

Contact Allergy to (Ingredients of) Toothpastes

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The literature on contact allergy to (ingredients of) toothpastes is critically reviewed. We have found 47 case reports, small case series ($n = 2-5$) and citations published between 1900 and 2016 describing more than 60 patients allergic to toothpastes, and in addition 3 larger case series and many descriptions of toothpaste allergy among selected groups of patients. Allergic reactions usually manifest as cheilitis with or without dermatitis around the mouth, less frequently by oral symptoms. Formerly, many reactions were caused by cinnamon derivatives; more recently, reported allergens are diverse. A semiopen test or closed patch test with the toothpaste “as is” may be performed as an initial test, but a positive reaction should always be followed by confirmatory tests. The role of contact allergy to toothpastes in patients with oral symptoms (stomatitis, glossitis, gingivitis, buccal mucositis, burning, soreness, and possibly burning mouth syndrome and recurrent aphthous ulcers) is unclear and should be further investigated.

Recently, I coauthored a publication describing a patient with cheilitis caused by contact allergy to olaflur, an amine fluoride, in a toothpaste.¹ Because there have been only few (limited) reviews on the subject of toothpaste allergy,²⁻⁴ of which 2 were published more than 20 years ago, this was an excellent opportunity to thoroughly and critically review the literature on this subject. The main questions to be answered were the following: (1) what is the composition of toothpastes; (2) how frequent (or infrequent) are contact allergic reactions to them; (3) what is the clinical picture of allergic reactions; (4) which are the causative ingredients (the allergens or more appropriately the haptens); and (5) what is the best method for patch testing these products?

LITERATURE REVIEW

Composition of Toothpastes

Toothpastes, also called dentifrices, are pastes or gels to be used with a toothbrush to maintain and improve oral health and aesthetics. They are complex formulations with often more than 20 ingredients. The chemical composition of toothpastes is constantly changing because of manufacturers' competition, (commercial) innovations, and scientific developments. The main functional classes of toothpaste ingredients are the following, with examples of chemicals in each class provided in Table 1^{2,5-7}:

1. Mild abrasives to remove debris and residual surface stains.
2. Fluoride to strengthen tooth enamel and to remineralize tooth decay (prevention of caries).
3. Humectants to prevent water loss in the toothpaste.
4. Flavoring agents for cosmetic and palatable reasons. They mask the often unpleasant taste of surfactants and provide breath freshening and sensorial cues, such as cooling, heating, or tingling, depending on the flavor compound being used. Universally, mint flavors (menthol, peppermint oil, spearmint oil) are most commonly used, usually at concentrations between 0.3% and 2.0% wt/wt.⁷
5. Sweeteners to improve the taste of toothpaste. All commonly used sweeteners are artificial.
6. Thickening agents or binders to stabilize the toothpaste formula.
7. Detergents to create foaming action. Only very few currently marketed toothpastes contain a surfactant other than sodium lauryl sulfate.⁷
8. Coloring materials to improve the appearance of the toothpaste. Many toothpastes are white, which can be combined with various colored stripes to suggest multiple benefits. Whiteness is achieved by adding titanium dioxide (approximately 1% wt/wt), whereas artificial colorants (approximately 0.1% wt/wt) are added to realize colored stripes or a colored core.⁷
9. Water to dissolve inorganic active ingredients and—most importantly—fluorides.

To some toothpastes, ingredients may be added to solve the following specific problems^{2,5,7}:

1. Periodontal disease (gingivitis): For the prevention and treatment of periodontal disease, the following ingredients may be used: natural plant extracts, essential oils, enzymes (lysozyme, lactoperoxidase, glucose oxidase), vitamins, antiseptic and antibacterial substances (such as chlorhexidine, triclosan, and

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TABLE 1. Examples of Chemicals in the Functional Classes of Toothpaste Ingredients^{2,5-7}

Functional Class	Examples of Chemicals
Abrasives	Alumina (aluminium oxide), calcium carbonate, calcium pyrophosphate, dicalcium phosphate dehydrate, (hydrated) silica, magnesium carbonate, sodium bicarbonate, sodium metaphosphate
Fluoride	Inorganic: sodium fluoride, sodium monofluorophosphate, stannous fluoride (SnF ₂); organic: octadecenylammonium fluoride (dectaflur), olaflur
Humectants	Erythritol, glycerin, isomalt, propylene glycol, sorbitol, xylitol
Flavoring agents	Cinnamon, herbal, lemon, and mint flavors (menthol, peppermint oil, spearmint oil)
Sweeteners	Sodium saccharin, sucralose, xylitol
Thickening agents	Crosscarmellose (carboxymethylcellulose), crosslinked polyacrylates, hydroxyethylcellulose, natural gums (agar, carrageenan, xanthan), seaweed colloids, thickening silicas
Detergents	Cocamidopropyl betaine, sodium cocoyl sarcosinate, sodium lauroyl sarcosinate, sodium lauryl sulfate, sodium C14-16 olefin sulfonate, steareth-30
Coloring materials	Artificial colorants, titanium dioxide (white)
Water	

triclosan copolymers), hydrogen peroxide, zinc citrate, zinc chloride, and stannous chloride.

2. Malodour: Antimalodour agents typically rely on the chemical reaction with volatile sulfur compounds such as methyl mercaptan and hydrogen sulfide. Zinc citrate and zinc chloride are most commonly used because they do not only possess antimicrobial properties, but zinc is also capable to react with volatile sulfur compounds, thereby turning them into non-volatile zinc salts.⁷
3. Tartar/calculus: Antitartar agents may be added to prevent and treat tartar (also called calculus), which is defined as “an incrustation on the teeth consisting of plaque that has become hardened by the deposition of mineral salts.” These agents prevent further growth of apatitic or other calcium phosphate phases. The most common ones are sodium or potassium salts of tripolyphosphate and zinc salts. Antitartar formulations need higher flavor contents to mask the taste of the condensed phosphate.⁷
4. Whitening/bleaching: Another specific purpose for toothpastes is whitening and bleaching. In the case of whitening toothpastes, by removing stained plaque, teeth will regain their natural whiteness. Plaque can be removed by abrasive substances or by enzymes (protease, papain) that stick to proteins in the pellicle, thus facilitating the removal of stained plaque. Sodium pyrophosphate, pentasodium triphosphate and other pyrophosphates absorb the stain molecules, also creating a whitening effect. Optical whiteners such as blue covarine are

also used for a whitening effect. Bleaching toothpastes contain hydrogen peroxide or calcium peroxide, but their efficacy is doubtful.

5. Dentin hypersensitivity: The relief of dentin hypersensitivity (“sensitive teeth”) can be accomplished through nerve desensitization and/or physical blockage (“plugging”) of dentinal tubules. Nerve desensitization can be accomplished by potassium salts such as potassium citrate and nitrate. Compounds used for tubule occlusion include strontium salts (acetate, chloride), stannous fluoride, calcium sodium phosphosilicate (“bioglass”), and arginine bicarbonate in combination with calcium carbonate.⁷
6. Dry mouth: Toothpastes containing olive oil, betaine, and xylitol can stimulate salivary secretion and may be helpful for people with dry mouth.⁵

Investigation of Toothpaste Composition Based on Ingredient Labelling and Manufacturers' Information

In Finland, 48 products, “virtually all toothpastes,” for sale in Finland in 1990, were examined for possible allergenic ingredients.² The toothpastes were from 19 manufacturers; 11 of the products were Finnish. The contents of the toothpastes were studied on the basis of the information provided by the manufacturers. The substances rated as “allergenic” are shown in Table 2.

Much information on the components of the 48 toothpastes was unspecified or insufficiently specified. Peppermint, rosemary, and/or anise oil were present in 21% of the products, and menthol was present in 10%. Furthermore, flavorings that could not be identified were used in 77% of the products. The commonest preservatives were benzoic acid and its esters and salts, including methylparaben and propylparaben (a total of 64%).² It should be realized that these data are from 1990 and therefore possibly dated.

In a more recent US investigation, the labels of 80 toothpastes available in the United States from the Walgreen pharmacy chain in 2009 were studied for potential allergens.⁸ Seventy five (93%) of the toothpastes contained unspecified flavors. Other potentially allergenic ingredients found were cocamidopropyl betaine (16/80 products, 20%), propylene glycol (8/80, 10%), essential oils and biological additives (5/80, 6%), parabens (5/80, 6%), peppermint (4/80, 5%), tocopherol (2/80, 3%), spearmint (2/80, 3%), propolis (1/80, 1%), and tea tree oil (1/80, 1%).⁸

In a similar investigation, of 153 toothpastes sold by the CVS pharmacy chain in 2009 in the United States evaluated by their ingredient lists, 95% did not list specific flavors.⁹ Potential allergens that were found in more than 3 (2%) of the 153 toothpastes were sorbitan sesquileate derivatives (61%), propylene glycol (20%), cocamidopropyl betaine (14%), sodium benzoate (16%), and benzoic acid (9%). What the authors considered to be “sorbitan sesquileate derivatives” was not specified.⁹

The differences between the 2 US studies are remarkable and are probably due to different interpretation of which ingredients are considered to be potential allergens.

TABLE 2. Allergenic Chemicals Found Present in 48 Toothpastes in Finland, 1990

Chemical	n (%)	Comments of Products Containing the Chemical (n = 48)
Sorbitol	38 (79)	Rare contact allergen
Flavors, unspecified	37 (77)	
Sodium lauryl sulfate	34 (71)	Rare contact allergen
Glycerin (glycerol)	22 (46)	Rare contact allergen
Methylparaben	18 (37)	Infrequent contact allergen in cosmetics
Polyethylene glycol	12 (25)	Molecular weight unspecified, rare contact allergen in cosmetic products
Benzoic acid, its salts and esters	11 (23)	Insufficiently specified
Essential oils (peppermint, rosemary, anise)	10 (21)	Insufficiently specified
Colors, unspecified	9 (19)	
Aluminium hydroxide trihydrate	6 (12)	INCI name: aluminium hydroxide; potential allergen: aluminium
Alcohol	5 (10)	Rare contact allergen in cosmetic products
Menthol	5 (10)	
Myrrh extract	5 (10)	Rare contact allergen
Propylene glycol	4 (8)	Risk of sensitization likely overrated
Agar	3 (6)	Rare contact allergen, if at all reported
Aluminium hydroxide	3 (6)	Potential allergen: aluminium
Xanthogenate	3 (6)	Salt of xanthinic acid; insufficiently specified chemical; rare contact allergen, if at all reported
Xanthan gum	3 (6)	Rare contact allergen
Allantoin	2 (4)	Rare contact allergen
Antioxidants, unspecified	2 (4)	
CI 47005	2 (4)	Quinoline yellow, rare contact allergen
Emulgators, unspecified	2 (4)	
Fragrance, unspecified	2 (4)	
Propylparaben	2 (4)	Infrequent contact allergen in cosmetic products
Thiazolinones	2 (4)	Insufficiently specified
Azulene	1 (2)	Rare contact allergen
Benzalkonium chloride	1 (2)	Infrequent contact allergen in cosmetic products
Benzyl alcohol	1 (2)	
CI 45430	1 (2)	Erythrosine, rare contact allergen
Cocamidopropyl betaine	1 (2)	
<i>Echinacea purpurea</i> leaf extract	1 (2)	Rare contact allergen, if at all reported
Glycyrrhizin	1 (2)	INCI name: glycyrrhizic acid; rare contact allergen
Guar gum	1 (2)	INCI name: <i>Cyamopsis tetragonoloba</i> gum; rare contact allergen, if at all reported
Lemon balm	1 (2)	Melissa (oil?); rare contact allergen
Olaflur	1 (2)	Rare contact allergen

Adapted from Sainio and Kanerva.²

It has been stated that most toothpaste is flavored with either a variation of mint or cinnamon.⁸ Other authors mention that spearmint is used in almost every brand of toothpaste as a flavor, together with other flavoring ingredients, such as menthol, peppermint, anethole, eugenol, and cinnamal.¹⁰ In neither publication, any evidence to back up these rather firm statements was given.

Toothpaste Contact Allergy in Selected Groups of Patients

As will be discussed later, the main symptoms of allergic reactions to toothpastes are eczema of the lips (cheilitis), with or without

eczema around the lips, and—to a lesser degree—intraoral affections such as glossitis, gingivitis, and stomatitis. Therefore, studies focusing on patients with these diagnoses, in which patch testing was performed, were evaluated for information on contact allergic reactions to toothpastes (frequency, clinical signs, allergens, patch testing procedures).

Patients With Cheilitis United States (2001–2011)

In Rochester, United States, 91 patients with cheilitis (70 women, 21 men) were patch tested in the period 2001 to 2011 and studied

retrospectively. Forty-one (45%) patients had allergic contact cheilitis, but only 1 patient was patch tested with toothpaste. The reaction was positive and was considered to be relevant; controls were not mentioned.¹¹

Israel (2007–2008)

In a prospective study in a tertiary referral center in Jerusalem, Israel, a group of 24 patients with cheilitis (20 women, 4 men; ages, 18–76 years) and a control group of 20 dermatitis patients without cheilitis were patch tested with the European standard series, a dental screening series, a series of allergens relevant to toothpastes, and their own toothpastes (tested as is) in a 1.5-year period (2007–2008).¹² Eleven patients in the cheilitis group had a total of 14 positive reactions to at least 1 of their own personal toothpastes, compared with none of the patients in the control group. A positive reaction either to an allergen in the toothpaste series or to the individual's personal toothpaste was noted in 14 patients (58%) in the cheilitis group versus 5 patients (25%) in the control group ($P < 0.05$). After examining the clinical relevance of the positive reactions, it was found that 11 patients (46%) in the cheilitis group were allergic to either an allergen of the toothpaste series or to their personal toothpaste, in contrast to only 1 patient (5%) in the control group ($P < 0.05$). In the cheilitis group, there were 2 reactions to *Myroxylon pereirae* and to fragrance mix I and 1 reaction each to benzyl alcohol, cinnamyl alcohol, cinnamal, eugenol, formaldehyde, l-carvone, and paraben mix, but their relevance was not specified and specific allergens in the toothpastes were not demonstrated. The results showed, according to the authors, a 45% rate of clinically relevant toothpaste allergy in the patients with cheilitis.¹² Because there was no positive patch test reaction to toothpaste in the control group, the authors conclude that toothpastes can be tested undiluted.

Comments. The patients in the control group were tested with their own toothpastes, not with the toothpastes that gave positive reactions in the cheilitis group. The 7 brands of toothpastes that reacted in the cheilitis group should all have been tested in a group of 20 controls. The conclusion of the authors that toothpastes can be tested undiluted, therefore, is too explicit. Data on the presence in the toothpastes used by the patients of those chemicals in the toothpaste series that gave positive patch tests are missing. Clinical data on the effect of avoiding the incriminated toothpastes were not provided.

Italy (2001–2006)

In Verona, Italy, 129 patients with cheilitis (106 women, 23 men) were patch tested in the period 2001 to 2006 and studied retrospectively.¹³ Sixty-five percent had positive patch test reactions considered to be of “possible” or “probable” relevance. There were 3 positive patch test reactions (2.3%) to toothpastes (not mentioned how many patients were tested with their toothpastes); all were considered to be relevant. The (possible) allergenic ingredients were not mentioned. Control tests were not performed, but the positive reactions were validated by executing stop-restart tests with the same product.¹³

Greece (1992–2006)

In Athens, Greece, 106 patients (80 women: mean age, 35 years; 26 men: mean age, 39 years) with cheilitis were patch tested in the period 1992 to 2006 and studied retrospectively. Thirty-six of them were patch tested with their own toothpastes (undiluted), and 8 had positive reactions. The individual ingredients of the toothpastes were not tested because they were not available.¹⁴

Comments. Although the authors state that toothpastes are often irritant under occlusive conditions because of the presence of surfactants, they still tested them undiluted. No controls were performed. No data on relevance were provided nor clinical data on the effect of avoiding the incriminated toothpastes.

Italy (2001–2005)

In Bologna, Italy, 83 patients with cheilitis or perioral eczema (59 women, 24 men) were investigated in the period 2001 to 2005 and studied retrospectively. In none, toothpaste was considered to be the cause.¹⁵

United States (2001–2004)

In a multicenter study of the North American Contact Dermatitis Group, of 10,061 patients patch tested in the period 2001 to 2004, 196 (2%) had the lips as solely involved site (84% women). They were studied in a retrospective manner. Of the 196 patients, 75 (38%) were considered to have allergic contact cheilitis. Toothpastes were not mentioned as causative products, and 1 patient reacted to an “oral hygiene product.”¹⁶

United Kingdom (1982–2001)

In Amersham, United Kingdom, 9980 patients were patch tested in the period 1982 to 2001 and studied retrospectively. Of these, 146 (1.5%) had cheilitis as the main complaint. Twenty-two (15%, 21 were women) had positive patch test reactions that were considered to be relevant to the cheilitis; this included 1 reaction to a patient's own toothpaste.¹⁷

Singapore (1996–1999)

In a tertiary referral center in Singapore, 202 patients (90% women) with primary symptoms and signs of eczematous cheilitis were patch tested in the period 1996 to 1999 and studied retrospectively.¹⁸ All patients were patch tested with the standard series of allergens at the National Skin Centre and to any additional suspected allergens and preparations that could have contributed to the patients' cheilitis. Toothpastes were patch tested at 50% aqueous. Sixty-nine patients (34%) were considered to have allergic contact cheilitis. Cosmetics accounted for more than half of these; toothpastes were considered to be causative in 21 patients (30% of the patients with allergic contact cheilitis, 10.4% of all patients with cheilitis). There were 19 positive patch test reactions to toothpastes, of which 16 were considered to be relevant. The causative ingredients were not specified in any of the patients diagnosed with allergic contact cheilitis from toothpastes, with the possible exception of menthol in 1 case.¹⁸

Comments. Control tests with the toothpastes were not performed, and no mention is made of stop-restart tests or clinical

data on resolution of symptoms after avoidance of the incriminated toothpastes.

Italy (1997–1998)

In a multicenter prospective study in Italy, 54 patients (33 women, 21 men, with a mean age of 37 years, age range of 15–74 years) presenting with eczematous lesions on the lips, occasionally also affecting other areas of the face (cheeks, chin), in whom the use of toothpastes was suspected to be the cause, were patch tested from June 1997 to June 1998.¹⁹ All patients underwent patch tests with the standard series of allergens and a “toothpaste cheilitis series,” containing 31 test materials (9 fragrances, 8 preservatives, 6 essential oils, 2 fluoride compounds, 6 miscellaneous chemicals). If possible, toothpastes were patch tested (as is), stop-restart tests were carried out as were use tests with other possible alternative products. Nineteen patients had 1 or more reactions in the standard series. Thirteen patients had positive reactions to haptens in the toothpaste cheilitis series, most frequently to spearmint oil ($n = 4$), propolis ($n = 3$), peppermint oil ($n = 2$), and hexylresorcinol ($n = 2$). Ten of 17 reactions were to flavor compounds (including essential oils). Patch tests with the suspected toothpastes (a total of 45 patch tests were carried out on 32 patients with 1 or more toothpastes) produced 11 positive reactions and 1 false-positive reaction. In 15 patients (28%, 13 women, 2 men), a final diagnosis of allergic contact cheilitis (and sometimes allergic contact dermatitis) from toothpastes was made. Three patients had positive patch tests only to their toothpaste, not any other reaction. In 12 patients, there were 16 reactions to components of the toothpaste cheilitis series, of which 11 (69%) were to flavors.¹⁹

Comments. Control tests with the toothpastes were not performed, but in 9 patients with a positive reaction, stop-restart tests with the toothpastes were positive. In no single case was the positively reacting substance in the toothpaste cheilitis series (the probable allergen) actually identified in the toothpaste. This makes the authors’ statement “The overall majority of sensitizations proved to be due to the flavoring substances” too explicit, a statement to which is often referred (eg, the studies by Zirwas et al⁸ and Van Baelen et al²⁰).

Australia (1991–1997)

In a tertiary referral center in Darlinghurst, Australia, 75 patients with cheilitis were patch tested during the period 1991 to 1997 and studied retrospectively.²¹ These represented 3.4% of the patients seen in the clinic. The group consisted of 53 women and girls and 22 men and boys. The age range was 9 to 79 years, with a median age of 41 years. Nineteen patients (25%, all women) had allergic contact cheilitis, of which 3 (16% of the patients with allergic contact cheilitis, 4% of the entire group) were caused by toothpaste. The causative allergens were triclosan in 2 patients and peppermint in 1 patient. The authors stated that before 1991, they had seen 4 patients with cheilitis caused by allergy to toothpaste flavors (mint and cinnamon). It was not stated whether the toothpastes themselves had been patch tested.²¹

Singapore (1989–1991)

In a tertiary referral center in Singapore, 27 patients (21 women, 6 men) with cheilitis were patch tested in the period 1989 to 1991 and studied retrospectively.²² All patients were patch tested with the standard series of allergens at the National Skin Centre, to additional allergens as indicated, and to their own lip preparations when available. Five patients had strong reactions to their toothpastes tested “as is,” and these patients were considered to have allergic contact cheilitis from their own toothpastes. It was not mentioned whether changing to another brand of toothpaste resolved the cheilitis, and control tests were not performed. Ingredient patch testing was not performed. In another 6 patients, there were slight erythematous reactions to toothpastes tested as is, not considered to be allergic.²²

Patients With Cheilitis Combined With Other Symptoms

Spain (1976–1977). Cheilitis, Fissures of the Lips, and Stomatitis

In Barcelona, Spain, 15 patients were patch tested because of cheilitis, fissures of the lips, and stomatitis in a 2-year period (1976–1977) and retrospectively studied.²³ Seven patients had positive patch test reactions to their toothpaste (test concentration not stated) and cinnamal; 5 of these coreacted to *M. pereirae*. It was not stated whether the toothpastes actually contained cinnamal (or cinnamon of cassia oil) and whether stopping the use of the incriminated toothpaste products cleared or improved the clinical signs and symptoms.²³

Patients With Gingivitis, Stomatitis, and/or Other Intraoral Symptoms

United States (1985–1998). Contact Stomatitis Caused by Cinnamon Flavoring Agents

In a retrospective study, the records from the database of the Stomatology Center at Baylor College of Dentistry in Dallas, TX were examined.²⁴ In the period 1985 to 1998, 65 cases were found classified as contact stomatitis caused by cinnamon flavoring agents. In 37 of the 65 cases, causative agents were identified, and the signs and symptoms disappeared after the patients discontinued the use of these agents (foods, toothpastes, and chewing gums). These 37 cases were the subject of the study. The other 28 cases were excluded because of the absence of records confirming the disappearance of lesions.

Fifteen patients were patch tested with cinnamic acid 5% pet and cinnamal 2% pet, and 12 reacted positively (not specified to which of the test materials). In 26 patients, toothpastes were considered to be the causative agents or contributory (in combination with foods and/or chewing gum). In 9 of these, patch tests had been performed with the cinnamon derivatives, but it was not specified how many and which ones were positives. The most frequent symptoms and signs of stomatitis were erythema (gingiva, buccal mucosa, tongue; $n = 8$), epithelial sloughing ($n = 5$), and burning or sore mouth ($n = 5$).²⁴

Comments. It was not mentioned whether toothpastes have been patch tested (presumably not) and whether the toothpastes used by the patients actually contained cinnamal or cinnamon. Also, the patch test concentration of 2% for cinnamal may induce false-positive patch test reactions.

United Kingdom (1989–1992). Intraoral Symptoms

In Glasgow, United Kingdom, between 1989 and 1992, 512 patients were patch tested because of intraoral symptoms and studied retrospectively.²⁵ Twelve patients reacted to menthol and/or peppermint oil, which were routinely tested; these 12 allergic patients were the subject of this report. One patient with recurrent oral ulcers had positive patch tests to Crest Tartar Control toothpaste and Blackness Herbal toothpaste (tested as is), but it was not mentioned whether these reactions were relevant. In 1 patient with a 3-year history of burning mouth syndrome and allergic to menthol, the symptoms cleared within 3 days of avoiding her menthol-containing toothpaste and mouthwash (which were not patch tested). Another individual with menthol allergy reported cessation of an 8-year history of recurrent mouth ulcers on changing to a menthol-free toothpaste and avoiding a peppermint-flavored mouthwash (which were not patch tested).²⁵

United States (1970–1971). Gingivitis and Stomatitis

At the Mayo Clinic, Rochester, in 1970 and 1971, 250 patients were seen with gingivitis and 94 with symptoms of stomatitis.²⁶ From this group, 19 patients were selected with “atypical gingivostomatitis” (selection criteria unclear) and retrospectively studied. In 9, 1 to 7 toothpastes were patch tested (probably as is) and 6 patients reacted to 1 to 3 toothpastes. These patients had symptoms such as gingivitis, glossitis, inflammation of the buccal mucosa, and/or angular cheilitis. Coded components of toothpastes were tested in 6 patients, and 3 reacted to 2 components, both flavors of unknown composition. In 1 patient, there was a contact urticarial reaction to a flavor, which may indicate the presence of cinnamal. None reacted to peppermint oil. Nineteen of 20 control tests to the toothpastes were negative. In 4 of 5 patients, challenge tests (use tests) reproduced the symptoms. All patients discontinued the use of chewing gum, and 2 patients could continue the use of toothpaste that had previously caused a positive patch test reaction. The authors admit that they did not confirm the specificity of these patch tests by subsequent rechallenge studies and suggest that some reactions may have been caused by irritants.²⁶

Other Groups of Patients

United States and United Kingdom (<1990). Patients With Possible Reactions to Cinnamal in Toothpastes

Sixteen patients, 3 men and 13 women (age range, 7–65 years), were studied in Dallas, United States, and Glasgow, United Kingdom, in an undefined period before 1990.²⁷ The patients’ oral complaints were temporally related (within days or weeks) to the use of particular types of toothpaste, mainly tartar control (in 3, the

brand was unknown), which “usually” contain approximately 2% cinnamal. Twelve patients had gingivitis, 9 ulceration (irregular, nonaphthous), 2 glossitis, and 2 cheilitis or swelling of the lips. Discontinuation of the toothpaste produced an almost total resolution of symptoms in all patients within 2 to 3 weeks.

Ten patients agreed to undergo patch testing and were tested with the European Standard Series, flavoring agents, food additives, and preservatives, along with the constituents of the tartar control toothpastes. All reacted to “cinnamon” (test concentration and vehicle unknown) at day 2 (reactions read only once), 7 to the flavoring in toothpaste (test concentration and vehicle not mentioned), and only 3 to their toothpaste. Challenge (use test) was positive in 8 of the 10 patients.

The authors were careful in their conclusions: “In the majority of patients included in the present study, there is strong evidence that a toothpaste constituent, particularly in tartar control preparations, was a possible initiating factor of their oral complaint. The allergy to cinnamonaldehyde detected by patch testing and the recurrence of oral lesions following rechallenge with a toothpaste would support this association.”²⁷

Comments. This study has limited value. It is unknown in what period the 16 patients were seen, and the selection process was not specified. In a number of patients, the toothpaste used was unknown, so the presence of cinnamal cannot be ascertained. The patch testing was performed with cinnamon (test concentration and vehicle unknown), but the reactions were ascribed to cinnamal. The patch test reaction was read only on day 2, which is notoriously unreliable. It was not specified what symptoms the patients with positive patch tests to cinnamon had. Only 3 of the 10 patients with a positive patch test to cinnamon also reacted to toothpaste; if the toothpaste indeed contained 2% cinnamal and the patients were allergic to it, one might have expected a positive reaction in all. In the 2 patients, a restart test was negative (though only for 3 days). Despite these shortcomings, it is likely that at least some of these patients were sensitized to (cinnamal in) their toothpaste.

Denmark (1971–1977). Sore Mouth, Stomatitis, and/or Dermatitis Around the Mouth and Dentist Personnel

In Hellerup, Denmark, results of patch testing performed in a group of 41 patients who presented with sore mouth, stomatitis, and/or dermatitis around the mouth or who were dentist personnel, seen in the period 1971 to 1977, were retrospectively studied.²⁸ The manufacturers of some of the common toothpastes in Denmark had supplied the ingredients for patch testing. The flavoring agents were all used in a concentration of 5% in pet and were Italian peppermint oil, American peppermint oil, spearmint oil, anethole, and carvone. Seven patients had positive patch tests to 1 or more of these toothpaste flavors. Six of the patients had stomatitis and/or perioral eczema, and the seventh was a dentist who had occupational allergic contact dermatitis of the hands. There were 2 reactions to Italian peppermint oil, zero to American peppermint oil, 4 to spearmint oil, 2 to anethole, and 4 to carvone.

The toothpastes themselves were not tested. It was not ascertained that the allergens found were present in the toothpastes used by the patients reacting to these flavors, and it was not mentioned whether the symptoms improved or cleared after avoidance of the toothpastes.²⁸

Comments. Later, authors often refer to this publication when stating that flavors are the most common cause of contact allergy to toothpastes (eg, the study by Poon and Freeman²⁹). However, in fact, this publication is about contact allergy to toothpaste *flavors* and not to toothpastes themselves.

Case Series

United Kingdom and Sweden (1972)

In the summer of 1972, a new toothpaste (Close-Up), containing oil of cassia as the main flavoring agent, was marketed in the United Kingdom and had been available in Sweden some months earlier. The components were an abrasive, 2% sodium lauryl sulfate, a humectant, 2 dyes, and a flavor mix at a strength of 1.25%. This comprised menthol, methyl salicylate, peppermint, anethole, and oil of cassia, the cinnamic components amounting to approximately 14% of the total (cinnamal <0.2%). From March 1972, 2 investigators in Malmö, Sweden, and Buckinghamshire, United Kingdom, saw 16 patients (13 women, 3 men; 3 in Sweden, 13 in United Kingdom) with symptoms related to the use of this toothpaste. Of these cases investigated, 8 patients were referred to skin departments because of their symptoms. The remaining 8 patients were discovered as the result of follow-up studies undertaken in association with the manufacturers.^{30–32}

The symptoms were soreness of the mouth or “burning” sensation (n = 14), soreness of the lips (n = 8), swelling or blistering of the lips (n = 3), burning or vesiculation of perioral skin (n = 3), swelling of the tongue (n = 3), and ulceration of the mouth (n = 2). All but 1 patient seemed to be sensitized by the use of the toothpaste, and only an 18-year-old girl had probably previously become sensitized to cinnamal in a “spicy” perfume. The investigators received all ingredients of the toothpaste from the manufacturer but concentrated on cassia oil and cinnamal after it was clear that the patients only reacted to these materials. Only 4 patients were tested with the toothpaste itself (all 4 positive), open tests in 3 patients were negative, and cinnamal 1% pet was positive in 15 of the 16 patients. Cassia oil 5% pet was positive in 4 of the 5 patients tested, cassia oil 1% pet in 5 of the 8 patients tested, and cassia oil 0.1% pet in 1 of the 2 patients tested. Oil of cinnamon 1% pet was tested twice and was positive in both cases. Four cases described in more detail are shown in the following table. The symptoms disappeared 4 to 10 days after changing the toothpaste in all patients. Several of them later tried the toothpaste again and had an immediate return of symptoms. As soon as it had become apparent that cinnamal was the responsible sensitizer and that methyl cinnamal was not a safe alternative flavor, the manufacturers withdrew stocks and reformulated the toothpaste. In the subsequent 18 months, the authors did not encounter further cases.³¹

The first 3 patients with contact allergy to Close-Up toothpaste had been reported in previous publications.^{33,34} The author in an addendum stated that after this article was accepted for publication, 12 other patients had been identified with a similar sensitivity to Close-Up. They all had had positive patch tests to 1% cinnamal.³³

United States (1931)

In the United States in 1931, 2 physicians in a period of 2 months saw 6 patients who reacted to toothpaste ST37, a toothpaste containing hexylresorcinol.³⁵ They all had active cheilitis with swelling of the lips and perioral eczema, which started within 4 to 14 days after first using the toothpaste. The dermatitis in all 6 patients healed after stopping its use and recurred in 1 patient who used it later once more. Five of the patients were patch tested (application to the volar aspect of the underarm) with the toothpaste as is and pure hexylresorcinol. The toothpaste was positive in all 5 patients (in a crescendo manner), and hexylresorcinol reacted (in a crescendo manner) in 3 patients. An unknown number of controls patients had no reaction to the toothpaste, and hexylresorcinol solution was used in full strength on many patients in their daily practice for more than a year without producing any instances of dermatitis.³⁵

Comments. The short period of time before the eruption started may indicate presensitization, irritation, or hexylresorcinol being a very strong allergen. Against the latter pleads that only 3 of the 5 patients reacted to a patch test with pure hexylresorcinol. However, the reactions were crescendo and controls were negative, which is in favor of contact allergy.

Case Reports

A total of 34 case reports and small series (n = 2–5) published between 1940 and 2016 describing 50 patients (plus an unknown number in the study by Poon and Freeman²⁹) allergic to toothpastes have been found in the literature. Their details are summarized in Table 3.

Cases With Incomplete Data

There are several reports of (presumed or proven) contact allergic reactions to toothpastes in the early literature, of which we have incomplete data or incomplete data were presented. These and some cases from non-English literature and from some publications we could not access are presented hereafter with the known information that is available to us.

1989. A clear association between the use of cinnamal containing toothpaste and inflammation of the lips, labial mucosa, and gingivae was described in a 59-year-old man. The sensitivity reaction was verified by a positive patch test with cinnamal. It is uncertain whether the toothpaste itself was tested.⁶⁵

1988. “Sensitivity to flavored toothpaste”⁶⁶ was caused by “undefined flavors or mixture” (cited in the study by Sainio and Kanerva²).

TABLE 3. Summary of Published Cases of Contact Allergic Reactions From (Ingredients of) Toothpastes

Reference	Sex/Age, y	Clinical Picture	Allergen(s) and PTCV	Comments
Van Baelen et al ²⁰	F/24	Cheilitis, dermatitis of the palm of the right hand	Unknown	Belgium (2016); coded ingredients obtained from the manufacturer; positive semiopen tests with Elmex "Erosion Protection" toothpaste in both patients; resolution of symptoms after cessation of use
Enamandram et al ³⁶	F/55	Lip swelling, urticaria	Stannous fluoride, tin. Concentration? Vehicle?	United States (2014); positive patch test to tin, but a picture only showed isolated papules; remission after stopping Crest Pro-Health toothpaste, exacerbation after reintroduction; toothpaste itself not tested
Foti et al ³⁷	F/50	Cheilitis	Amine fluoride, 5% water (active ingredients 0.9%) ¹	Italy (2014); Elmex Erosion Protection toothpaste 3% in pet and ROAT with toothpaste as is positive; clearing and no relapse after stopping use; see the study by De Groot et al ¹ for additional information
Ghosh and Bandyopadhyay ³⁸	F/25 M/18 F/32	Cheilitis, dermatitis of the right index finger	Unknown	India (2011); all 3 patients used their right index finger instead of a toothbrush to spread the toothpaste over their teeth; resolution after switching to another toothpaste; the ingredients were not tested, but 2 had positive patch test reactions to the fragrance mix 1 and the third to <i>M. pereirae</i>
Zirwas and Otto ⁸	M/81	Cheilitis, dermatitis around the mouth	Flavorings	United States (2010); positive patch tests to fragrance mix 1, cinnamic alcohol and Arm & Hammer Advance white fresh mint toothpaste (as is?); it was not ascertained that cinnamic alcohol was in the toothpaste; resolution after switching to another toothpaste
Robertshaw and Leppard ³⁹	F/52	Blistering eruption of the lips and the buccal mucosa	Triclosan 2% pet	United Kingdom (2007); positive patch test to active natural toothpaste (probably tested as is); no further problems after using triclosan-free toothpaste
Poon and Freeman ²⁹	F/63	Cheilitis	Anethole 2% pet	Australia (2006); the toothpaste itself was not tested, but there was a positive reaction to anethole, which was considered to be the culprit; however, its presence was not ascertained and spearmint oil does not contain anethole ⁴⁰ ; resolution after cessation
Agar and Freeman ⁴¹	F/10	Cheilitis	Cocamidopropyl betaine 1% water	Australia (2005); the toothpaste itself (Colgate "2-in-1 toothpaste and mouthwash") was not tested; avoidance of the product resolved the cheilitis within a few weeks
Corazza et al ⁴²	F/68	Cheilitis	Carvone 5% pet	Italy (2002); the patient reacted to carvone and to 2 toothpastes (Colgate and AZ protezione carie), tested undiluted; the presence of carvone in both products was established by thin-layer chromatography and gas chromatography; healing of the lesions after stopping the toothpastes

Lee et al ⁴³	F/38	Erythematous edematous patches on and around the lips	Sodium lauryl sulfate 1% and 0.1% water	Korea (2000); the patient reacted to toothpaste 2% in water
	F/62	Erythematous scaly patches around the lips	Sodium lauryl sulfate 1% and 0.1% water	Korea (2000); the patient reacted to toothpaste 1% in water
	F/71	Sore mouth, cheilitis, angular cheilitis, eczema around the mouth	Spearmint oil 5% pet	Denmark (1998); the patient's toothpastes were not tested; not ascertained that spearmint oil was present in the products
Franks ⁴⁴	F/64	Dry mouth, erythema and desquamation of oral mucosa, cheilitis, perioral eczema, loss of taste	Anethole 5% pet	United Kingdom (1998); the patient reacted to Kingfisher toothpaste 2% water but not to Colgate toothpaste 2% water; Colgate toothpaste contained anethole, the other fennel, a natural source of anethole; slow resolution of symptoms on avoidance of anethole
	F/58	Erosive (angular) cheilitis	L-carvone 0.27% and 0.067% vehicle? spearmint oil 1% vehicle?	Germany (1998); Colgate toothpaste testing was positive after tape stripping only; the patient was also allergic to mouthwash containing the same allergens; tested with all ingredients; complete resolution on flavor-free toothpaste
Downs et al ⁴⁶	Unknown	Lip dermatitis and stomatitis	α -Amylcinnamal 1% pet	United Kingdom (1998); positive reaction to Colgate toothpaste 50% pet, which contains α -amyl-cinnamal; patient "responded well" to alternative toothpaste
Aguirre et al ⁴⁷	M/28	Edematous cheilitis	Sodium benzoate 1% and 2% aq and pet	Spain (1993); positive patch test to toothpaste Enciodontyl; tested with a number of its ingredients; exacerbation of cheilitis from a mucolytic syrope containing sodium benzoate; exacerbation of cheilitis each morning after brushing the teeth; this may well be due to immediate contact reaction to sodium benzoate, which was, quite remarkably, not suggested by the authors
	F/2 F/2 M/3	Pruritic infiltrated and excoriated plaques at the anterior thighs at the site of previous triple vaccine injections containing aluminium hydroxide; no local allergic reaction	Aluminium (AlCl ₃ 2% water)	Denmark (1993); all patients reacted to aluminium chloride; they used Zendum toothpaste containing 30%-40% aluminium oxide; after stopping strong improvement; provocation tests using Zendum again were positive in 2/3; systemically aggravated contact dermatitis, no local symptoms
Macháčkova and Šmíd ⁴⁹	M/71	Cheilitis	Flavorings 1% alc and chloroacetamide 0.2% water	Czechoslovakia (1991); the patient reacted to 2 toothpastes tested as is and the flavors in both and to the preservative chloroacetamide (present in one or both?); clearance after cessation of using these toothpastes

(Continued on next page)

TABLE 3. (Continued)

Reference	Sex/Age,y	Clinical Picture	Allergen(s) and PTCV	Comments
Young ⁵⁰	M/55	Stomatitis and throat complaints	Propolis as is, 20% pet and 5% pet	The Netherlands (1987); the patients used propolis tablets and propolis-containing toothpaste (not patch tested); after stopping all symptoms disappeared
Maibach ⁵¹	F/82	Cheilitis	Cinnamal 1% pet	United States (1986); the patient used a sunscreen lipstick and a toothpaste containing cinnamal; the toothpaste was not patch tested; the cheilitis cleared after avoidance
Ormerod and Main ⁵²	F/47	Gingivitis, moderate cheilitis	Formaldehyde 2% water	United Kingdom (1985); the patient was presensitized; when she first used Mclean sensitive teeth formula containing 1.3% formalin (formaldehyde solution), gingivitis and moderate cheilitis appeared after 2 d
Grattan and Peachey ⁵³	F/65	Sore mouth, cheilitis	Spearmint oil 1% pet, l-carvone 1% pet, anethole 2% pet	United Kingdom (1985); the patient reacted to 2 toothpastes 10% pet; 30 controls were negative; the allergens in 1 toothpaste were spearmint oil and its main ingredient carvone, in the other product spearmint flavor and anethole, which is not an ingredient of spearmint oil; the eruption resolved after stopping the use of toothpastes containing spearmint oil; 30 controls were tested with the 2 toothpastes <i>undiluted</i> and 9 gave slight irritant reactions
Balato et al ⁵⁴	F/26	Gingivitis, perioral eczema	Azulene 1% pet	Italy (1985); the patient reacted to A-Z 15 toothpaste (probably as is) and its ingredient azulene, not to other ingredients; rapid clearing after cessation of the toothpaste; in another report, ⁵⁵ the allergen in this toothpaste was described as guaiazulene
Duffin and Cowan ⁵⁶	M/64	Swelling of the upper lip (later also eyelids), ulceration of the inner part of the lip and gingiva	Formaldehyde 1% water	Ireland (1985); the patient had applied undiluted Mclean sensitive teeth formula toothpaste for 30 min; the toothpaste contained 1.3% formaldehyde solution (formalin); the medical authorities received >100 reports of adverse reactions to this toothpaste
Hausen ⁵⁷	M/74	Cheilitis, erythema, and burning of the oral mucosa	L-Carvone 1% DEP; peppermint oil 0.5% DEP	Germany (1984); very strong reaction to L-carvone, weak (cross-)reaction to D-carvone; L-carvone was 20%-30% of the flavor; positive patch test to the toothpaste as is; recurrence of cheilitis from refreshment lozenges; control tests with L-carvone and peppermint oil were negative
Angelini and Vena ⁵⁵	?? (n = 5)	Cheilitis; 2 had loss of taste, burning of the mouth, or soreness	Guaiazulene 1% pet	Italy (1984); all patients used A-Z 15 toothpaste, which was probably not tested; a use test in 3 patients was positive; prompt improvement after withdrawal of the toothpaste; in another report, ⁵⁴ the allergen in this toothpaste was described as azulene

Monti et al ⁵⁸	F/age?	Swollen gums, which bled easily	Propolis as natural extract and in alcoholic solution	Italy (1983); the toothpaste itself was not tested, but clearing after avoidance; the patient also had dermatitis of the face from a cream containing propolis
Drake and Maibach ⁵⁹	M/52	Cheilitis, stomatitis, eczema of the fingers of the left hand	Cinnamal 1% pet, cinnamon bark oil and cassia oil 1% pet	United States (1976); the patient reacted to the toothpaste 5% in pet
Magnusson and Wilkinson ³⁰	M/60	Stomatitis	Cassia oil 1% pet	United Kingdom/Sweden (1975); positive reaction to the toothpaste; coreaction to oil of cinnamon but not to cinnamal; rapid clearing after changing to a new brand of toothpaste
	M/40	Cheilitis	Cassia oil, cinnamal	Positive reaction to the toothpaste as is; clearing after stopping, exacerbation after using toothpaste again
	F/18	Oral ulcers	Cinnamal	Positive reaction to the toothpaste and a spicy perfume, which had previously caused allergic contact dermatitis, probably, this was the source of sensitization to cinnamal
	F/35	Burning mouth, soreness, and swelling of the tongue	Cinnamal 1% pet, cassia oil 1% pet	Positive reaction to toothpaste as is; also reaction to a perfumed cream, which was previously tolerated well; clearance after changing to another brand of toothpaste. All 4 patients had used Close-Up toothpaste, which contained cassia oil
Millard ³³	F/35	Sore mouth, cheilitis, perioral eczema, gingivitis	Cinnamon 5% olive oil, cinnamon 0.5% pet	United Kingdom (1973); the toothpaste itself (Close-Up) was not tested; 2 patients had started using the toothpaste 6-14 d before the onset, the third 3 months before; in all 3, the symptoms and signs disappeared upon stopping the use of the toothpaste
	M/30	Gingivitis, glossitis, perioral eczema, angular cheilitis	1% Cinnamal (not in text but according to data in addendum)	United States (1953); ammoniated toothpaste;
	F/22	Gingivitis, oral ulcers, glossitis	Dichlorophene 5% pet	the toothpaste was tested and positive in 2; in all 3 patients, prompt relief after discontinuation and recurrence after provocation; in 1 patient, all other constituents were tested and negative; the authors mentioned 4 more such patients, details not provided; dichlorophene 5% was negative in controls
	F/29	(Angular) cheilitis, glossitis	Dichlorophene 5% pet	United States (1953); positive patch test to the toothpaste; clearing in 5 d after discontinuing the use of the toothpaste; natural cinnamon oil 5% in olive oil was also positive; the other ingredients were negative
	F/20	Angular cheilitis, perioral eczema, glossitis, stomatitis		United States (1951); ammoniated toothpaste, the toothpaste was positive; 10 controls were negative to the toothpaste; prompt clearance after avoiding the toothpaste and recurrence with reuse
	M/53	Stomatitis, glossitis, perioral eczema, cheilitis	Dichlorophene 5% pet	
Laubach et al ⁶¹	F/22	Vesicular dermatitis around the mouth, later small patches under the right eye and on the dorsum of the right hand	Synthetic cinnamon oil 1% in 70% alcohol	
Fisher and Lipton ⁶²	M/53	(Angular) cheilitis, glossitis, marked loss of taste	Dichlorophene 5% pet	

(Continued on next page)

TABLE 3. (Continued)

Reference	Sex/Age, y	Clinical Picture	Allergen(s) and PTCV	Comments
Leifer ⁶³	F/36	Eczema of the hands, face, and chest, no stomatitis or cheilitis	Cinnamon oil 1% alc	United States (1951); a patch test with the toothpaste was strongly positive; the patient had previously become sensitized to cinnamon powder and had longstanding hand dermatitis; dermatitis of the face and chest and worsening of hand dermatitis was apparently caused by the toothpaste; all symptoms disappeared after stopping the toothpaste; oral provocation with cinnamon oil resulted in hand dermatitis on 2 occasions (systemic contact dermatitis)
Cummer ⁶⁴	M/41	Eczema of the left hand holding the toothbrush; no cheilitis or stomatitis	Cinnamon oil 1% or 50% alc (not specified)	United States (1940); positive reaction to the toothpaste and prompt clearing after avoidance; positive patch test to the flavoring material, later to cinnamon oil, 1 of the 6 flavoring oils

DEP indicates diethyl phthalate; PTCV, patch test concentration and vehicle; F, female; M, male.

1984. One patient from Germany was allergic to L-carvone (tested 1% pet) in the spearmint oil flavor in a toothpaste; there was no reaction to D-carvone.⁶⁷

1976. A patient allergic to *M. pereirae* (Balsam of Peru) was sensitized to cinnamon in a toothpaste; his dermatitis flared after drinking vermouth that contained cinnamon (the study by Fisher⁶⁸ cited in the study by Rietschel and Fowler⁶⁹).

1967. In Denmark, 3 positive reactions to toothpaste flavors among 206 consecutive eczema patients were found.⁷⁰ The authors used a flavor mixture for patch testing in a concentration of 5% in pet and the flavor ingredients in a concentration of 2% in pet. The flavor mixture was actually used in a concentration of 0.8 % in some of the most common toothpastes in Denmark consisting of peppermint oil 30%, spearmint oil 25%, carvone 25%, anethole 10%, and menthol 10%. Later, they found 3 more patients with positive reactions. Among these 6 patients, 2 were sensitive to peppermint oil, both the American and the Italian variants, and 4 were sensitive to carvone and spearmint oil; 1 of these was also sensitive to anethole (data cited in the studies by Andersen²⁸ and Hausen⁵⁷). We do not know whether these patients were allergic to toothpastes or only to flavors used in such products.

1967. One or more cases of contact allergy to eugenol in toothpaste(s)⁷¹ were cited in the studies by Sainio and Kanerva² and Millard.³³ However, in Fishers' contact dermatitis, it is stated that eugenol in *impression paste* caused allergic cheilitis and stomatitis.⁶⁹

1961. In a monograph on contact allergy to balsams,⁷² one or more cases of contact allergy to menthol (cited in the studies by Sainio and Kanerva², Hausen⁵⁷, and De Groot et al⁷³) and to cinnamal (cited in the studies by Sainio and Kanerva² and Hausen⁵⁷) in toothpastes were apparently described.

1950. Contact allergy to laurel oil in toothpaste was described in the 1950s (data by Spier and Sixt,⁷⁴ cited in the study by Sainio and Kanerva²).

1952. A patient was described in a US journal with the title "Eczematous contact dermatitis of the palm due to toothpaste."⁷⁵ The allergen was cited as formaldehyde in the study by De Groot et al⁷³; Fisher and Tobin⁶⁰ mentioned that it was a toothpaste "that contained compound G-4" (which is dichlorophene) and Cronin⁷⁶ in her book states "Patch testing with the toothpaste was positive."

1948. A patient was described having "allergic manifestations caused by the use of a nonproprietary dentifrice containing orris root powder."⁷⁷ According to Sainio and Kanerva² and Lippert,⁷ the patient was not only allergic to the toothpaste but also to orris root.

1933. Three patients with reactions of the oral mucosa and the adjacent skin were reported, in which the condition was due to a toothpaste, which contained a solution of formaldehyde. One case was thought to be a "true idiosyncrasy," and in the 2 others, the author considered the condition to be due to an allergy, which was later exacerbated by the use of a mouthwash (data by Weinberger⁷⁸ cited in the studies by Sainio and Kanerva² and Beinhauer⁷⁹).

1900 to 1936. Phenyl salicylate (salol) in a toothpaste was already incriminated in lip contact dermatitis in 1900 (data by Axmann⁸⁰ cited in the study by Marchand et al⁸¹). In France in

1936, phenyl salicylate in toothpastes was considered as one of the most frequent causes of lip dermatitis (data by Fernet⁸² cited in the studies by Sainio and Kanerva² and Marchand et al⁸¹).

EVALUATION AND DISCUSSION

Ideally, a patient with contact allergy to toothpaste has a positive patch test reaction to the toothpaste; next, the patch test reaction is validated as allergic by a repeat patch test and/or a serial dilution test and/or negative reactions in 20 control patients and/or a positive ROAT. The eruption clears after stopping the use of the incriminated toothpaste and is provoked by using it again. All ingredients, obtained from the manufacturer in the proper concentrations and vehicles, are tested, and 1 or more positive reactions are obtained, identifying the allergenic culprit(s), the exact nature of which is verified. If an adequate (nonirritant) test concentration of a chemical thus found is not known, the material is also tested in 20 controls to exclude irritancy. Unfortunately, the reality is that the available literature is far from ideal. Not one single study fulfills all of these criteria and most only a few.

A major problem is the patch test procedure. As will be explained later, most authors agree that testing with toothpaste as is may produce false-positive, irritant, patch test reactions, and such reactions have indeed been observed.^{22,53} However, with few exceptions,^{26,30,62} positive patch test reactions to undiluted toothpaste have not been followed by control testing, or inadequate controls were used.¹² In many reports,^{10,33,36,48,50–52,55,58} the toothpastes themselves were not tested, but the diagnosis was made on the basis of a positive reaction to an ingredient known or merely supposed^{8,10,29} to be present in the product and clearing of symptoms after avoidance of toothpaste, sometimes in combination with positive provocation (use) tests.^{48,55} Only in a limited number of studies were patients tested with all ingredients^{20,30} (first few patients, later only cinnamon derivatives).^{37,39,49,53,54,57,61,64} Also, the studies in groups of patients (eg, patients with cheilitis, patients with intraoral symptoms, patients suspected to have toothpaste allergy) differ widely in study design and most were retrospective. Third, there is quite a lot of (very) early literature on this issue, when patch testing was less reliable; moreover, some of the information will be dated or outdated.

Thus, there are various difficulties in assessing the reliability of many publications and in assessing and comparing the results of the studies performed in selected groups of patients. The answers hereafter to the questions raised before entering this review should therefore be viewed and assessed with these problems, limitations, and uncertainties in mind.

Frequency of Allergic Reactions to Toothpastes

There are no data on the frequency of toothpaste allergy in the general population or in patients with dermatitis seen for routine patch testing. We have found 34 case reports and small series ($n = 2–5$) published between 1940 and 2016 describing more than 50 patients allergic to toothpastes (Table 3), 2 case series with a total of

31 patients allergic to cinnamal from the presence of oil of cassia in 1 particular brand of toothpaste^{30–34} (7 of them are also presented in Table 3), a case series of 6 patients reacting to 1 brand of toothpaste (of which 3 may have been caused by hexylresorcinol),³⁵ and 13 case reports or small series in publications with incomplete data.^{65–68,70–72,74,75,77,78,80,82} A summary of the frequency of toothpaste reactions in the groups of patients with cheilitis, which were discussed previously, is shown in Table 4.

In these groups of patients investigated for cheilitis, probably the most frequent symptom of toothpaste allergy, the frequency of allergic reactions to toothpaste has ranged from 0% to 47%. This may partly be explained by differences in study design. It can be expected that studies specifically looking for toothpaste allergy and performed in patients suspected of reactions to toothpastes¹² will have higher rates than retrospective studies of individual case files.^{11,15,16,21} Also, the level of suspicion of the investigator is important. If not considered at all or investigators perceive contact allergy to toothpastes to be very infrequent, their patients may not always be adequately investigated for this possibility. This may have been the case in studies with very low rates.^{11,15,16,42} Conversely, in some studies with very high frequencies of toothpaste allergy (eg, the studies by Lavy et al¹² and Romaguera and Grimalt²³), there may be an overestimation of the importance of such reactions. These investigations had certain important flaws, such as no or inadequate controls for positive reactions to toothpastes (tested undiluted, which can most likely induce irritant, false-positive, reactions), no information of whether chemicals with positive patch tests were actually present in the incriminated toothpastes, and missing clinical data (whether the symptoms improve or heal after stopping the toothpaste).

Can these data be extrapolated to the general patch test population? The frequency of the lips being the sole or most prominent localization of dermatitis (cheilitis) in a patch test population was 2% in a multicenter study of the North American Contact Dermatitis Group (196 of 10,061 patients patch tested in the period 2001 to 2004¹⁶), 1.5% in Amersham, United Kingdom (146 of 9980 patients patch tested in the period 1982 to 2001¹⁷), and 3.4% in Darlinghurst, Australia (75 of 2206 patients patch tested during the period 1991 to 1997²¹). Thus, patients with cheilitis (in these studies) represent 1.2% to 3.4% of a patch test population in highly specialized clinics. Estimating that the cheilitis in 10% of the patients (estimated from the data in Table 4) is caused by contact allergy to toothpastes, this would represent approximately 0.1% to 0.3% of this patient population. Contact allergy to toothpastes would then be infrequent, but not rare. This largely corresponds to the number of published case reports, rather infrequent but not really rare.

Several factors may contribute to toothpaste contact allergy occurring infrequently:

1. Under normal conditions of use, the product is strongly diluted with water and saliva; this also applies to potential allergens in the toothpastes.

TABLE 4. Frequency of Allergic Reactions to Toothpastes in Selected Groups of Patients

Reference	Year, Country	Selection Criteria	No. Patients		
			Tested	Reacting to Toothpaste	%
O'Gorman and Torgerson ¹¹	2001–2011, United States	Cheilitis	91	1	1
Lavy et al ¹²	2007–2008, Israel	Cheilitis	24	11	46
Schena et al ¹³	2001–2006, Italy	Cheilitis	129	3	2.3
Katsarou et al ¹⁴	1992–2006, Greece	Cheilitis	106	8	7.5
Zoli et al ¹⁵	2001–2005, Italy	Cheilitis or perioral dermatitis	83	0	0
Zug et al ¹⁶	2001–2004, United States	Cheilitis	196	0	0
Strauss and Orton ¹⁷	1982–2001, United Kingdom	Cheilitis	146	1	0.7
Lim and Goh ¹⁸	1996–1999, Singapore	Cheilitis	202	21	10
Francalanci et al ¹⁹	1997–1998, Italy	Cheilitis	54	15	28
Freeman and Stephens ²¹	1991–1997, Australia	Cheilitis	75	3	4
Lim et al ²²	1989–1991, Singapore	Cheilitis	27	5	19
Romaguera and Grimalt ²³	1976–1977, Spain	Cheilitis and stomatitis	15	7	47

2. Rinsing after brushing the teeth removes most residual toothpaste ingredients from the oral mucosa. Of sodium lauryl sulfate, for example, which is usually contained in toothpaste at 0.5% to 2.0%, 96% is removed by rinsing within 2 minutes.⁸³
3. The contact time with toothpastes is short, and the frequency of contact is low, usually 2 minutes 2 to 3 times per day.
4. Modern toothpastes do not contain ingredients with a high risk of sensitization, because these have been removed by manufacturers on the basis of previous experience. In early studies (1940–1953), there have been several cases of contact sensitization to cinnamon oil in toothpaste,^{61,63,64} and in the early and mid-1970s in the United Kingdom and Sweden, many patients were sensitized to cinnamal in 1 brand of toothpaste containing cassia oil as flavor.^{30–34} This particular toothpaste was reformulated and the most recent case of toothpaste allergy ascribed to cinnamal dates from before 1990.^{27,65} In the early 1950s, in the United States, several patients were sensitized to dichlorophene, probably in 1 brand of toothpaste,^{60,62} but since then, no new cases have appeared. In 1985, a toothpaste containing 1.3% formaldehyde solution caused many adverse reactions,^{52,56} but since then, no new cases have emerged in the literature. In the 1930s, phenyl salicylate was apparently a common cause of toothpaste allergy (data by Fernet⁸² cited in the studies by Sainio and Kanerva² and Marchand et al⁸¹). In another early study in the 1930s, hexyl-resorcinol in toothpaste gave a cluster of (allergic?) reactions in toothpaste.³⁵ It seems reasonable to assume that manufacturers of the incriminated toothpastes will either have withdrawn their products or have reformulated them to exclude allergenic ingredients. Indeed, in the more recent literature, in case reports, various chemicals have been found as the cause of allergic reactions to toothpastes, but none is an important and frequent cause of contact allergy in either toothpastes or other cosmetic products (discussed hereafter).
5. Possibly, the mucous membranes are less susceptible than the skin to both sensitization and elicitation of allergic reactions. The following tentative explanations have been given^{16,84}:

- The anatomic structure of the buccal mucosa, with its extensive vascularization, aids in rapid dispersion and absorption of the allergen, thereby preventing prolonged contact of the allergen with the mucosa.
- Saliva dilutes and removes potential allergens and may buffer and neutralize chemicals.
- The concentration of allergens necessary to elicit macroscopic reactions in the mucosa is 5 to 12 times higher than in the skin.⁸⁵

Indeed, substances contacting the oral mucosa may even induce tolerance rather than immunogenic responses.⁸⁶

Alternatively, it is conceivable that some allergic reactions to toothpastes go unrecognized. Most patients investigated for possible toothpaste allergy have cheilitis without or with oral symptoms. Possibly, in a number of cases, the allergic reaction is limited to the oral mucosa with symptoms such as soreness, burning, burning mouth syndrome, aphthous or nonaphthous ulcers, or lichenoid reactions.²⁵ When symptoms appear, patients may switch to another brand of toothpaste, solving the problem themselves, or they are diagnosed as having stomatitis, glossitis, gingivitis, or aphthous ulcers^{26,27} of unknown cause by general practitioners, dentists, ear-nose-throat specialists, or oral surgeons. Very likely, only a few of these patients will be referred to a dermatologist for patch testing.

Clinical Picture of Contact Allergic Reactions to Toothpastes

Contact allergy to toothpastes occurs both in women and in men, with a female preponderance. The time between the first use of the toothpaste and the development of allergic contact cheilitis and/or stomatitis has varied in different studies from (less than) 2 weeks^{30,33,60,61} to 2 to 10 months^{33,37,53,60} and to some years.^{54,55} Often, the interval was not specified. In most cases, patients have become sensitized from the use of the toothpaste itself, which was the case in 15 of 16 patients in a large case series.^{30–32} In a few

TABLE 5. Chemicals Identified or Incriminated as Contact Allergens in Toothpastes

Chemical	Nr. Pat.	Year, Country	Comments	Reference
Contact allergy proven/very likely				
Aluminium	3	1993, Denmark	Presensitization to aluminium from vaccination; no local symptoms, but exacerbation of plaques at vaccination sites	Veien et al ⁴⁸
Amine fluoride	1	2014, Italy	The amine fluoride was likely olaflur	Foti et al ³⁷
α-Amyl/cinnamal	1	1998, United Kingdom		Downs et al ⁴⁶
Anethole	1	1998, United Kingdom		Franks ⁴⁴
Azulene	1	1985, Italy	Same toothpaste as used by the guaiazulene allergic patients ⁵⁵	Balato et al ⁵⁴
Carvone	1	2002, Italy	Carvone was identified by chemical analysis	Corazza et al ⁴²
L-Carvone	1	1998, Germany	Also reaction to spearmint oil (containing carvone)	Worm et al ⁴⁵
L-Carvone	1	1985, United Kingdom	Also reaction to spearmint oil (containing carvone)	Grattan and Peachey ⁵³
Cassia oil	1		See cinnamal 1976 United States ⁵⁹ in this table	
Cassia oil	4	1975, United Kingdom/Sweden	Three also reacted to cinnamal, the main ingredient of the oil; 1 patient was presensitized to cinnamal in a "spicy" perfume; the toothpaste was the same as in Millard, ³³ where the flavor was termed cinnamon oil; these oils have different botanical origins, but cinnamal is in both by far the most important component	Magnusson and Wilkinson ³⁰
Chloroacetamide	1 or 2	1991, Czechoslovakia	Also reaction to unspecified flavor in 2 patients	Macháková and Šmíd ⁴⁹
Cinnamal	1	1976, United States	Also reaction to cinnamon bark oil and cassia oil; both contain high concentrations of cinnamal	Drake and Maibach ⁵⁹
Cinnamal			See cassia oil 1975 United Kingdom/Sweden ³⁰ in this table	
Cinnamal			See cinnamon oil 1973 United Kingdom ³³ in this table	
Cinnamon bark oil	1		See cinnamal 1976 United States ⁵⁹ in this table	
Cinnamon oil	3	1973, United Kingdom	The patients also reacted to cinnamal; the toothpaste was the same as in Magnusson, ³⁰ where the flavor was termed cassia oil; these oils have different botanical origins, but cinnamal is in both by far the most important component	Millard ³³
Cinnamon oil	1	1951, United States	The names cinnamon oil and cassia oil were used as synonyms, which is <i>sensu stricto</i> incorrect	Leifer ⁶³
Cinnamon oil	1	1940, United States		Cummer ⁶⁴
Cinnamon oil, synthetic	1	1953, United States	The patient also reacted to natural cinnamon oil	Laubach et al ⁶¹
Cocamidopropyl betaine	1	2005, Australia	The toothpaste was not tested	Agar and Freeman ⁴¹
Dichlorophene	3	1953, United States	The authors mentioned having seen 4 similar patients, but details were not provided	Fisher and Tobin ⁶⁰
Dichlorophene	1	1951, United States		Fisher and Lipton ⁶²
Flavor, unspecified	2	1991, Czechoslovakia	One or 2 also reacted to chloroacetamide	Macháková and Šmíd ⁴⁹
Formaldehyde	1	1985, United Kingdom	The patient was presensitized to formaldehyde	Ormerod and Main ⁵²
Formaldehyde	1	1985, Ireland		Duffin and Cowan ⁵⁶
Guaiazulene	5	1984, Italy	Same toothpaste as the azulene allergic patient ⁵⁴	Angelini and Vena ⁵⁵
Olaflur	1	2016, Netherlands	No controls, but report probably reliable	De Groot ¹

(Continued on next page)

TABLE 5. (Continued)

Chemical	Nr. Pat.	Year, Country	Comments	Reference
Propolis	1	1983, Italy	The toothpaste was not tested	Monti et al ⁵⁸
Sodium benzoate	1	1993, Spain	Probably also immediate contact reaction	Aguirre et al ⁴⁷
Spearmint oil	1	1998, Germany	Also reaction to ingredient L-carvone	Worm et al ⁴⁵
Spearmint oil	1	1985, United Kingdom	Also reaction to ingredient L-carvone	Grattan and Peachey ⁵³
Triclosan	1	2007, United Kingdom		Robertshaw and Leppard ⁴⁹
Contact allergy likely				
Cinnamal	1	1986, United States	The patient also used a lipstick containing cinnamal; the toothpaste containing cinnamal was not tested	Maibach ⁵¹
Propolis	1	1987, The Netherlands	The patient also used propolis tablets; toothpaste containing propolis was not tested	Young ⁵⁰
Sodium lauryl sulfate	2	2000, Korea	No controls performed with 0.1% sodium lauryl sulfate and 0.1% aqua, a known irritant	Lee et al ⁴³
Tin	1	2014, United States	Present in stannous fluoride; dubious patch test reaction	Enamandram et al ³⁶
Presence of incriminated allergen in toothpaste not ascertained				
Anethole	1	2010, Australia		Poon and Freeman ²⁹
Anethole	1	1985, United Kingdom		Grattan and Peachey ⁵³
Cinnamal	7	1976-1977, Spain	In 5, coreaction to <i>M. pereirae</i>	Romaguera and Grimalt ²³
Cinnamyl alcohol	1	2010, United States		Zirwas and Otto ⁸
Spearmint oil	1	1998, Denmark		Skrebova et al ¹⁰
Insufficient data to assess likelihood of contact allergy				
Anethole			See the section: Cases With Incomplete Data	
Cinnamal				
Cinnamon oil				
Eugenol				
Flavor, undefined				
Formaldehyde				
Laurel oil				
Menthol				
Orris root powder				
Peppermint oil				
Phenyl salicylate (salol)				
Spearmint oil				

cases, patients were already allergic to an ingredient of a new toothpaste they started using, resulting in allergic reactions within 2 to 14 days.^{30,48,52,63}

The Skin

The most common symptoms of contact allergic reactions to toothpastes seem to be dermatitis of the lips (cheilitis)^{8,10,20,26,29,30,33,35,37,39,41,43,45–47,49,51,52,54,55,57,60,62} and dermatitis around the mouth,^{8,10,30,33,35,43,44,54,60} which often accompanies allergic contact cheilitis. Cheilitis usually presents as dry lips, mild erythema and (some) swelling,^{9,30,47,67} cracks, mild fissuring, and/or angular cheilitis (perlèche).^{10,33,45,57,60,62} Acute allergic contact cheilitis with vesiculation is uncommon.^{39,59,61} Some patients may develop dermatitis of the hand holding the toothbrush from toothpaste running down the brush, thereby contaminating the skin.^{20,59,64,75}

Single reports describe patients with cutaneous symptoms of toothpaste allergy apparently caused by systemic absorption,^{36,48,63} sometimes without local signs of cheilitis or stomatitis.^{48,63} Urticaria may have been caused by contact allergy to tin in a stannous fluoride-containing toothpaste.³⁶ Pruritic infiltrated and excoriated plaques at the anterior thighs at the site of previous triple vaccine injection containing aluminium hydroxide developed in 3 children sensitized to aluminium, when using a toothpaste having 30% to 40% aluminium oxide as component.⁴⁸ One patient who was presensitized to cinnamon developed dermatitis of the face and chest and noticed worsening of hand dermatitis from using a toothpaste containing cinnamon.⁶³ Some patients, who use their index finger instead of a toothbrush for scrubbing toothpaste over their teeth, may develop allergic contact dermatitis of this finger combined with cheilitis from contact allergy to toothpaste.³⁸

Oral Mucosa

Symptoms of the oral mucosa from contact allergy to toothpastes are seen less frequently and are most often described as stomatitis,^{26,30,46,50,55,60} glossitis/swelling of the tongue,^{10,26,30,33,60,62} and gingivitis.^{26,33,52,58} Reported clinical features include erythema,^{8,44} swelling, desquamation,^{8,44} peeling, epithelial sloughing, ulceration,^{30,33} and temporary loss of taste.^{44,55,62} Vesiculation of the oral mucosa is rarely seen,^{39,59} because vesicles quickly rupture to form erosions.⁸⁴ The subjective symptoms are often more prominent than the physical signs. Patients may complain of numbness, a burning sensation, and soreness of the mouth. Rarely, burning mouth syndrome⁴⁶ and recurrent aphthous ulcers^{46,87} have been ascribed to toothpaste allergy.

When considering the manifestations of toothpaste contact allergy, it should be appreciated that toothpastes have been tested especially in patients with cheilitis, which may contribute to the fact that cheilitis and perioral eczema are the most observed clinical features of toothpaste allergy. Far less often, patients with oral symptoms without cheilitis have been investigated, which may lead to underestimation of oral complaints as symptoms of toothpaste allergy. Nevertheless, if both the oral mucosa and the

lips are exposed to an allergen, cheilitis will often be the sole manifestation,¹⁶ because the mucous membranes may be less susceptible than the skin to both sensitization and elicitation of allergic reactions (see the previous data).

The Allergens in Toothpastes

In publications on contact allergy to toothpastes, it is often stated that the flavors are the most important causes of contact allergic reactions. For this statement, a 1978 Danish study is often given as reference.²⁸ However, in that investigation, patients suspected of toothpaste allergy (on the basis of the presence of sore mouth, stomatitis, and/or dermatitis around the mouth and patients being dentist personnel) were tested with flavors *only*, so any non-flavor-relevant allergen could not have been identified. In addition, the toothpastes themselves were not tested, it was not ascertained that the allergens found (peppermint oil, spearmint oil, carvone, anethole) were present in the toothpastes used by the patients reacting to these flavors, and it was not mentioned whether the symptoms improved or cleared after avoidance of the incriminated (if incriminated at all) toothpastes.²⁸

Another investigation frequently cited (eg, the studies by Zirwas and Otto⁸ and Van Baelen et al²⁰) as a proof that flavors are the most frequent allergens in toothpastes is a multicenter prospective study in Italy, in which 54 patients presenting with eczematous lesions on the lips, occasionally also affecting other areas of the face (cheeks, chin), in which the use of toothpastes was suspected to be the cause, were investigated.¹⁹ In these patients, patients were tested with a toothpaste cheilitis series, which not only contained 9 fragrances and 6 essential oils (the flavors) but also contained 8 preservatives, 2 fluoride compounds, and 6 miscellaneous chemicals. In 15 patients, a final diagnosis of allergic contact cheilitis from toothpastes was made. In 12 of these patients, there were 16 reactions to components of the toothpaste cheilitis series, of which 11 (63%) were to flavors.¹⁹ However, in no single case was the positively reacting substance in the toothpaste cheilitis series (the probable allergen) actually identified in the toothpaste. This makes the authors' statement "The overall majority of sensitizations proved to be due to the flavoring substances" too explicit.

Table 5 summarizes the allergens identified or incriminated in toothpastes in case reports and small case series (as presented in Table 3). On the basis of available data (patch tests with toothpaste, test concentration, controls testing, healing of lesions after avoidance, stop-restart test, other positive patch tests, ingredient patch testing, knowledge of ingredients in toothpastes), the cases have been scored as "proven/very likely," "likely," "presence of incriminated allergen in toothpaste not ascertained," or "insufficient data." Lacking decisive criteria, this scoring inevitably bears subjective elements and others may well reach different scores.

In Table 6, allergens mentioned in studies in groups of patients and case series are evaluated.

Thus, what are the allergens in toothpastes? In early studies, most reactions have been caused by cinnamal—cinnamon

TABLE 6. Allergens Mentioned in Studies in Groups of Patients and Case Series

Chemical	Nr. Pat.	Year and Country	Comments	Reference
Cinnamal	12	1972, United Kingdom and Sweden	All from the same toothpaste, which was later reformulated; 4 more case reports from this study are shown in Table 3; Close-Up toothpaste	Magnusson et al ³⁰ and Kirton and Wilkinson ³¹
Cinnamal	12	1973, United Kingdom	Three case reports are shown in Table 3; the authors stated in an addendum to have seen 12 more similar patients reacting to cinnamal in Close-Up toothpaste	Kirton and Wilkinson ³² Franks ⁴⁴
Cinnamal	? (1–10)	<1990, United Kingdom and United States	Unreliable report	Lamey et al ²⁷
Flavors	4	<1991, Australia	Not specified, but termed mint and cinnamon	Freeman and Stephens ²¹
Flavor	2	1970–1971, United States	Not specified, but one caused a contact urticarial reaction, which suggests cinnamal to be present	Perry et al ²⁶
Hexylresorcinol	3	1931, United States	Two other patients did react to the toothpaste but not to its ingredient hexylresorcinol	Templeton and Lunsford ³⁵
Menthol	2	1985–1992, United Kingdom	No patch tests with toothpaste; both also used a mouthwash containing menthol	Morton et al ²⁵
Peppermint	1	1991–1997, Australia	No details	Freeman and Stephens ²¹
Triclosan	2	1991–1997, Australia	No details	Freeman and Stephens ²¹

oil—cassia oil.^{30–34,61,63,64} No such reports have appeared in the literature in the last 25 years. Small “outbreaks” of reactions to dichlorophene^{60,62} and hexylresorcinol³⁵ were one time only. Phenyl salicylate (salol) was apparently an important sensitizer in toothpastes in the 1930s in France⁸² (data cited in the studies by Sainio and Kanerva² and Marchand et al⁸¹), but there have been no case reports since then. In 1985, a toothpaste containing 1.3% formaldehyde solution caused many adverse reactions,^{52,56} but no new cases have emerged in the literature later. In the last 25 years, allergens in toothpaste scored as proven/likely or likely (Table 5) include aluminium (n = 3, presensitization), amine fluoride/olaflur (n = 2), α -amylcinnamal, anethole, carvone/spearmint oil (n = 2), chloroacetamide (n = 1 or 2), cocamidopropyl betaine, flavor, unspecified (n = 2), sodium benzoate, sodium lauryl sulfate (n = 2), tin (in stannous fluoride), and triclosan. This indicates that there is no specific pattern of components of toothpaste that cause contact allergy. Of course, the possibility of publication bias must be kept in mind; cases with new or rare allergens are more likely to be published than chemicals already known as the cause of toothpaste contact allergy.

Allergy to *fluoride* in toothpastes and other products has been claimed by several authors, allegedly causing urticaria, dermatitis, stomatitis, oral ulcers (including aphthous ulcers), and gastrointestinal disturbances.^{87–90} However, we have not found any report of allergic contact dermatitis or stomatitis from fluoride in toothpaste with positive patch tests to fluoride. Indeed, several reviews found no evidence to support claims that fluoride is allergenic.⁹¹

What Is the Best Method for Patch Testing Toothpastes?

There is no consensus on the patch test method to investigate possible toothpaste allergies. Many authors state (or cite) that

patch tests with undiluted toothpastes may induce false-positive, irritant reactions from the presence of abrasives and detergents such as sodium lauryl sulfate.^{4,8,14,28,29,41,53,84,92,93} Few studies have addressed this issue. In 1 investigation, 2 toothpastes were tested as is in 30 control patients and 9 had mild irritant reactions.⁵³ In a study from Singapore, slight erythematous reactions, not considered to be allergic, were observed in 6 patients tested with toothpastes as is.²² Of the 246 dermatitis patients tested with a cinnamon-containing toothpaste that had caused 16 cases of contact allergy, 1 had an allergic patch test reaction, but no mention was made of any irritant reactions.³⁰ Ten control patients tested with a dichlorophene-containing toothpaste as is were negative in an early study⁶²; later, the author stated (and would be cited numerous times) that testing toothpastes undiluted may induce irritant reactions.⁹² Israeli investigators consider toothpastes in undiluted form not to be irritant and to be suitable for patch testing, because they only saw positive patch tests in patients with cheilitis and none in a control population not having cheilitis. However, they did *not* test the control group with the toothpastes that had caused allergic reactions in patients with cheilitis.¹² Conversely, testing with pure toothpastes may also result in false-negative reactions.⁶⁰

Diluting the toothpaste will reduce its irritant potential but also increases the risk of false-negative reactions. Only a few investigators have observed positive reactions with dilutions of 5% pet,⁵⁹ 3% pet,³⁷ 1% and 2% aq,⁴³ 1% aq,¹ or 2% aq.⁴⁴ In the latter study, however, another patient had a false-negative patch test to this dilution.

On the basis of the available data, it is not possible to give firm advice on which patch test concentration is suitable for most toothpastes. To avoid false-negative reactions, a semiopen test or closed patch test with the toothpaste undiluted can be performed

as starting point. However, a positive patch test *alone* cannot be taken as proof of contact allergy. Additional confirmatory investigations should include retesting and/or testing a dilution series (eg, pure, 50% pet or water and 20% pet or water) and/or control testing. To confirm clinical relevance, a stop-restart test is useful. Patient counseling can only be optimal when ingredient testing is performed to identify the offending chemical(s). Positive concurrent patch tests in any series, for example, to flavors or essential oils, should not lead to the conclusion that these will (probably) be the causative allergens, without confirming their presence in the toothpaste from ingredient labelling, from information obtained from the manufacturer, or from analytical investigations.

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