Introduction

Gallic acid esters, or gallates, as they are also known, are antioxidants that have been used industrially in cosmetics, topical drugs, and food since 1947. Their function is to prevent the oxidation of the unsaturated fatty acids in these...
products to ensure that they do not acquire an unpleasant smell or appearance. The main gallates used for this purposes are propyl gallate, octyl gallate, and dodecyl gallate, which differ from each other in terms of the length of their side chain. Gallates are potential allergens and although they are used extensively in cosmetic products and foodstuffs, relatively few cases of contact dermatitis due to gallates have been reported to date.

The aim of the present study was to retrospectively review all the cases of sensitization to gallates diagnosed by the Dermatology Department at the Consorcio Hospital General Universitario de Valencia, Spain between January 1985 and December 2006.

Materials and Methods

The study was conducted at the Allergy Unit of the Dermatology Department at Consorcio Hospital General Universitario de Valencia and involved a retrospective review of all the patients diagnosed with sensitization to gallates in the preceding 21 years (January 1985 to December 2006).

The data required for the study was retrieved from the computerized database maintained by the allergy unit. We included all patients with suspected allergic contact dermatitis who tested positive for sensitization to gallates (at least 1 positive patch test reaction to propyl gallate, octyl gallate, or dodecyl gallate). The dermatology department at our hospital works with specific series of patch test allergens; the 3 types of allergens reviewed in the present study—propyl gallate, octyl gallate, and dodecyl gallate—formed part of the preservative and cosmetics series and the specific bakery series. Octyl gallate was applied in petrolatum at a concentration of 0.25% in the preservative and cosmetics series and of 1% in the bakery series; both series were manufactured by Chemotechnique Diagnostics AB (Vellinge, Sweden). Propyl gallate was applied at a concentration of 1% in petrolatum in both series (supplied by J Martí Tor, Barcelona, Spain), and dodecyl gallate was applied at a concentration of 0.25% in petrolatum in both series (preservative and cosmetics series supplied by Chemotechnique Diagnostics AB and bakery series supplied by J Martí Tor).

The following clinical data were recorded for each patient: age and sex, profession, personal or family history of atopy, type and location of skin lesions, type of gallate to which the patient was sensitized, relevance of patch test results, and source of sensitization. With the exception of patients working with bakery products—who were tested using the specific bakery series—all the patients were tested using the standard set of allergens recommended by the Spanish Contact Dermatitis Research Group (abbreviated in Spanish to GEIDC). Other allergens, products, and allergen series were used where considered necessary. The patches were applied to the patient’s back using adhesive Finn-Chamber strips (Epitest Ltd Oy, Tuusula, Finland) and left there for 48 hours. Test results were read at 48 and 96 hours and positive reactions were scored as follows: weak (+), strong (++), and extreme (+++). Results were considered to have present relevance when the clinical presentation was attributable to the use of cosmetics or topical drugs, the ingestion of foodstuffs, or the handling of products that contained gallic acid esters. Relevance was considered unknown when no evidence of contact could be found.

Results

A total of 6441 patients were patch tested between January 1985 and December 2006. Of these, 1173 patients were tested with octyl gallate, propyl gallate, and dodecyl gallate (1104 using the preservative and cosmetics series and 69 using the specific bakery series). Forty-six of these patients tested positive for at least 1 of the 3 gallates. This corresponds to a sensitization rate of 3.92%. The sensitization rates observed with the preservative and cosmetics series and the bakery series were 3.53% and 10.14%, respectively.

Sixty-three percent of patients initially consulted for persistent or recurrent cheilitis (Figure 1). The second most common reason for consultation was dermatitis of the face and neck (30%), followed by dermatitis of the hands (28.26%) (Table 2). In addition to eczema, which represented the most common clinical lesion, there were 2 particularly interesting cases. The first of these involved a 44-year-old man sensitized to propyl gallate and dodecyl gallate who developed angioedema of the lip after eating packaged food containing gallates. The second case involved a 26-year-old woman who had persistent cheilitis caused by sensitization to propyl gallate in the lip product she used. Although the symptoms disappeared on cessation of use, they returned when her partner used the same lip product without telling her (cannibal contact dermatitis).

There were 30 positive patch test results for propyl gallate (65.2% of all cases studied), 27 for octyl gallate (58.69%) (Figure 2), and 6 for dodecyl gallate (13.04%). Sixteen patients (34.78%) tested positive for more than 1 of the 3 allergens. Relevance was considered present in 35 (76%) of the 46 patients and unknown in 10 (21.7%). There was 1 case of active sensitization to propyl gallate. The patient involved was a 34-year-old woman who presented with atopic dermatitis affecting the eyelids. None of the allergens tested produced a positive patch test result at 96 hours. The patient, however, returned 14 days after the patches had been applied with a strong positive reaction to propyl gallate. Propyl gallate at a concentration of 1% in petrolatum was
reapplied and the patient developed a strong positive reaction within 48 hours, confirming active sensitization to the substance.

Source of sensitization was attributed to cosmetics in 29 patients and lip products in particular in 24 patients (52.17% of total). Sensitization occurred at the workplace in 7 patients (15.2%), all of whom had handled bakery products. As mentioned, there was 1 case of active sensitization to propyl gallate. Table 3 shows the relationship between sources of sensitization and the most common causative allergens.

**Discussion**

We detected an overall rate of sensitization to gallates of 3.92% in our series (the specific sensitization rates for the 3 gallates are shown in Table 4). The rates we observed are higher than those reported by other studies. One study, for example, found a rate of 0.3% for propyl gallate, 0.6% for dodecyl gallate, and 1.1% for octyl gallate.1

Gallates are used industrially to preserve edible fats and oils, and are normally mixed with other synthetic antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene.4 Their use as additives is permitted in a wide range of food products in Spain.5 The maximum usage level of gallates in combination is 200 mg/kg, expressed in terms of fat content, although there are several exceptions (European Parliament and Council Directive 95/2/EC of 20 February 1994 on food additives other than colours and sweeteners).6 The maximum permitted levels in cosmetic and pharmaceutical products range from 0.001% to 0.1%.7
Although gallates are widely used in food and cosmetic products, relatively few cases of contact dermatitis due to gallates have been published. One possible explanation for this discrepancy could be the development of oral tolerance due to repeated exposure to gallates in many everyday products (chewing gum, food, etc.). This hypothesis was tested in an experiment by Khan et al; they induced tolerance to propyl gallate in guinea pigs through feeding and then immunized them intradermally against both propyl gallate and dinitrochlorobenzene. The guinea pigs were subsequently patch tested with the 2 substances and the results were negative for propyl gallate and positive for dinitrochlorobenzene.

Chemically, gallates are alkyl esters of trihydroxibenzoic acid and differ from each other in terms of the length of their side chain (Figures 3, 4, and 5). This structural feature has been associated with the sensitizing capacity of gallates.

In 1992, Hausen and Beyer, on sensitizing guinea pigs to 8 different types of gallates intradermally, found that increased side-chain length was correlated with increased sensitizing capacity, and that dodecyl gallate had the greatest sensitizing capacity of the 8 gallates studied. Nonetheless, in a multicentre study that involved the patch testing of different preservatives, antimicrobials, and biocides, Schnuch et al found that, in practice, octyl gallate had the greatest sensitizing capacity, followed by dodecyl gallate and propyl gallate.

Despite the above findings, most cases of contact dermatitis due to gallates reported in the literature correspond to propyl gallate, as it is the most common gallate used industrially. This coincides with our findings as most of the sensitizations we detected were due to propyl gallate (followed by octyl gallate). We believe that we detected so few cases of sensitization to dodecyl gallate (13.04% of all cases) because it is not as widely used for industrial purposes as the other 2 gallates.

Because gallates are chemically related to each other, they can give rise to cross reactions, and it is sometimes difficult to differentiate between cross sensitization and

Table 3. Relationship Between Source of Sensitization and Causative Allergen

<table>
<thead>
<tr>
<th>Source of Sensitization</th>
<th>Main Allergen</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipstick</td>
<td>Propyl gallate</td>
<td>Present in all cases</td>
</tr>
<tr>
<td>Bakery products</td>
<td>Octyl gallate</td>
<td>Present in all cases</td>
</tr>
<tr>
<td>Medication</td>
<td>Octyl gallate (3)</td>
<td>Unknown in all cases</td>
</tr>
<tr>
<td></td>
<td>Dodecyl gallate (1)</td>
<td>Unknown in all cases</td>
</tr>
<tr>
<td>Unknown</td>
<td>Octyl gallate</td>
<td>Unknown in all cases</td>
</tr>
<tr>
<td>Active sensitization</td>
<td>Propyl gallate</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Gallate Sensitization Rates in Patients Patch Tested With Gallates Between 1985 and 2006

<table>
<thead>
<tr>
<th>Positive Patch Test Result</th>
<th>Total</th>
<th>Preservative and Cosmetics Series</th>
<th>Bakery Series</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1173</td>
<td>1104</td>
<td>69</td>
</tr>
<tr>
<td>Propyl gallate, No. (%)</td>
<td>30 (2.55)</td>
<td>30 (2.72)</td>
<td>0</td>
</tr>
<tr>
<td>Octyl gallate, No. (%)</td>
<td>27 (2.30)</td>
<td>21 (1.90)</td>
<td>6 (8.69)</td>
</tr>
<tr>
<td>Dodecyl gallate, No. (%)</td>
<td>6 (0.50)</td>
<td>5 (0.45)</td>
<td>1 (1.45)</td>
</tr>
</tbody>
</table>
concomitant sensitization. Hemmer et al. suggested that gallates might also be involved in cross reactions with other compounds such as catechol, protocatechuic acid, and 4-tert-butylcatechol, all of which have 2 hydroxide groups at the ortho position. They ruled out cross reactivity with substances with OH groups at the meta and para positions.

Sensitization to gallates can produce a variety of clinical manifestations depending on the source of exposure. The most common sources of sensitization to gallates are cosmetics, and lip products in particular; this explains why cheilitis is the most common clinical manifestation observed. This is also corroborated by our findings, as 63% of the patients in our series had persistent or recurrent cheilitis. Sensitization to gallates in food may occur at the workplace (in patients producing gingerbread, selling cheese, and handling chicken fat or peanut butter), but there are also reports of sensitization caused by the ingestion of food containing gallates (the clinical manifestations included oral and perioral dermatitis). It is noteworthy that of all the patients in our series with sensitization to propyl gallate, 83.3% had cheilitis. Moreover, 96.6% of these were women, and the source of sensitization was lip products in all of these patients. Also of note is that fact that sensitization in the group of bakery workers was due to octyl gallate and of present relevance in all cases. All of the patients in this group had been exposed at the workplace.

According to a study by De Groot, appropriate concentrations for patch testing with gallates are propyl gallate at 1% (Laboratorios Aristegui, Chemotechnique Diagnostics AB, and J Martí Tor), octyl gallate at 0.25% (Chemotechnique Diagnostics AB), and dodecyl gallate at 0.25% (Chemotechnique Diagnostics AB). The same author also recommended using petrolatum and olive oil as vehicles.

Methods aimed at preventing contact dermatitis due to gallates are limited almost exclusively to avoiding contact with certain cosmetics and foods. To facilitate actions in this area, the European Union introduced a special directive obliging member states to draw up regulations governing the inclusion of the full list of ingredients on the packaging of drugs and cosmetics; in the area of food, European Parliament and Council Directive 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners obliges manufacturers to specify all the food additives used, including antioxidants, on the package, to classify them by category (antioxidant, preservative, color, etc) and to identify them by either their name or their E number. The corresponding E numbers for gallates are E-310 (propyl gallate), E-311 (octyl gallate), and E-312 (dodecyl gallate).

In conclusion, the use of preservative and cosmetics allergen presented with cheilitis; the main causative allergen in these patients was propyl gallate, and the main source of sensitization was lip products (findings that coincide with those reported in the literature). We also recommend testing for sensitization to gallates in patients with probable occupational dermatitis related to bakery products or the handling of edible fats and oils. This recommendation is also supported by evidence from the literature and the findings of the present study given that octyl gallate was the most common allergen detected in the group of bakery workers and was considered relevant in all cases.

Conflicts of Interest
The authors declare no conflicts of interest.

References