

# Multicentre study of allergic contact cheilitis from toothpastes

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The present work reports the results of a multicentre study of toothpaste allergic contact cheilitis (TACC) conducted by GIRDCA (Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali). The study examined 54 patients with eczematous lesions on the lips, the possible cause of which was suspected to be the use of toothpastes. Patch tests were conducted with a standard series, a specially-targeted series (toothpaste cheilitis series, TCS), and with suspected toothpaste(s). A stop-restart test (SRT) was carried out with these, together with a use test to identify possible alternative products. The TCS produced 17 positive reactions in 13 patients, the most frequent being to spearmint oil. Of the 54 patients, 5 displayed positive reactions only to the TCS. The patch tests with toothpaste produced positive reactions in 11/32 patients, the SRT a positive response in 10/12 cases. The diagnosis of TACC was confirmed in 15/54 patients. Alternative products were identified for 5 patients. In conclusion, the allergens most frequently responsible for TACC were the flavourings, and the additional series proved to be useful in many cases (together with patch tests with toothpastes and the SRT) for correct diagnosis and to initiate effective prevention.

**Key words:** allergic contact cheilitis; contact allergens; toothpaste; flavourings; spearmint oil; patch testing; non-standard allergens; additional series; prevention. © Munksgaard, 2000.

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The term cheilitis is understood as referring to an inflammatory process that affects the lips, either the cutaneous section or the contiguous semi-mucosal area called the vermillion (the lips in the common use of the term), and the mucosal section of the internal lip (1, 2). The inflammatory processes that can affect this structure (either overall or the individual components just described) may be due to many different causes, among which there are also contacts of an irritant or allergic nature (3, 4). Irritant contact cheilitis can be caused by numerous agents capable of acting upon the lips. Recently, numerous cases have been attributed to tar-tar-control toothpastes containing large quantities of pyrophosphates (5). Allergic contact cheilitis can be caused by nail varnishes, foods, metallic objects, materials used in dentistry, lipsticks, lip balms, etc. (2). Among the products for oral hy-

giene, in addition to mouthwashes, toothpastes can also be responsible for allergic contact cheilitis. In reality, reports of this kind of pathology are not numerous, and in the majority of cases, they are limited to single cases or to case groups of only a few units (2, 6–10). The main categories of substances used in the formulation of a toothpaste are abrasives, detergents, binding agents, humectants, preservatives, colouring agents, antiseptics and antacids, fluoride salts, flavourings, with various kinds of action: only in some cases has sensitization activity been demonstrated (11). In the majority of cases described, the responsibility for toothpaste allergic contact cheilitis has lain with the flavouring substances, while other components of the toothpastes have more rarely been found to be the cause (11–14). However, patients have rarely been investigated through the con-

ducting of patch tests with an appropriate series of allergens (2).

In this multicentre study, the Italian Environmental and Contact Dermatitis Group (Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali – GIRDCA) investigated, in a case group drawn from a number of different Italian cities, some of the clinical and allergological characteristics (substances responsible, commercial products involved, possible alternative products) of toothpaste allergic contact cheilitis (TACC).

### Patients and Methods

The study was carried out from June 1997 to June 1998 by 4 GIRDCA research units (Bergamo, Florence, Milan, Rome) and involved the examination of 54 patients (33 female, 21 male, with an average age of 37, and an age range from 15 to 74 years) who presented eczematous lesions on the lips (located on the semimucosa or the cutaneous portion of the lips, or both), occasionally also affecting other areas of the face (cheeks, chin), in relation to which one might suspect (on the basis of clinical and anamnestic data) the use of toothpastes to be the cause. A record was also kept, where relevant, of eczematous lesions on other parts of the body.

All the patients underwent patch tests with the standard series of allergens adopted by GIRDCA (GSS) in 1997 (subsequently integrated with other allergens), and with a specially-targeted series (toothpaste cheilitis series, TCS) that was created specially for the purpose (see below). The research project also involved carrying out (where possible, depending on the compliance of the patients) patch tests with the anamnesticly suspected toothpaste/s (which were tested as is); stop-restart tests (SRT) with these toothpastes; and a use test with other possible alternative products. A record was also kept of the duration of the lesions, their location, and any instances of a history of personal and family atopy.

The allergens used for the patch tests were supplied by: Chemotechnique Diagnostics (Malmö, Sweden), Trolab Hermal (Reinbek, Germany), and FIRMA S.p.A. (Florence, Italy). The latter undertook to specially prepare for the research project a number of allergens that were otherwise not commercially available. The toothpastes supplied by the patients were tested as is. The patch tests were carried out with Van der Bend Square Chamber (Van der Bend, Brielle, Holland) or Finn Chamber on Scanpor tape (Epitest Ltd Oy, Tuusula, Finland). The patch test strips were applied to the subject's back using Scanpor tape (Alphafarma, Norgesplaster Facility, Norway) and left in place for 2

days. The 1st reading took place 30 to 60 min after the patch test strips were removed, and further readings were made at day (D) 3 or 4, and finally at D 7. The scoring methods were those recommended by the International Contact Dermatitis Research Group.

The patients who showed positive reactions to the GSS allergens (those which could be judged to be significant for the current lesions) and/or the TCS, and/or the toothpastes used, were invited to discontinue use of the suspected toothpaste and to start using it again several weeks later: any variation in the clinical pattern was recorded. Patients for whom the diagnosis of allergic contact cheilitis was confirmed, were, where it was possible to identify the toothpaste responsible, advised to use an alternative product on the basis of the results of the tests that had been carried out. The use test with the alternative toothpaste was conducted under the clinical control of the researchers.

### Results

The patch tests produced in 19 patients a total of 27 positive reactions to the allergens of the integrated GSS (Table 1). The allergen with the largest number of positive reactions was nickel sulfate, followed by fragrance mix, thimerosal, and potassium dichromate. As regards the TCS allergens, 13 subjects produced a total of 17 patch tests positive to 10 different substances (Table 2). Of these, 1st place was occupied by spearmint oil, followed by propolis. The majority of instances of sensitization could be attributed to flavouring substances. The subdivision of the case group on the basis of the results of the patch tests (positive or negative), in relation to the integrated GSS and the TCS shown in Table 3, makes it possible to underline, among other possible associations, that a group of 5 patients (9.3% of the case group) produced reactions exclusively to the TCS.

*Table 1.* Positive reactions observed regarding the integrated GSS in 19 of the 54 patients

|                                       |    |
|---------------------------------------|----|
| nickel sulfate                        | 10 |
| fragrance mix                         | 4  |
| thimerosal                            | 3  |
| potassium dichromate                  | 2  |
| p-tert-butylphenol-formaldehyde resin | 1  |
| lanolin                               | 1  |
| colophonium                           | 1  |
| formaldehyde                          | 1  |
| Amerchol L-101                        | 1  |
| cobalt chloride                       | 1  |
| Euxyl K400                            | 1  |
| tosylamide/formaldehyde resin         | 1  |
|                                       | 27 |

Table 2. Allergens of the toothpaste cheilitis series (TCS) used in the patch tests, and positive reactions observed in 13 patients; where not otherwise indicated, the vehicle is petrolatum

|                            | Concentration | Positive reactions |
|----------------------------|---------------|--------------------|
| aluminium chloride         | 2%            |                    |
| anethole                   | 5%            | 1                  |
| azulene                    | 1%            | 1                  |
| benzalkonium chloride      | 0.1%          |                    |
| benzoic acid               | 5%            |                    |
| carvone                    | 5%            | 1                  |
| chloroacetamide            | 0.2%          |                    |
| cinnamal                   | 2%            |                    |
| dichlorophene              | 1%            |                    |
| eucalyptus oil             | 2%            |                    |
| eugenol                    | 5%            |                    |
| hexylresorcinol            | 0.5%          | 2                  |
| imidazolidinyl urea        | 1% (aq.)      |                    |
| isoeugenol                 | 5%            | 1                  |
| laurus oil                 | 2%            |                    |
| lemon oil                  | 2%            |                    |
| limonene R                 | 2%            |                    |
| limonene S                 | 2%            |                    |
| menthol                    | 1%            | 1                  |
| peppermint oil             | 2%            | 2                  |
| phenyl salicylate          | 1%            |                    |
| propolis                   | 20%           | 3                  |
| quaternium 15              | 1%            |                    |
| rosemary oil               | 5%            |                    |
| sodium benzoate            | 1%            |                    |
| sodium fluoride            | 0.5% (aq.)    |                    |
| sodium lauryl sulfate      | 0.1% (aq.)    |                    |
| sodium monofluorophosphate | 0.5% (aq.)    |                    |
| spearmint oil              | 2%            | 4                  |
| thymol                     | 1%            |                    |
| vanillin                   | 10%           | 1                  |

Table 3. Comparison of the results of the 54 patients grouped on the basis of the positive and negative reactions observed regarding the allergens of the integrated GSS and the TCS

|      | GSS+ | GSS- |
|------|------|------|
| TCS+ | 8    | 5    |
| TCS- | 11   | 30   |

Patch tests with the suspected toothpastes (a total of 45 patch tests were carried out on 32 patients with 1 or more toothpaste) produced 11 positive reactions (Colgate: 4; Actifluor: 2; AZ15: 1; Iodosan: 1; Emoform: 1; Gen Aid: 1; Sanità e Bellezza: 1) in a total of 11 patients and 1 false-positive reaction (soap effect) to Mentadent P. The

stop-restart test with the toothpaste considered to be responsible (on the basis of anamnestic data or the patch test results) for the lesions was conducted on 12 patients and had a positive result in 10 cases. The toothpastes which produced a positive result on the SRT were: Colgate (3 cases), Actifluor (2 cases), Gen Aid, Iodosan, Mentadent P, Emoform, AZ15 (1 case each).

The final diagnoses regarding the whole case group are indicated in Table 4. For some patients (6 in total), in addition to a diagnosis of cheilitis, a diagnosis of allergic contact dermatitis (ACD) was also made, due to the involvement of skin areas, besides that of the lips, the anamnestic data, and the results of allergological tests. At the conclusion of the tests, a diagnosis of TACC could thus be made for 15 patients: Table 5 shows the outcome of the patch tests on these patients with the GSS, the TCS, and the toothpastes, and also that of the SRT.

In 4 patients (nos. 17, 19, 37 and 46), it was not possible to identify (due to non-execution and/or a negative outcome of the patch test with toothpastes, or due to non-execution and/or negative outcome of the SRT with the products) the product thought to be responsible. However, the positive response observed in relation to the TCS and GSS allergens and the temporary abstention from use of any tooth-cleaning product whatsoever, which led to healing of the lesions, suggested a diagnosis of toothpaste allergic cheilitis. In patient no. 13 (who was diagnosed as TACC and nail varnish ACD), sensitization to tosylamide/formaldehyde resin was considered responsible for the eczematous lesions located on other areas of the face (the eyelids) and on other parts of the body (neck). Patient no. 12 is not listed in the table; this patient had positive reactions to fragrance mix, propolis, and Sanità e Bellezza toothpaste, but the negative outcome of the SRT with this toothpaste and the cessation of use of the propolis lip cream used by the patient (which led to the healing of the lesions) suggested a diagnosis of lip cream allergic contact cheilitis.

For 5 of the 6 patients who had positive reactions to the TCS allergens and the toothpastes, and were positive on the SRT (patient nos. 11, 16, 20, 21 and 22), it was possible to identify an alterna-

Table 4. Final diagnosis in the 54 patients

|                                       |    |                                  |
|---------------------------------------|----|----------------------------------|
| toothpaste allergic contact cheilitis | 15 | (associated in 2 cases with ACD) |
| lip cream allergic contact cheilitis  | 1  | (associated in 1 case with ACD)  |
| irritant contact cheilitis            | 28 | (associated in 2 cases with ACD) |
| cheilitis in atopic dermatitis        | 8  | (associated in 1 case with ACD)  |
| actinic cheilitis                     | 1  |                                  |
| exfoliative cheilitis                 | 1  |                                  |

ACD: allergic contact dermatitis.

Table 5. Results of the patch tests, with the GSS, TCS, the toothpastes as is, and the SRT, in the 15 patients with a diagnosis of TACC

| No. | GSS                                       | TCS                      | Toothpaste as is                                       | SRT                     |
|-----|-------------------------------------------|--------------------------|--------------------------------------------------------|-------------------------|
| 8   | lanolin, Amerchol L-101                   | hexylresorcinol          | Colgate pos.                                           | NT                      |
| 11  | fragrance mix                             | anethole, peppermint oil | Colgate pos.                                           | Colgate pos.            |
| 13  | tosylamide/formaldehyde resin             | menthol                  | Avonal neg.<br>Gen Aid pos.                            | Gen Aid pos.            |
| 14  | —                                         | —                        | Iodosan pos.                                           | Iodosan pos.            |
| 15  | nickel sulfate, thimerosal, fragrance mix | peppermint oil, vanillin | Mentadent P FP                                         | Mentadent pos.          |
| 16  | —                                         | spearmint oil            | Actifluor pos.                                         | Actifluor pos.          |
| 17  | fragrance mix, colophonium                | propolis, isoeugenol     | NT                                                     | NT                      |
| 19  | —                                         | hexylresorcinol          | NT                                                     | NT                      |
| 20  | nickel sulfate, potassium dichromate      | carvone, spearmint oil   | Actifluor pos.                                         | Actifluor pos.          |
| 21  | —                                         | spearmint oil            | Actifluor pos.                                         | Actifluor pos.          |
| 22  | Euxyl K400, formaldehyde                  | azulene                  | AZ15 pos.                                              | AZ15 pos.               |
| 27  | —                                         | —                        | Colgate pos.                                           | Colgate pos.            |
| 32  | nickel sulfate                            | —                        | Colgate pos.                                           | Colgate pos.            |
| 37  | —                                         | propolis                 | AZ15 neg.<br>Pasta del Capitano neg.<br>Mentadent neg. | NT                      |
| 46  | —                                         | peppermint oil           | Pasta del Capitano neg.                                | Pasta del Capitano neg. |

Abbreviations: neg.: negative. pos.: positive. FP: false-positive. NT: not tested.

tive product (chosen on the basis of the results of allergological tests and, in some cases, on the basis of information supplied by the toothpaste manufacturers), the use of which was not followed by relapses of the cheilitis. The alternative toothpastes were Firma (patient no. 11), Sensodyne (patient nos. 16 and 21), Zendium (patient no. 20), and Odontovax (patient no. 22); the principal allergological data of these patients (reported sensitization, the toothpastes responsible) are listed in Table 5. In Table 6, the principal clinical-anamnestic data (sex, age, location and duration of the lesions, anamnesis for atopy) regarding the 15 patients with a diagnosis of toothpaste allergic contact cheilitis are compared to those of the 39 patients for whom a different diagnosis was made.

### Discussion

Epidemiological data on TACC are hard to find in the literature. In 1967, Hjorth & Jervoe (15) reported 5 cases out of a total of 46,000 patients over 26 years. Andersen (16) subsequently reported having observed 7 cases over 6 years, while Romaguera & Grimalt (17) noted 7 cases in 2 years. More recently, in Singapore, 9 patients have been found over a 30-month period to be affected by allergic contact cheilitis; of these, toothpaste was considered responsible in 5 of the cases (18). Commercial data indicate an annual per capita consumption of toothpaste in Finland in 1990 of 190 ml (19). In Italy, there has been a progressive increase in recent years, from 130 million units sold in 1996 to 135 units in 1998, equivalent to an an-

nual per capita consumption of over 200 ml (Unilever, personal communication).

Although the sensitizing activity of toothpastes is a debated issue, being considered by some as low-risk products, but by others as "allergy bombs", it is reasonable to suspect that allergic contact cheilitis from these products is underestimated in terms of frequency (11, 20). In fact, Ophaswongse & Maibach (2), in their review of the subject, conclude that "... we suspect that the literature does not adequately document the frequency and etiologic factors involved". Our investigation did not have epidemiological objectives, but the occurrence of 15 cases in 24 months in 4 different dermatological centres is data that, when projected on a national scale, requires consideration.

The data of our study also suggest further considerations. The specific series adopted determined a considerable number of positive reactions which confirmed the diagnostic suspicion in a high number of cases: it proved particularly useful in relation to those patients who did not have positive reactions to the GSS. The overall majority of sensitizations proved to be due to the flavouring substances, substantially confirming the data available in the literature on this subject. Indeed, in the majority of the cases that have been described, the substances most frequently responsible for toothpaste allergic contact cheilitis (and sometimes also stomatitis and perioral dermatitis) are cinnamal (9, 17, 21–25), spearmint (8, 16), peppermint (16, 26), carvone (6, 16, 27) and anethole (7, 16). Of those that we observed, the ones of particular import-

Table 6. Principal clinical-anamnestic data relating to the 15 patients with a diagnosis of toothpaste allergic contact cheilitis (TACC) and to the 39 patients with other diagnoses

|                              | TACC                                      | Other diagnoses                           |
|------------------------------|-------------------------------------------|-------------------------------------------|
|                              | 15                                        | 39                                        |
| Sex                          | 13 F (86.7%)<br>2 M (13.3%)               | 20 F (51.3%)<br>19 M (48.7%)              |
| Age (years)                  | average 40.3 years<br>(range 22–66 years) | average 35.5 years<br>(range 15–74 years) |
| Location of lesions          |                                           |                                           |
| UL+LL                        | 10 (66.6%)                                | 24 (61.5%)                                |
| UL+LL+O                      | 1 (6.7%)                                  | 4 (10.2%)                                 |
| UL+LL+OF                     | 1 (6.7%)                                  | 3 (7.7%)                                  |
| LL                           | 1 (6.7%)                                  | 2 (5.1%)                                  |
| UL+OF                        | 1 (6.7%)                                  | 1 (2.6%)                                  |
| UL                           | —                                         | 4 (10.2%)                                 |
| UL+LL+OF+O                   | —                                         | 1 (2.6%)                                  |
| LL+OF+O                      | 1 (6.7%)                                  | —                                         |
| Duration of lesions          |                                           |                                           |
| >1 week ≤1 month             | 2 (13.3%)                                 | 2 (5.1%)                                  |
| >1 month ≤1 year             | 10 (66.7%)                                | 21 (53.8%)                                |
| >1 year                      | 3 (20.0%)                                 | 16 (41.1%)                                |
| Positive anamnesis for atopy |                                           |                                           |
| Personal                     | 5 (33.3%)                                 | 9 (23.1%)                                 |
| —RC+As                       | 5                                         | —                                         |
| —AD                          | —                                         | 5                                         |
| —AD+RC                       | —                                         | 2                                         |
| —RC                          | —                                         | 2                                         |
| Family                       | 5 (33.3%)                                 | 10 (25.6%)                                |
| Family+personal              | 4                                         | 3                                         |

Abbreviations: UL: upper lip; LL: lower lip; OF: other areas of face; O: other areas of body; AD: atopic dermatitis; RC: rhinoconjunctivitis; As: asthma.

ance were those relating to derivatives extracted from the main varieties of mint (*Spicata*, *Piperita*), such as spearmint, peppermint, menthol, and carvone, widely used in toothpastes to produce a sensation of freshness.

Furthermore, worth pointing out are the positive reactions found in relation to propolis, the use of which in toothpastes (because of the multiple activities it performs, including flavouring, antiseptic action, etc.) has long been noted (28, 29). These sensitizations could be linked to the actual presence of propolis or one of its components in the toothpastes, or to possible cross-reactivity in relation to other flavouring substances used in the formulation. The identification of sensitization to these substances is not always straightforward, in that the composition listed on the label (now obligatory in Italy) simply indicates “aromas” in the majority of cases, without the components being specified.

Of the other sensitizations found, it is also worth mentioning a case regarding azulene, a substance used in toothpastes because of its anti-inflammatory properties, and which is noted as being responsible for allergic contact cheilitis (30, 31). The 2 positive reactions observed regarding hexylresorcinol are of doubtful interpretation in that this hal-

ogenated phenol, studied in the past for its anti-plaque effects and also used in the formulation of toothpastes, does not currently seem to be used in such products (31, 32).

The GSS, unlike the specific series, also proved to be of limited use because the flavouring substances contained in it (fragrance mix, Myroxylon *Pereirae*) are not a good marker of sensitization to essences used in the formulation of toothpastes. This is clearly indicated by the results of the patch tests on patient nos. 13, 16, 20, 21 and 37: they were sensitized to 1 or more flavouring agents but were either negative on the GSS or displayed sensitizations that cannot be correlated with this category of substances.

In the investigation, the toothpastes were tested as is: although some authors advise conducting the patch test with a diluted form of the product in order to avoid false-positive reactions (due to the presence amongst the components of substances with irritant activity, such as detergents and abrasives), this only occurred in 1 instance out of a large number of clearly positive reactions (2). Besides, the latter displayed a high concordance with the SRT, which was confirmation of their specificity. The patch test with the toothpaste can, on the other hand, prove to be false-negative due to too

low a concentration of the sensitizing agent (16). This could also have occurred in some of our cases, such as patient nos. 37 and 46.

Considering the subjects in whom a diagnosis of toothpaste allergic contact cheilitis was made, it should be underlined that in order to arrive at such a diagnosis, it is necessary in our opinion to conduct both patch tests with the TCS and with the toothpastes under suspicion, and also the SRT with these. Doing all this makes it possible to increase the possibility of correct diagnosis. It is also the indispensable premise for the identification of alternative products, which in our investigation was successful in  $\frac{1}{3}$  of the cases. This % of success is not insignificant if one also takes account of the length of time it takes to arrive at a diagnosis of toothpaste allergic contact cheilitis. This was also possible thanks to the collaboration of the toothpaste manufacturers, who sometimes made available to the researchers the exact composition of the aromatic mixes.

Examination of the clinical-anamnestic data relating to the subjects with toothpaste allergic contact cheilitis and those with other diagnoses makes it possible to highlight some differences between the 2 groups. The most significant one appears to be the clear predominance of females in the group of patients with toothpaste allergic contact cheilitis. This could in part be explained by the greater exposure of women to other products containing perfumed essences (cosmetics), or one could hypothesise a more frequent use of toothpastes on the part of females.

A smaller though still distinct difference between the 2 groups regards the duration of the lesions, which is greater in the patients for whom other diagnoses have been made. This could be attributed to the greater acuteness and spread of the lesions of allergic contact cheilitis compared to that of irritant contact cheilitis, with a consequently more rapid recourse to medical consultation, while in the group of the other diagnoses, there are numerous cases of cheilitis in subjects with atopic dermatitis, the course of which is notoriously protracted over time. The anamnesis for both personal and family atopy reveals a predominance in the toothpaste allergic contact cheilitis group, even though the difference between the 2 groups is limited. The data concerning the age of the subjects and the location of lesions basically overlap.

Aside from the comparison of the 2 groups, what finally needs to be highlighted is that in almost all cases, both lips are affected, sometimes associated with lesions in other areas of the face, in patients sensitized to these oral hygiene products.

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