Clin Dent. 1995;6 Spec No:54-58.
47. White DJ, Cox ER, Liang N, et al. A new Plaque Glycolysis and Regrowth Method (PGRM) for the in vivo determination of antimicrobial dentifrice/rinse efficacy towards the inhibition of plaque growth and metabolism--method development, validation and initial activity screens. J Clin Dent. 1995;6 Spec No:59-70.
48. Kasturi R, White DJ, Lanzalaco AC, et al. Effects of nine weeks' use of a new stabilized stannous fluoride dentifrice on intrinsic plaque virulence expressed as acidogenicity and regrowth: a modified PGRM study. J Clin Dent. 1995;6 Spec No:71-79.
49. Liang N, White DJ, Cox E, et al. Antimicrobial effects of a stabilized stannous fluoride dentifrice in reducing plaque acid production--a single-brushing PGRM study. J Clin Dent. 1995;6 Spec No:80-83.

50. White DJ, Cox ER, Gwynn AV. Effect of a stabilized stannous fluoride dentifrice on plaque acid (toxin) production. J Clin Dent. 1995;6 Spec No:84-88.
51. Faller RV, Best JM, Featherstone JD, Barrett-Vespone NA. Anticaries efficacy of an improved stannous fluoride toothpaste. J Clin Dent. 1995;6 Spec No:89-96.
52. Weber DA, Howard-Nordan K, Buckner BA, et al. Microbiological assessment of an improved stannous fluoride dentifrice. J Clin Dent. 1995;6 Spec No:97-104.
53. White DJ. Tartar control dentifrices: current status and future prospects - Clinical and biological aspects of dentifrices. Graham Embery (Ed). Oxford. Oxford University Press. 1992. 277-291.
54. White DJ, McClanahan SF, Lanzalaco AC, et al. The comparative efficacy of two commercial tartar control dentifrices in preventing calculus development and facilitating easier dental cleanings. J Clin Dent. 1996;7(2 Spec No):58-64.
55. Perlich MA, Berman E, Frataneangelo P, et al. Desensitizing efficacy of a 5% KNO3/0.243% NAF dentifrice. J Dent Res 1994; 73:166.
56. Faller RV, Shaffer JB, Eversole S, et al. In vitro fluoride uptake from dentifrices containing sodium fluoride and potassium nitrate. J Dent Res 1994; 73:241.
57. Lehne RK, Winston AE. Abrasivity of sodium bicarbonate. Clin Prev Dent. 1983 Jan-Feb;5(1):17-18.
58. Ramji N, Baig A, He T, et al. Sustained antibacterial actions of a new stabilized stannous fluoride dentifrice containing sodium hexametaphosphate. Compend Contin Educ Dent. 2005;26(9 Suppl 1):19-28.
59. Mankodi S, Bartizek RD, Winston JL, Biesbrock AR, McClanahan SF, He T. Anti-gingivitis efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice. J Clin Periodontol. 2005;32(1):75-80. doi:10.1111/j.1600-051X.2004.00639.x.
60. He T, Huang S, Yue F, et al. A randomized, controlled comparison of a stannous-containing dentifrice for reducing gingival bleeding and balancing the oral microbiome relative to a positive control. American Journal of Dentistry. 2021 Aug;34(4):222-227. PMID: 34370916.
61. Kruse AB, Schlueter N, Kortmann VK, Frese C, Anderson A, Wittmer A, Hellwig E, Vach K, Al-Ahmad A. Long-Term Use of Oral Hygiene Products Containing Stannous and Fluoride Ions: Effect on Viable Salivary Bacteria. Antibiotics. 2021; 10(5):481. https://doi.org/10.3390/antibiotics10050481
62. Baig A, He T, Buisson J, Sagel L, Suszcynsky-Meister E, White DJ. Extrinsic whitening effects of sodium hexametaphosphate—a review including a dentifrice with stabilized stannous fluoride. Compend Contin Educ Dent. 2005;26(9 Suppl 1):47-53.
63. Terézhalmy G, Chaves E, Bsoul S, Baker R, He T. Clinical evaluation of the stain removal efficacy of a novel stannous fluoride and sodium hexametaphosphate dentifrice. Am J Dent. 2007;20(1):53-58.
64. Schiff T, He T, Sagel L, Baker R. Efficacy and safety of a novel stabilized stannous fluoride and sodium hexametaphosphate dentifrice for dentinal hypersensitivity. J Contemp Dent Pract. 2006;7(2):1-8. Published 2006 May 1.
65. Johnson G, Brännström M. The sensitivity of dentin. Changes in relation to conditions at exposed tubule apertures. Acta Odontol Scand. 1974;32(1):29-38. doi:10.3109/00016357409002530.
66. Favaro Zeola L, Soares PV, Cunha-Cruz J. Prevalence of dentin hypersensitivity: Systematic review and meta-analysis. J Dent. 2019 Feb;81:1-6. doi: 10.1016/j.jdent.2018.12.015. Epub 2019 Jan 11. PMID: 30639724.
67. Soares ARDS, Chalub LLFH, Barbosa RS, Campos DEP, Moreira AN, Ferreira RC. Prevalence and severity of non-carious cervical lesions and dentin hypersensitivity: association with oral-health related quality of life among Brazilian adults. Heliyon. 2021 Mar 13;7(3):e06492. doi: 10.1016/j.heliyon.2021.e06492. PMID: 33748509; PMCID: PMC7970350.
68. Brännström M, Johnson G, Nordenvall KJ. Transmission and control of dentinal pain: resin impregnation for the desensitization of dentin. J Am Dent Assoc. 1979;99(4):612-618. doi:10.14219/jada.archive.1979.0337.

69. Petrou I, Heu R, Stranick M, et al. A breakthrough therapy for dentin hypersensitivity: how dental products containing 8% arginine and calcium carbonate work to deliver effective relief of sensitive teeth. J Clin Dent. 2009;20(1):23-31.
70. Litkowski L, Greenspan DC. A clinical study of the effect of calcium sodium phosphosilicate on dentin hypersensitivity--proof of principle. J Clin Dent. 2010;21(3):77-81.
71. Gendreau L, Barlow AP, Mason SC. Overview of the clinical evidence for the use of NovaMin in providing relief from the pain of dentin hypersensitivity. J Clin Dent. 2011;22(3):90-95.
72. Melo Alencar, et al. Clinical efficacy of nano-hydroxyapatite in dentin hypersensitivity: A systematic review and meta-analysis, Journal of Dentistry, Volume 82, 2019, Pages 11-21, ISSN 0300-5712, https://doi.org/10.1016/j.jdent.2018.12.014.
73. White DJ, Lawless MA, Fatade A, et al. Stannous fluoride/sodium hexametaphosphate dentifrice increases dentin resistance to tubule exposure in vitro. J Clin Dent. 2007;18(2):55-59.
74. Stookey GK, Mau MS, Isaacs RL, Gonzalez-Gierbolini C, Bartizek RD, Biesbrock AR. The relative anticaries effectiveness of three fluoride-containing dentifrices in Puerto Rico. Caries Res. 2004;38(6):542-550. doi:10.1159/000080584.
75. Mallatt M, Mankodi S, Bauroth K, Bsoul SA, Bartizek RD, He T. A controlled 6-month clinical trial to study the effects of a stannous fluoride dentifrice on gingivitis. J Clin Periodontol. 2007;34(9):762-767. doi:10.1111/j.1600-051X.2007.01109.x.
76. Schiff T, Saletta L, Baker RA, Winston JL, He T. Desensitizing effect of a stabilized stannous fluoride/Sodium hexametaphosphate dentifrice. Compend Contin Educ Dent. 2005;26(9 Suppl 1):35-40.
77. Hooper SM, Newcombe RG, Faller R, Eversole S, Addy M, West NX. The protective effects of toothpaste against erosion by orange juice: studies in situ and in vitro. J Dent. 2007;35(6):476-481. doi:10.1016/j.jdent.2007.01.003.
78. Huysmans MC, Jager DH, Ruben JL, Unk DE, Klijn CP, Vieira AM. Reduction of erosive wear in situ by stannous fluoride-containing toothpaste. Caries Res. 2011;45(6):518-523. doi:10.1159/000331391.
79. Bellamy PG, Harris R, Date RF, et al. In situ clinical evaluation of a stabilised, stannous fluoride dentifrice [published correction appears in Int Dent J. 2014 Jun;64(3):171. Manly, Andrew [corrected to Manley, Andrew]]. Int Dent J. 2014;64 Suppl 1:43-50. doi:10.1111
80. Faller RV, Eversole SL. Enamel protection from acid challenge--benefits of marketed fluoride dentifrices. J Clin Dent. 2013;24(1):25-30.
81. Eversole SL, Saunders-Burkhardt K, Faller RV. Erosion protection comparison of stabilised SnF2 , mixed fluoride active and SMFP/arginine-containing dentifrices. Int Dent J. 2014;64 Suppl 1:22-28. doi:10.1111/idj.12099.
82. Eversole SL, Saunders-Burkhardt K, Faller RV. Erosion Prevention Potential of an Over-the-Counter Stabilized SnF2 Dentifrice Compared to 5000 ppm F Prescription-Strength Products. J Clin Dent. 2015;26(2):44-49.
83. Faller RV, Eversole SL, Tzeghai GE. Enamel protection: a comparison of marketed dentifrice performance against dental erosion. Am J Dent. 2011;24(4):205-210.
84. Baig AA, Faller RV, Yan J, Ji N, Lawless M, Eversole SL. Protective effects of SnF2 - Part I. Mineral solubilisation studies on powdered apatite. Int Dent J. 2014;64 Suppl 1:4-10. doi:10.1111/idj.12096.
85. Khambe D, Eversole SL, Mills T, Faller RV. Protective effects of SnF2 - Part II. Deposition and retention on pellicle-coated enamel. Int Dent J. 2014;64 Suppl 1:11-15. doi:10.1111/idj.12097.
86. Lussi A, Carvalho TS. The future of fluorides and other protective agents in erosion prevention. Caries Res. 2015;49 Suppl 1:18-29. doi:10.1159/000380886.
87. Lussi A. Erosive tooth wear – a multifactorial condition of growing concern and increasing knowledge - Dental Erosion: From Diagnosis to Therapy. Lussi A (Ed). Basel, NY. Karger. 2006. 1-8.
88. Dugmore CR, Rock WP. A multifactorial analysis of factors associated with dental erosion. Br Dent J. 2004 Mar 13;196(5):283-286. doi:10.1038/sj.bdj.4811041.

89. Lussi A, Jaeggi T, Zero D. The role of diet in the aetiology of dental erosion. Caries Res. 2004;38 Suppl 1:34-44. doi:10.1159/000074360.
90. Gambon DL, Brand HS, Veerman EC. Dental erosion in the 21st century: what is happening to nutritional habits and lifestyle in our society? Br Dent J. 2012 Jul 27;213(2):55-57. doi:10.1038/sj.bdj.2012.613.
91. Cheaib Z, Lussi A. Impact of acquired enamel pellicle modification on initial dental erosion. Caries Res. 2011;45(2):107-112. doi:10.1159/000324803.
92. Vieira A, Overweg E, Ruben JL, Huysmans MC. Toothbrush abrasion, simulated tongue friction and attrition of eroded bovine enamel in vitro. J Dent. 2006 May;34(5):336-342. doi:10.1016/j.jdent.2005.07.010.
93. von Fraunhofer JA, Rogers MM. Dissolution of dental enamel in soft drinks. Gen Dent. 2004 Jul-Aug;52(4):308-12.
94. Hooper SM, Newcombe RG, Faller R et al. The protective effects of toothpaste against erosion by orange juice: studies in situ and in vitro. J Dent. 2007 Jun;35(6):476-481. doi:10.1016/j.jdent.2007.01.003.
95. Baig AA, Faller RV, Yan J, et al. Protective effects of SnF2 - Part I. Mineral solubilisation studies on powdered apatite. Int Dent J. 2014 Mar;64 Suppl 1:4-10. doi:10.1111/idj.12096.
96. Khambe D, Eversole SL, Mills T et al. Protective effects of SnF2 - Part II. Deposition and retention on pellicle-coated enamel. Int Dent J. 2014 Mar;64 Suppl 1:11-15. doi:10.1111/idj.12097.
97. Faller RV, Eversole SL. Protective effects of SnF2 - Part III. Mechanism of barrier layer attachment. Int Dent J. 2014 Mar;64 Suppl 1:16-21. doi:10.1111/idj.12098
98. Eversole SL, Saunders-Burkhardt K, Faller RV. Erosion protection comparison of stabilised SnF2 , mixed fluoride active and SMFP/arginine-containing dentifrices. Int Dent J. 2014 Mar;64 Suppl 1:22-28. doi:10.1111/idj.12099.
99. Faller RV, Eversole SL, Saunders-Burkhardt K. Protective benefits of a stabilised stannous-containing fluoride dentifrice against erosive acid damage. Int Dent J. 2014 Mar;64 Suppl 1:29-34. doi:10.1111/idj.12100.
100. Hooper S, Seong J, Macdonald E, et al. A randomised in situ trial, measuring the anti-erosive properties of a stannous-containing sodium fluoride dentifrice compared with a sodium fluoride/potassium nitrate dentifrice. Int Dent J. 2014 Mar;64 Suppl 1:35-42. doi:10.1111/idj.12101.
101. Bellamy PG, Harris R, Date RF, et al. In situ clinical evaluation of a stabilised, stannous fluoride dentifrice. Int Dent J. 2014 Mar;64 Suppl 1:43-50. doi:10.1111/idj.12102.
102. Eversole SL, Saunders-Burkhardt K, Faller RV. Erosion prevention potential of an over-the-counter stabilized SnF2 dentifrice compared to 5000 ppm F prescription-strength products. J Clin Dent 2015;26:44-49.
103. West NX, He T, Hellin N, et al. Randomized in situ clinical trial evaluating erosion protection efficacy of a 0.454% stannous fluoride dentifrice. Int J Dent Hyg. 2019;17(3):261-267. doi:10.1111/idh.12379.
104. West NX, Hellin N, Eusebio R, He T. The erosion protection efficacy of a stabilized stannous fluoride dentifrice: An in situ randomized clinical trial. Am J Dent. 2019;32(3):138-142.
105. West N, He T, Hellin N, et al. Erosion protection efficacy of a 0.454% stannous fluoride dentifrice versus an arginine-containing dentifrice. Am J Dent. 2018;31(2):63-66.
106. Zhao X, He T, He Y, Cheng C, Chen H. A Randomized Clinical Trial to Measure the Erosion Protection Benefits of a Novel Stabilized Stannous Fluoride Dentifrice versus a Control Dentifrice. J Clin Dent. 2017;28(4 Spec No B):B17-B20.
107. American Dental Association. Joint Report of the American Dental Association Council on Access, Prevention and Interprofessional Relations and Council on Scientific Affairs to the House of Delegates: Response to Resolution 73H-2000. 2001 Oct. Accessed June 17, 2023.
108. Imfeld T. Dental erosion. Definition, classification and links. Eur J Oral Sci. 1996;104(2 (Pt 2)):151-155. doi:10.1111/j.1600-0722.1996.tb00063.x.

109. ten Cate JM, Imfeld T. Dental erosion, summary. Eur J Oral Sci. 1996;104(2 (Pt 2)):241-244. doi:10.1111/j.1600-0722.1996.tb00073.x.
110. Johansson AK, Lingström P, Imfeld T, Birkhed D. Influence of drinking method on tooth-surface pH in relation to dental erosion. Eur J Oral Sci. 2004;112(6):484-489. doi:10.1111/j.1600-0722.2004.00172.x.
111. Jin Y, Yip HK. Supragingival calculus: formation and control. Crit Rev Oral Biol Med. 2002;13(5):426-441. doi:10.1177/154411130201300506.
112. Bollmer BW, Sturzenberger OP, Vick V, Grossman E. Reduction of calculus and Peridex stain with Tartar-Control Crest. J Clin Dent. 1995;6(4):185-187.
113. Pradeep AR, Agarwal E, P AR, Rao MS, Faizuddin M. Study of orthophosphate, pyrophosphate, and pyrophosphatase in saliva with reference to calculus formation and inhibition. J Periodontol. 2011;82(3):445-451. doi:10.1902/jop.2010.100355.
114. White DJ. A new and improved "dual action" whitening dentifrice technology—sodium hexametaphosphate. J Clin Dent. 2002;13(1):1-5.
115. White D, Cox E, Suszcynskymeister E, Baig AA. In vitro studies of the anticalculus efficacy of a sodium hexametaphosphate whitening dentifrice. J Clin Dent. 2002;13(1):33-37.
116. Segreto VA, Collins EM, D'Agostino R, Cancro LP, Pfeifer HJ, Gilbert RJ. Anticalculus effect of a dentifrice containing 0.5% zinc citrate trihydrate. Community Dent Oral Epidemiol. 1991;19(1):29-31. doi:10.1111/j.1600-0528.1991.tb00100.x.
117. Schemehorn BR, Moore MH, Putt MS. Abrasion, polishing, and stain removal characteristics of various commercial dentifrices in vitro. J Clin Dent. 2011;22(1):11-18.
118. Hattab FN, Qudeimat MA, al-Rimawi HS. Dental discoloration: an overview. J Esthet Dent. 1999;11(6):291-310. doi:10.1111/j.1708-8240.1999.tb00413.x.
119. Hefferren JJ. A laboratory method for assessment of dentifrice abrasivity. J Dent Res. 1976;55(4):563-573. doi:10.1177/00220345760550040301.
120. St John S, White DJ. History of the Development of Abrasivity Limits for Dentifrices. J Clin Dent. 2015;26(2):50-54.
121. He T, Baker R, Bartizek RD, Biesbrock AR, Chaves E, Terézhalmy G. Extrinsic stain removal efficacy of a stannous fluoride dentifrice with sodium hexametaphosphate. J Clin Dent. 2007;18(1):7-11.
122. Feng X, Chen X, Cheng R, Sun L, Zhang Y, He T. Breath malodor reduction with use of a stannous-containing sodium fluoride dentifrice: a meta-analysis of four randomized and controlled clinical trials. Am J Dent. 2010;23 Spec No B:27B-31B.
123. Silva MF, Leite FRM, Ferreira LB, Pola NM, Scannapieco FA, Demarco FF, Nascimento GG. Estimated prevalence of halitosis: a systematic review and meta-regression analysis. Clin Oral Investig. 2018 Jan;22(1):47-55. doi: 10.1007/s00784-017-2164-5. Epub 2017 Jul 4. PMID: 28676903.
124. Liu XN, Shinada K, Chen XC, Zhang BX, Yaegaki K, Kawaguchi Y. Oral malodor-related parameters in the Chinese general population. J Clin Periodontol. 2006;33(1):31-36. doi:10.1111/j.1600-051X.2005.00862.x.
125. Miyazaki H, Sakao S, Katoh Y, Takehara T. Correlation between volatile sulphur compounds and certain oral health measurements in the general population. J Periodontol. 1995;66(8):679-684. doi:10.1902/jop.1995.66.8.679.
126. Silva MF, Leite FRM, Ferreira LB, Pola NM, Scannapieco FA, Demarco FF, Nascimento GG. Estimated prevalence of halitosis: a systematic review and meta-regression analysis. Clin Oral Investig. 2018 Jan;22(1):47-55. doi: 10.1007/s00784-017-2164-5. Epub 2017 Jul 4. PMID: 28676903.
127. Iwanicka-Grzegorek E, Michalik J, Kepa J, Wierzbicka M, Aleksinski M, Pierzynowska E. Subjective patients' opinion and evaluation of halitosis using halimeter and organoleptic scores. Oral Dis. 2005;11 Suppl 1:86-88. doi:10.1111/j.1601-0825.2005.01101.x.
128. Bornstein MM, Kislig K, Hoti BB, Seemann R, Lussi A. Prevalence of halitosis in the population of the city of Bern, Switzerland: a study comparing self-reported and clinical data. Eur J Oral Sci. 2009;117(3):261-267. doi:10.1111/j.1600-0722.2009.00630.x.

129. Preti G, Clark L, Cowart BJ, et al. Non-oral etiologies of oral malodor and altered chemosensation. J Periodontol. 1992;63(9):790-796. doi:10.1902/jop.1992.63.9.790.
130. ADA Council on Scientific Affairs. Oral malodor. J Am Dent Assoc. 2003;134(2):209-214. doi:10.14219/jada.archive.2003.0135.
131. Kleinberg I, Westbay G. Salivary and metabolic factors involved in oral malodor formation. J Periodontol. 1992 Sep;63(9):768-775. doi: 10.1902/jop.1992.63.9.768.
132. Rosenberg M. The science of bad breath. Sci Am. 2002;286(4):72-79. doi:10.1038/scientificamerican0402-72.
133. Rosenberg M. Bad breath: Research perspectives. Ramat Aviv: Ramot Publishing-Tel Aviv University 1997.
134. Haraszthy VI, Zambon JJ, Sreenivasan PK, et al. Identification of oral bacterial species associated with halitosis. J Am Dent Assoc. 2007;138(8):1113-1120. doi:10.14219/jada.archive.2007.0325.
135. De Boever EH, Loesche WJ. Assessing the contribution of anaerobic microflora of the tongue to oral malodor. J Am Dent Assoc. 1995;126(10):1384-1393. doi:10.14219/jada.archive.1995.0049.\
136. Rosenberg M. Clinical assessment of bad breath: current concepts [published correction appears in J Am Dent Assoc 1996 May;127(5):570]. J Am Dent Assoc. 1996;127(4):475-482. doi:10.14219/jada.archive.1996.0239.
137. Lee CH, Kho HS, Chung SC, Lee SW, Kim YK. The relationship between volatile sulfur compounds and major halitosis-inducing factors. J Periodontol. 2003;74(1):32-37. doi:10.1902/jop.2003.74.1.32.
138. Yaegaki K, Sanada K. Volatile sulfur compounds in mouth air from clinically healthy subjects and patients with periodontal disease. J Periodontal Res. 1992;27(4 Pt 1):233-238. doi:10.1111/j.1600-0765.1992.tb01673.x.
139. Ratcliff PA, Johnson PW. The relationship between oral malodor, gingivitis, and periodontitis. A review. J Periodontol. 1999;70(5):485-489. doi:10.1902/jop.1999.70.5.485.
140. Bakdash B. Current patterns of oral hygiene product use and practices. Periodontol 2000. 1995;8:11-14. doi:10.1111/j.1600-0757.1995.tb00041.x.
141. van der Weijden GA, Hioe KP. A systematic review of the effectiveness of self-performed mechanical plaque removal in adults with gingivitis using a manual toothbrush. J Clin Periodontol. 2005;32 Suppl 6:214-228. doi:10.1111/j.1600-051X.2005.00795.x.
142. Donovan-Brand R. A comparison of the breath and antimicrobial efficacies of various antimicrobial systems present in commercial dental products. J Dent Res 2003; 82 (Sp Iss):501.
143. Navada R, Kumari H, Le S, Zhang J. Oral malodor reduction from a zinc-containing toothpaste. J Clin Dent. 2008;19(2):69-73.
144. Chen X, He T, Sun L, Zhang Y, Feng X. A randomized cross-over clinical trial to evaluate the effect of a 0.454% stannous fluoride dentifrice on the reduction of oral malodor. Am J Dent. 2010;23(3):175-178.
145. Mäkinen KK. Sugar alcohol sweeteners as alternatives to sugar with special consideration of xylitol. Med Princ Pract. 2011;20(4):303-320. doi:10.1159/000324534.
146. Biesbrock, A et al. The Effects of Bioavailable Gluconate Chelated Stannous. Fluoride Dentifrice on Gingival Bleeding: Meta-Analysis of Eighteen Randomized Controlled Trials. J Clin Periodontal, 2019.
147. West N. et al. Bioavailable gluconate chelated stannous fluoride toothpaste meta-analyses: Effects on dentine hypersensitivity and enamel erosion. Journal of Dentistry, Volume 105, 2021
148. Zsiska M, Schneiderman E, Jin Y, Farrell S, Grender J. Investigation of oral malodor prevention by dentifrices as measured by VSC reduction. J Breath Res. 2021 Apr 13;15(3). doi: 10.1088/1752-7163/abf209. PMID: 33765667.

Additional Resources

- No Additional Resources Available.

About the Author

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Beth Jordan, RDH, MS is a graduate of Westbrook College, UNE, Dental Hygiene and held an adjunct clinical faculty position for a number of years. She worked in private practice until 2001 when she became an employee of the Procter & Gamble Company (Crest Oral B) where her role is Global Professional & Scientific Relations. She lectures locally to both small and large audiences of dental professionals, as well as dental students and faculty. She is a volunteer at the Dental Wellness Center Free Clinic in Biddeford, ME. She and her family currently reside in Southern Maine.

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