J Istanbul Univ Fac Dent 2016;50(2):61-69.
http://dx.doi.org/10.17096/jiufd.72103 *REVIEW ARTICLE*

POTENTIAL HAZARDS DUE TO FOOD ADDITIVES IN ORAL HYGIENE PRODUCTS

Oral Hijyen Ürünlerinin İçeriğindeki Gıda Katkı Maddelerinin Olası Yan Etkileri

Damla TUNCER-BUDANUR [1], Murat Cengizhan YAŞ [2], Elif SEPET [1]

Received: 16/09/2015
Accepted:22/01/2016

ABSTRACT

Food additives used to preserve flavor or to enhance the taste and appearance of foods are also available in oral hygiene products. The aim of this review is to provide information concerning food additives in oral hygiene products and their adverse effects. A great many of food additives in oral hygiene products are potential allergens and they may lead to allergic reactions such as urticaria, contact dermatitis, rhinitis, and angioedema. Dental practitioners, as well as health care providers, must be aware of the possibility of allergic reactions due to food additives in oral hygiene products. Proper dosage levels, delivery vehicles, frequency, potential benefits, and adverse effects of oral health products should be explained completely to the patients. There is a necessity to raise the awareness among dental professionals on this subject and to develop a data gathering system for possible adverse reactions.

Keywords: *Food additives; Oral health; Adverse effects; Oral care; Hypersensitivity*

ÖZ

Gıdaların tat ve görünümünü korumak ya da geliştirmek amacıyla kullanılan gıda katkı maddeleri aynı zamanda oral hijyen ürünlerinde de mevcuttur. Bu derlemenin amacı, oral hijyen ürünlerinde bulunan gıda katkı maddeleri ve bildirilen yan etkileri hakkında bilgi vermektir. Oral hijyen ürünleri içeriğindeki pek çok gıda katkı maddesi alerjendir ve ürtiker, kontakt dermatit, rinit, anjiyoödem gibi reaksiyonlara yol açabilir. Diş hekimlerinin yanı sıra sağlık personeli de oral hijyen ürünleri ve dental materyallerin içeriğindeki gıda katkı maddelerinin alerjik reaksiyonlara neden olma potansiyelinin farkında olmalıdır. Oral hihyen ürünlerinin kullanım önerileri, potansiyel yararları ve yan etkilerinin hastalara açıklanması gerekmektedir. Diş hekimleri ve sağlık personeli arasında bu konuda farkındalığın artırılması ve yan etkiler hakkında bir veri toplama sistemi geliştirilmesi zorunluluğu vardır.

Anahtar kelimeler: *Gıda katkı maddeleri; Ağız sağlığı; Ağız bakımı; Hipersensitivite*

[1] Department of Pedodontics Faculty of Dentistry Istanbul University
[2] General Dental Practitioner

Introduction

"Food additive" term describes any substance which is not normally consumed as a food by itself and not normally used as a typical ingredient of the food, whether or not it has nutritive value, the intentional addition of which to food for a technological (including organoleptic) purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food results, or may be reasonably expected to result, (directly or indirectly) in it or its by-products becoming a component of or otherwise affecting the characteristics of such foods (1). This term does not include "contaminants" or substances added to food for maintaining or increasing nutritional quality (1, 2). Food additives used to preserve flavor or enhance the taste and appearance of foods are also available in dental materials (2-6).

The mouth is subjected to a wide spectrum of antigenic agents, including foodstuffs and drugs, cosmetics, metals in eating utensils, dental materials together with toothpastes and filling materials, and microorganisms. Hypersensitivity to such antigens may manifest in a number of diverse ways, including angioedema and ulceration or lichenoid reactions (7). Patients undergoing dental treatment can be exposed to many potential allergens, but adverse events are infrequent. Patients with symptoms or signs of stomatitis, burning, tingling, cheilitis, oral lichenoid lesions, lip and facial swelling may relate these problems to dental treatment or to the use of dental products. Gawkrodger (2), reported patients with oral mucosal diseases are more likely to have demonstrable hypersensitivity to food additives, especially benzoic acid, perfumes and flavorings, especially cinnamaldehyde. Cheilitis is an inflammatory eruption on the lip which can have several causes. Some food additives reported to cause cheilitis such as potassium persulphate in denture cleansers, castor oil in chewing gum and colophonium in dental floss (3-6).

The aim of this review is to provide information concerning food additives in oral hygiene products along with their reported adverse effects.

Food Labelling and "E" Numbers

The International Codex Alimentarius Commission (Codex Alimantarius Comission-CAC) was established by collaborative working of The World Health Organization (WHO) and the Food and Agriculture Organization (Food and Agriculture Organization-FAO) (1, 8). Categories of food additives are indicated according to purpose of their usage and following special names, "E" numbers on prepared food packages. Classification of food additives according to basic functions are*;* Colours (E100-180), Preservatives (E200-297)*,* Antioxidants (E300-321), Emulsifiers and Stabilizers (E322-500), Acidity Regulators (E500-578), Sweeteners and Provider Odor (E620-637), Wide purpose (E900-927) (9).

Food Additives in Oral Hygiene Products
Toothpastes

Toothpastes are presented in different concentrations of fluoride and special versions present natural components (e.g. propolis and jua), for specific functions, (e.g.tooth bleaching, dental erosion control or to reduce sensitivity) (10). Ingredients used in modern toothpaste formulations include abrasive agents, tensoactives, humectants, thickening agents, flavoring, coloring agents and antimicrobial agents (11). Abrasives represent a minimum of 50% of a typical toothpaste. Representative abrasives include calcium carbonate, dehydrated silica gels, hydrated aluminum oxides, magnesium carbonate, phosphate salts and silicates to remove debris and residual surface stains. Fluoride in various forms is the preferred active ingredient in toothpaste to prevent dental caries. Several toothpastes contain sodium lauryl sulfate (SLS) or related surfactants (detergents). Antibacterial agents, such as Triclosan or zinc chloride prevent gingivitis, helps reduce tartar and bad breath. Toothpastes have different colors, and flavors intended to encourage use of the product. Three commonest flavorants are peppermint,spearmint, and wintergreen. Humectants to prevent water loss within the dentifrice include glycerol, propylene, glycol and sorbitol. Thickening agents or binders to stabilize the toothpaste formula include mineral colloids, natural gums, seaweed colloids or synthetic cellulose (11, 12). Hydroxyapatite nanocrystals and a variety of calcium phosphates are included in toothpaste formulations for remineralization (13).

Reports have suggested triclosan, an active ingredient in several toothpastes, can combine with chlorine in tap water to make chloroform, that the United States Environmental Protection Agency classifies as a probable human carcinogen (14). Lawrence *et al.* (15) reported an eleven-year old

patient with multiple, asymptomatic ulcerated lesions located in the oral cavity associated with triclosan found within the patient's dentifrice. Abdollahi *et al*. (16) reported that dentifrice hypersensitivity reactions seem to be more common since the advent of tartar-control toothpastes. Kowitz *et al*. (17) evaluated four completely different toothpastes in ninety two dental students and dental hygiene students. They reported increased rates of mucosa reactions (e.g. ulceration, sloughing, erythema, etc.) with tartar-control toothpastes. Flavorings in toothpastes provide the 'fresh clean taste' and mask the bitter taste of pyrophosphates in tartar-control toothpastes (11). According to a multicenter study of allergic contact cheilitis from toothpaste, flavoring agents especially derivatives extracted from the main varieties of mint (such as spearmint, peppermint, menthol, and carvone) were the most related agents with allergic contact cheilitis (18). Case reports of plasma cell gingivitis have been reported with the use of herbal toothpaste containing cinnamon (19). Cinnamonaldehyde, which is usually added to dentifrices to cover the unpleasant taste of pyrophosphate, has been related to the development of plasma cell gingivitis (19, 20). Miller *et al*. (21) represented fourteen cases of cinnamon induced stomatitis.

The effectiveness of toothpastes significantly increases by the addition of surface-active agents. These surface-active materials not solely provide the effervescent action of dentifrices and enhance the removal of food particles, but they also help within the distribution of the toothpaste in the oral cavity (22). Sodium lauryl sulphate (SLS) and sodium lauryl sarcosinate are the two most common surface-active agents (23). Industrially, SLS is used in hard surface cleansing products, grease cleaners, car washing and detergents, personal hygiene products (e.g. shampoos and shower gels, bath foams, face cleansing soaps), and toothpastes as detergents and foaming agents. The frequent use of this material may lead to multiple allergic and toxic reactions (6, 24-28). Ersoy *et al*. (29) reported a case with abdominal gas, cramps, bloatedness and diarrhea complaints due to SLS in patient's toothpaste. Researchers have concluded that the local application of toothpastes containing SLS may cause oral lesions due to absorption of the material sublingually or from the oral mucosa (6, 23, 27, 29). Hypersensitivity reaction to toothpastes is rare. Some flavor and color additives used in toothpastes may cause allergic reactions such as scaling on lips and tongue, edema, perioral dermatitis, angular chelitis, gingivitis and intraoral ulcers. These symptoms appear within a few minutes after using toothpaste (30).

Mouthwashes

Mouthwash is defined as a non sterile solution used principally for its deodorant, refreshing or antiseptic effect and also they are designed to remove food particles, temporarily reduce halitosis and offer a pleasant taste (31). Ingredients of mouthwashes are determined by American Dental Association (ADA) as follows: basic ingredients include water, alcohol, cleansing agents, flavoring ingredients and coloring agents. Active ingredients vary depending on the type of mouthrinse, however they can be placed into four general groups: First group include antimicrobial agents which act directly on oral microorganism to help reduce plaque, decrease the severity of gingivitis and control bad breath. Second group includes fluoride which helps reduce tooth decay and make teeth more resistant to caries. Third group includes astringent salts which can serve as temporary deodorizers that mask bad breath. Finally, fourth group includes the odor neutralizers which act by chemically inactivating odor causing compounds (12).

The Food and Drug Administration (FDA) classifies mouthrinses as either cosmetic or therapeutic, or a mixture of the two. The cosmetic mouthrinses are over the counter products that are mainly intended as mouth fresheners. Therapeutic mouthrinses can be sold as prescription or over the counter products that have an additional active ingredient and are marketed as antiplaque/antigingivitis and anticaries drug products (32). The localized oral lesions induced by mouthrinses include lesions of the primary irritant type and lesions generated through activation of specific immunologic pathways such as type I and type IV hypersensitivity reactions (33-36). Kowitz *et al*.(37) have reported the irritating effect of mouthwashes to the oral mucosa by demonstrating the occurrence of epithelial peeling, mucosal ulceration and inflammation, gingivitis, and petechiae in twenty fifth of 104 dental and dental hygiene students who used 20 ml of a mouthwash for five seconds, twice daily, during a 2-week period. The reported symptoms disappeared completely when use of the mouthwashes was interrupted. In a susceptible host, mouthwashes have also been shown to produce hypersensitive reactions, triggered by a range of ingredients. Hypersensitive reactions triggered by mouthrinses

have been reported in the literature (38-40). Mathias *et al.*(39) reported a case of contact urticaria that developed after use of a cinnamic aldehyde-containing mouthwash in which lip swelling occurred. Lim *et al*.(38) reported perioral and mucosal edema caused by contact allergy to proflavine (an antiseptic) in an acriflavine (a proflavine derivative) mouthwash. In another case report, benzydamine mouthwash use was shown to provoke a maculopapular rash on the trunk and limbs of a patient (40).

Chlorhexidine (CHL) is a synthetic topical disinfectant. It is usually insoluble in water thus it has to be formulated with either gluconic or acetic acid to create watersoluble digluconate or diacetate salts. Chlorhexidine, especially as digluconate ester, is widely used in various topical applications (mouthwash solutions, dental gels and toothpaste) for its capability to bind oral mucosal surfaces inhibiting plaque formation (41). The adverse effects of chlorhexidine are reported as altered taste sensation, superficial desquamation of the oral mucosa, brownish discoloration of the tongue and teeth, increased calculus formation and stomach upsets (42). Rare reports are published about cutaneuos adverse reactions following the use of CHL in mouth-wash rinses resembling fixed drug eruption or contact stomatitis, urticaria and anaphylaxis are reported after the use of CHL mouth-wash rinses (34, 35, 43-46). The patients in many reported cases later tested positive for chlorhexidine induced hypersensitivity reaction by means of intradermal, scratch, and epicutaneous tests (43, 45, 47, 48). Practitioners should be aware of the potential for both minor and serious adverse side effects of CHL.

Ethanol is contained in a number of ready-to-use mouthwashes in a concentration generally between 5% - 27% volume (49, 50). However, ethanol itself is not thought to have a direct carcinogenic effect on the oral mucosa. Acetaldehyde, the primary metabolite of ethanol is known to be a mutagenic and carcinogenic agent, and is assumed to play the main role in carcinogenesis (51). Mouthwashes with a high alcohol content have been shown to produce hyperkeratotic lesions in both human and animal models (52). Bemstein (33) reported two cases of oral mucosal white lesions associated with Listerine mouthwash. There is limited and conflicting epidemiological evidence on the link between the use of ethanol in the oral cavity within the form of mouthwashes and oral cancer. Some studies pointed to an increased risk of oral cancer due to locally produced acetaldehyde, operating via the same mechanism to that found after alcoholic beverage ingestion (53, 54). A review article by McCullough and Farah (54) concluded that there is sufficient evidence to accept the proposition that developing oral cancer is increased or contributed to by the use of alcohol-containing mouthrinsees. Lachenmeier *et al.* (53) investigated acetaldehyde levels in saliva after use of alcohol-containing mouthwashes. They reported a twice-daily use of alcohol-containing mouthwashes leads to a systemic acetaldehyde exposure of 0.26 lg/kg bodyweight/day on average, that corresponds to a lifetime cancer risk of 3E-6. Reidy *et al*.(51) reviewed the literature on the effects of alcohol on the oral mucosa.

They conluded the evidence concerning the carcinogenic effect of alcohol-containing mouthrinses is conflicting, and also the relationship between alcohol-containing mouthrinses and oral cancer has not yet been firmly established. Two meta-analysis on the relationship between alcohol-containing mouthrinses and oral cancer by La Vecchia (55) and Gandini *et al*. (56) concluded that a link between mouthrinse use, specifically alcohol-containing mouthrinses, and oral cancer is not supported by epidemiological evidence. Reviews by Cole *et al*. (57) and Elmore and Horowitz (58) also concluded that the available epidemiological evidence failed to support a link between alcohol-containing mouthrinse use and oral cancer. It has been demonstrated that alcohol-free oral rinses are as effective as their alcohol-containing counterparts, and so the need for ethanol in mouthwashes and oral rinses seems to be non-existent (59-61). Products without alcohol have also been shown to have a lower incidence of other adverse effects (62). The use of alcohol-containing mouthrinses should be limited to short-term therapeutic situations for a limited and controlled period of time.

Chewing Gum

Chewing Gum removes plaque and food debris on the teeth, stimulates the flow of saliva, raises of plaque pH, encourages remineralisation, stops demineralisation, reduces gingivitis, but may have adverse effects on TMJ (63-65). Chewing gum consists of a gum base, sweetener, flavoring and aromatic agent. Gum base consists a combination of elastomers, naturel or/and synthetic resins, oils, emulsifiers, waxes, antioxidants and fillers (66, 67). Sweetener is defined by Codex Alimentarius Commission as “which give sweet taste to food

but which is not sugar". Sweeteners have shown completely different physical, chemical, physico-chemical structures as they have different chemical structures. "Sugar-Free" label is only given to sugar alcohols, artificial sweeteners and mixtures of them by FDA (68). Most chewing gums sold are sweetened with sugar substitutes (69). Sugar substitutes are food additives that duplicate the taste of sugar in food, however don't supply food energy or calories. Some sugar substitutes are natural and others are synthetically produced. These synthetically produced sweeteners are usually called artificial sweeteners (70). The predominant sugar substitutes are polyols, which are low-caloric substances sometimes referred to as 'sugar alcohols' because their chemical structure is similar to that of both sugar and alcohol.

The most common polyols in sugar-free chewing gum are sorbitol, which is a hexatol derived from glucose, and xylitol, which is a pentatol that occurs widely in nature (69, 71). Substances which do not give calories or do not increase blood sugar and tastes sweet are called "artificial sweeteners". The main artificial sweeteners are; Aspartame, Acesulfame K, Saccharin, Sucralose, and Cyclamate (72). Xylitol is entirely natural and added to pastilles, chewing gums, toothpastes and mouthwashes as a 'tooth friendly' component (73). Consumption of large amounts of polyols have laxative effect. They may cause bloating, intestinal gas and diarrhea (72). Polyol-based sugar-free products may decrease caries incidence however they may bring another dental health risk, dental erosion, if they contain acidic flavoring (74).

Clinicians may consider recommending xylitol use to moderate or high caries-risk patients. The changes in caries risk status must be checked and also the frequency of xylitol use and recommendations must be adjusted accordingly (75). Although frequent consumption of food additives, advers reactions related to these substances are more rare in general population (0.01%-0.23%) while more common in atopic people (2%-7%). Reported reactions are mostly mild and they can have an effect on digestive or respiratory tracts, skin and they can rarely cause anaphylaxis (76). There is very little information regarding side effects of food additives on oro-dental health. While an undisturbed oral mucosa with normal salivation is characterized by a certain resistance and regeneration ability, decreased saliva production, microbial mucosal colonization, mechanical trauma and long-term exposure to irritation and allergen like substances disrupt its barrier function and create conditions for the development of a delayed hypersensitivity (77). The oral cavity, including the lips, is consistently exposed to a large number of potentially irritating and sensitizing substances. Dental materials, oral hygiene products and food additives may cause contact allergic reactions in the mouth with varied clinical presentation. Oral lichenoid lesions may be evoked by hypersensitivity to dental restorative metals, acrylates, flavorings and other substances (78). The clinical manifestations of contact hypersensitivity in the mouth vary from subjective difficulties like burning, pain and dryness of the mucosa (burning mouth syndrome) to objective changes within the form of nonspecific stomatitis and cheilitis with reddish, edematous mucosae, erosions and ulcers (1, 79, 80).

These chronic changes are most frequently related to long-term exposure of the oral mucosa to dental metals, and additionally to acrylates, composite materials, additives and other substances, that cause the development of a delayed hypersensitivity reaction (81, 82). The cause of an immediate (type I) reaction (contact urticaria) is identified by skin prick/scratch testing (83). Skin prick testing provides information about the presence of specific IgE to protein and peptide antigens (allergens).However, the low concentration of the allergen in a product may be too low to give a positive reaction. As in all forms of contact allergy, the best treatment is avoidance of the product and allergen if identified (84).Due to the premalignant character of oral lichenoid lesions, epicutaneous tests to verify suspect intraoral allergens and follow up of these patients are important. Co-operation with dentists is necessary for the correct identification of potential allergens in the used dental materials. The replacement of suspect dental materials and other substances must be performed (78). When educating patients on oral health, dental professionals need to not solely discuss the benefits of oral hygiene products but also potential side effects; recommended frequency of use; and proper dosage levels. Recommendations of delivery or product type should be given to patients on a case-by-case basis, taking into consideration age, dental health status, systemic health considerations, and patient preference (75).

Conclusion

Dental practitioners as well as health care providers must be aware of the possibility of allergic reactions due to food additives in oral hygiene products. Proper dosage levels, delivery vehicles, frequency, potential benefits, and adverse effects of oral health products must be explained completely to patients. There is a necessity to raise the awareness among dental professionals on this subject and to develop a data gathering system for adverse reactions.

Source of funding
None declared

Conflict of interest
None declared

References

1. Codex Alimentarius Commission Procedural Manual (Twenty-first edition) (2013): Issued by the secretariat of the Joint FAO/WHO Food Standards Programme, FAO, Rome http://www.fao.org/docrep/018/i3243e/i3243e.pdf
2. Gawkrodger DJ. Investigation of reactions to dental materials. Br J Dermatol 2005;153(3):479-485.
3. Freeman S, Stephens R. Cheilitis: Analysis of 75 cases referred to a contact dermatitis clinic. Am J Contact Dermat 1999;10(4):198-200.
4. le Coz CJ, Ball C. Recurrent allergic contact dermatitis and cheilitis due to castor oil. Contact Dermatitis 2000;42(2):114-115.
5. Le Coz CJ, Bezard M. Allergic contact cheilitis due to effervescent dental cleanser: Combined responsibilities of the allergen persulfate and prosthesis porosity. Contact Dermatitis 1999;41(5):268-271.
6. Lee AY, Yoo SH, Oh JG, Kim YG. 2 cases of allergic contact cheilitis from sodium lauryl sulfate in toothpaste. Contact Dermatitis 2000;42(2):111.
7. Wray D, Rees SR, Gibson J, Forsyth A. The role of allergy in oral mucosal diseases. QJM 2000;93(8):507-511.
8. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) http://apps.who.int/food-additives-contaminants-jecfa-database/search.aspx
9. Food Standards Agency (14 March 2012) Current EU approved additives and their E numbers.http://www.food.gov.uk/policyadvice/additivesbranch/enumberlist#.Uk6aANI72Zs
10. Jardim JJ, Alves LS, Maltz M. The history and global market of oral home-care products. Braz Oral Res 2009;23 (Suppl 1):17-22.
11. Stamm JW. Multi-function toothpastes for better oral health: A behavioural perspective. Int Dent J 2007;57(S5):351-363.
12. American Dental Association; Product Category Information, http://www.ada.org/1322.aspx
13. Wolfgang Weinert in "Oral Hygiene Products" Ullmann's Encyclopedia of Industrial Chemistry, 2005, Wiley-VCH, Weinheim doi:10.1002/14356007.a18_209
14. Rule KL, Ebbett VR, Vikesland PJ. Formation of chloroform and chlorinated organics by free-chlorine-mediated oxidation of triclosan. Environ Sci Technol 2005;39(9):3176-3185.
15. Lawrence LM, Farquharson A, Brown RS, Vatanka HO. Oral tissue irritants in toothpaste: A case report. J Clin Pediatr Dent 2013;38(1):75-78.
16. Abdollahi M, Rahimi R, Radfar M. Current opinion on drug-induced oral reactions: A comprehensive review. J Contemp Dent Pract 2008;9(3):1-15.
17. Kowitz G, Jacobson J, Meng Z, Lucatorto F. The effects of tartar-control toothpaste on the oral soft tissues. Oral Surg Oral Med Oral Pathol 1990;70(4):529-536.
18. Francalanci S, Sertoli A, Giorgini S, Pigatto P, Santucci B, Valsecchi R. Multicentre study of allergic contact cheilitis from toothpastes. Contact Dermatitis 2000;43(4):216-222.
19. Anil S. Plasma cell gingivitis among herbal toothpaste users: A report of three cases. J Contemp Dent Pract 2007;8(4):60-66.
20. Lamey PJ, Lewis MA, Rees TD, Fowler C, Binnie WH, Forsyth A. Sensitivity reaction to the cinnamonaldehyde component of toothpaste. Br Dent J 1990;168(3):115-118.
21. Miller RL, Gould AR, Bernstein ML. Cinnamon-induced stomatitis venenata, clinical and characteristic histopathologic features. Oral Surg Oral Med Oral Pathol 1992;73(6):708-716.
22. Carranza FA. Glickman's Clinical Periodotology. 9th ed. Philadelphia: WB Saunders Co.; 2002. p.651-74
23. Herlofson BB, Barkvoll P. The effect of two toothpaste detergents on the frequency of recurrent aphthous ulcers. Acta Odontol Scand

1996;54(3):150-153.
24. Babich H, Babich JP. Sodium lauryl sulfate and triclosan: In vitro cytotoxicity studies with gingival cells. Toxicol Lett 1997;91(3):189-196.
25. Baer PN. Toothpaste allergies. J Clin Pediatr Dent 1992;16(3):230-231.
26. Barkvoll P, Rolla G. Possible effects of sodium lauryl sulfate(SLS) on the oral mucosa. J Dent Res 1989;68:991.
27. Herlofson BB, Barkvoll P. Sodium lauryl sulfate and recurrent aphthous ulcers. A preliminary study. Acta Odontol Scand 1994;52(5):257-259.
28. Skaare A, Kjaerheim V, Barkvoll P, Rolla G. Skin reactions and irritation potential of four commercial toothpastes. Acta Odontol Scand 1997;55(2):133-136.
29. Ersoy M, Tanalp J, Ozel E, Cengizlier R, Soyman M. The allergy of toothpaste: A case report. Allergol Immunopathol (Madr) 2008;36(6):368-370.
30. Zirwas MJ, Otto S. Toothpaste allergy diagnosis and management. J Clin Aesthet Dermatol 2010;3(5):42-47.
31. John T, Darrell K, Kathleen V, Cleef T. Chemical composition of everyday products. 2nd Edition, Green Wood publishing group Inc., USA, 2005, 48-49
32. Zero DT. Dentifrices, mouthwashes, and remineralization/caries arrestment strategies. BMC Oral Health 2006;6 (Suppl 1):S9.
33. Bernstein ML. Oral mucosal white lesions associated with excessive use of listerine mouthwash. Report of two cases. Oral Surg Oral Med Oral Pathol 1978;46(6):781-785.
34. Moghadam BK, Drisko CL, Gier RE. Chlorhexidine mouthwash-induced fixed drug eruption. Case report and review of the literature. Oral Surg Oral Med Oral Pathol 1991;71(4):431-434.
35. Yusof WZ, Khoo SP. Mucosal sensitivity to chlorhexidine mouthwash. Singapore Dent J 1988;13(1):39-40.
36. Yusof ZA. Chlorhexidine mouthwash: A review of its pharmacological activity, clinical effects, uses and abuses. Dent J Malays 1988;10(1):9-16.
37. Kowitz GM, Lucatorto FM, Cherrick HM. Effects of mouthwashes on the oral soft tissues. J Oral Med 1976;31(2):47-50.
38. Lim J, Goh CL, Lee CT. Perioral and mucosal oedema due to contact allergy to proflavine. Contact Dermatitis 1991;25(3):195-196.
39. Mathias CG, Chappler RR, Maibach HI. Contact urticaria from cinnamic aldehyde. Arch Dermatol 1980;116(1):74-76.
40. Motley RJ. Benzydamine oral rinse and rash. Br Med J (Clin Res Ed) 1988;296(6633):1402.
41. Lim KS, Kam PC. Chlorhexidine--pharmacology and clinical applications. Anaesth Intensive Care 2008;36(4):502-512.
42. Daly B, Sharif MO, Newton T, Jones K, Worthington HV. Local interventions for the management of alveolar osteitis (dry socket). Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No: CD006968. DOI: 10.1002/14651858.CD006968.pub2.
43. Cheung J, O'Leary JJ. Allergic reaction to chlorhexidine in an anaesthetised patient. Anaesth Intensive Care 1985;13(4):429-430.
44. Garvey LH, Roed-Petersen J, Husum B. Anaphylactic reactions in anaesthetised patients - four cases of chlorhexidine allergy. Acta Anaesthesiol Scand 2001;45(10):1290-1294.
45. Okano M, Nomura M, Hata S, Okada N, Sato K, Kitano Y, Tashiro M, Yoshimoto Y, Hama R, Aoki T. Anaphylactic symptoms due to chlorhexidine gluconate. Arch Dermatol 1989;125(1):50-52.
46. Sharma A, Chopra H. Chlorhexidine urticaria: A rare occurrence with a common mouthwash. Indian J Dent Res 2009;20(3):377-379.
47. Bergqvist-Karlsson A. Delayed and immediate-type hypersensitivity to chlorhexidine. Contact Dermatitis 1988;18(2):84-88.
48. Calogiuri GF, Di Leo E, Trautmann A, Nettis E, Ferrannini A, Vacca A. Chlorhexidine hypersensitivity: A critical and updated review. J Allergy Ther 2013;4:141.
49. Gagari E, Kabani S. Adverse effects of mouthwash use. A review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80(4):432-439.
50. Lachenmeier DW. Safety evaluation of topical applications of ethanol on the skin and inside the oral cavity. J Occup Med Toxicol 2008;3:26.
51. Reidy J, McHugh E, Stassen LF. A review of the relationship between alcohol and oral cancer. Surgeon 2011;9(5):278-283.
52. Bernstein ML, Carlish R. The induction of hyperkeratotic white lesions in hamster cheek pouches with mouthwash. Oral Surg Oral Med Oral Pathol 1979;48(6):517-522.
53. Lachenmeier DW, Gumbel-Mako S, Sohnius EM, Keck-Wilhelm A, Kratz E, Mildau G. Salivary acetaldehyde increase due to alcohol-containing

mouthwash use: A risk factor for oral cancer. Int J Cancer 2009;125(3):730-735.
54. McCullough MJ, Farah CS. The role of alcohol in oral carcinogenesis with particular reference to alcohol-containing mouthwashes. Aust Dent J 2008;53(4):302-305.
55. La Vecchia C. Mouthwash and oral cancer risk: An update. Oral Oncol 2009;45(3):198-200.
56. Gandini S, Negri E, Boffetta P, La Vecchia C, Boyle P. Mouthwash and oral cancer risk quantitative meta-analysis of epidemiologic studies. Ann Agric Environ Med 2012;19(2):173-180.
57. Cole P, Rodu B, Mathisen A. Alcohol-containing mouthwash and oropharyngeal cancer: A review of the epidemiology. J Am Dent Assoc 2003;134(8):1079-1087.
58. Elmore JG, Horwitz RI. Oral cancer and mouthwash use: Evaluation of the epidemiologic evidence. Otolaryngol Head Neck Surg 1995;113(3):253-261.
59. Bahna P, Hanna HA, Dvorak T, Vaporciyan A, Chambers M, Raad I. Antiseptic effect of a novel alcohol-free mouthwash: A convenient prophylactic alternative for high-risk patients. Oral Oncol 2007;43(2):159-164.
60. Eldridge KR, Finnie SF, Stephens JA, Mauad AM, Munoz CA, Kettering JD. Efficacy of an alcohol-free chlorhexidine mouthrinse as an antimicrobial agent. J Prosthet Dent 1998;80(6):685-690.
61. Herrera D, Roldan S, Santacruz I, Santos S, Masdevall M, Sanz M. Differences in antimicrobial activity of four commercial 0.12% chlorhexidine mouthrinse formulations: An in vitro contact test and salivary bacterial counts study. J Clin Periodontol 2003;30(4):307-314.
62. Almerich JM, Cabedo B, Ortola JC, Poblet J. Influence of alcohol in mouthwashes containing triclosan and zinc: An experimental gingivitis study. J Clin Periodontol 2005;32(6):539-544.
63. Addy M, Perriam E, Sterry A. Effects of sugared and sugar-free chewing gum on the accumulation of plaque and debris on the teeth. J Clin Periodontol 1982;9(4):346-354.
64. Elman ES. Gum chewing and the temporomandibular joint. J Am Dent Assoc 1965;71(6):1416-1418.
65. Leach SA, Lee GT, Edgar WM. Remineralization of artificial caries-like lesions in human enamel in situ by chewing sorbitol gum. J Dent Res 1989;68(6):1064-1068.
66. Imfeld T. Chewing gum--facts and fiction: A review of gum-chewing and oral health. Crit Rev Oral Biol Med 1999;10(3):405-419.
67. Ly KA, Milgrom P, Rothen M. The potential of dental-protective chewing gum in oral health interventions. J Am Dent Assoc 2008;139(5):553-563.
68. Ly KA, Milgrom P, Rothen M. Xylitol, sweeteners, and dental caries. Pediatr Dent 2006;28(2):154-163; discussion 192-158.
69. Burt BA. The use of sorbitol- and xylitol-sweetened chewing gum in caries control. J Am Dent Assoc 2006;137(2):190-196.
70. FDA No Calories. Sweet! [Last accessed on 2011 Feb 1]. Available from:http://www.fda.gov/fdac/features/2006/406_sweeteners.html.
71. Deshpande A, Jadad AR. The impact of polyol-containing chewing gums on dental caries: A systematic review of original randomized controlled trials and observational studies. J Am Dent Assoc 2008;139(12):1602-1614.
72. Raben A, Richelsen B. Artificial sweeteners: A place in the field of functional foods? Focus on obesity and related metabolic disorders. Curr Opin Clin Nutr Metab Care 2012;15(6):597-604.
73. Aguirre-Zero O, Zero DT, Proskin HM. Effect of chewing xylitol chewing gum on salivary flow rate and the acidogenic potential of dental plaque. Caries Res 1993;27(1):55-59.
74. Nadimi H, Wesamaa H, Janket SJ, Bollu P, Meurman JH. Are sugar-free confections really beneficial for dental health? Br Dent J 2011;211(7):E15.
75. Guideline on xylitol use in caries prevention. Handbook of Pediatric Dentistry. 4th ed. Chicago: American Academy of Pediatric Dentistry 2011:166–169.
76. Randhawa S, Bahna SL. Hypersensitivity reactions to food additives. Curr Opin Allergy Clin Immunol 2009;9(3):278-283.
77. Rietschel RL , Fowler JF Jr. Fisher´s contact dermatitis.5th ed. Philadelphia: Lippincott Williams & Wilkins, 2001.
78. Ditrichova D, Kapralova S, Tichy M, Ticha V, Dobesova J, Justova E, Eber M, Pirek P. Oral lichenoid lesions and allergy to dental materials. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2007;151(2):333-339.
79. Koch P, Bahmer FA. Oral lesions and symptoms related to metals used in dental restorations: A clinical, allergological, and histologic study. J

Am Acad Dermatol 1999;41(3 Pt 1):422-430.
80. Torgerson RR, Davis MD, Bruce AJ, Farmer SA, Rogers RS, 3rd. Contact allergy in oral disease. J Am Acad Dermatol 2007;57(2):315-321.
81. Hoskyn J, Guin JD. Contact allergy to cinnamal in a patient with oral lichen planus. Contact Dermatitis 2005;52(3):160-161.
82. Hougeir FG, Yiannias JA, Hinni ML, Hentz JG, el-Azhary RA. Oral metal contact allergy: A pilot study on the cause of oral squamous cell carcinoma. Int J Dermatol 2006;45(3):265-271.
83. Heddle R, Tao B. Guidelines for performing a skin prick test. Medicine Today 2002;3:67-70.
84. Smith W. Skin prick testing for the diagnosis of allergic disease. A manual for practitioners. ASCIA updated November 2013.

Corresponding Author:
Damla TUNCER-BUDANUR
Department of Pedodontics
Faculty of Dentistry Istanbul University
34093 - Çapa Fatih, Istanbul / Turkey
Phone: +90 212 414 20 20/30309
e-mail: damlabudanur@gmail.com