Abstract. Introduction. Euxyl K400 is a widely used preservative in cosmetics, topical drugs, cutting fluids, etc. This antimicrobial product has two active components—methyldibromo glutaronitrile (MDGN), also known as 1,2-dibromo-2,4-dicyanobutane, and 2-phenoxyethanol, in a proportion of 1 to 4. The aim of this study was to assess the prevalence of sensitization to this preservative in cases in our dermatology department over a 5-year period. We also assessed the prevalence of sensitization to the two active components of Euxyl K400 and calculated the agreement with sensitization to Euxyl K400.

Material and methods. In this retrospective study, we analyzed the medical records of 1,092 patients attended in our skin allergy unit between January 2000 and December 2005. We undertook testing with a standard battery that included, in addition to the allergens recommended by the Spanish Group for Research Into Dermatitis and Skin Allergies (GEIDAC), 0.3 % MDGN and 1 % 2-phenoxyethanol in Vaseline (Trolab®). Results. Only 15 patients developed a positive reaction to Euxyl K400. Of these, 11 were positive to MDGN and 2 to phenoxyethanol. Sensitization to Euxyl K400 was significantly more common in men. The agreement between sensitization to Euxyl K400 and MDGN was good (Kp = 0.68), whereas agreement between Euxyl K400 and phenoxyethanol was poor (Kp = 0.23).

Conclusions. The prevalence of Euxyl K400 sensitization in this study was 1.4 %. Most cases of Euxyl K400 sensitization were associated with the MDGN component, as indicated by the good agreement between the two substances.

Key words: contact allergic dermatitis, Euxyl K400, methyldibromo glutaronitrile, 2-phenoxyethanol.
Introduction

Euxyl K-400 is a widely used preservative in the manufacture of cosmetics, topical drugs, cutting fluids, etc., due to effective biocidal action against bacteria, molds, and yeasts. It was introduced in Europe in 1985 and in North America in 1990 as an alternative to other, more highly sensitizing biocides, such as isothiazolinones (Kathon GC). The sensitizing capacity of Euxyl K-400 was discovered at a late date; hence, it is widely used in the home and at work.

In reality, Euxyl K-400 has 2 active components: 1,2-dibromo-2,4-dicyanobutane, currently known as methyl dibromo glutaronitrile (MDGN), and 2-phenoxyethanol, in a proportion of 1 to 4. Phenoxyethanol is rarely responsible for sensitization, whereas MDGN is the main source of sensitization caused by the preservative.

Material and Methods

We conducted a retrospective study and reviewed the medical histories of 1092 patients studied in our Skin Allergy and Occupational Skin Disease Unit between January 2000 and December 2005.

All patients underwent patch testing with a standard panel that included 0.3% 1,2-dibromo-2,4-dicyanobutane in petroleum jelly and 1% 2-phenoxyethanol in petroleum jelly, both supplied by Trolab, along with all the allergens in the standard GEIDAC panel from the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC, Grupo Español de Investigación en Dermatitis de Contacto y Alergia Cutánea).

The allergens were mounted on Curatest adhesive strips for patch testing (Lohmann-Rauscher) and fixed to the skin by Omnifix (Hartmann) adhesive strips. The strips were applied to normal skin on the upper back in vertical bands, while the patient was sitting down and leaning slightly forward. The patches were removed 48 hours after they had been applied; the exact site of the patches was marked with a permanent marker. When the back was too small or could not be used, patches were applied to the anterior aspect of the forearms or the outer area of the upper arms.

The patches were read at 48 and 96 hours, following the recommendations of the International Contact Dermatitis Research Group (ICDRG). The panel was also read at times later than 96 hours whenever necessary and possible. Specific panels were included if considered appropriate according to the patient’s occupation or hobbies.

Reactions with morphology or clinical relevance suggestive of an irritative reaction were not included. The clinical relevance of positive reactions was established from the medical history and physical examination. We also collected the personal and family history of atopy, based on the diagnostic criteria defined by Hanifin and Rajka.

The statistical analysis was performed with contingency tables, using the Pearson $\chi^2$ test for the categorical variables and the Student $t$ test for the quantitative variables. In our work, the statistical significance level was set at $P<.05$, and the 95% confidence intervals (CI) were calculated. The value of the association was expressed as the odds ratio (OR) with the respective 95% CI, while logistic regression was used as the multivariate analytical method. The following groups were established to perform the analysis according to age: 1–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years.

The agreement between the sensitization to Euxyl K-400 or to its components was calculated by contingency tables, using the weighted $\kappa$ coefficient. The values used to determine agreement based on the $\kappa$ index were 0 to 0.2 (slight, nonsignificant agreement), 0.2 to 0.4 (fair or acceptable agreement), 0.4 to 0.6 (moderate agreement), 0.6 to 0.8 (considerable or good agreement), and 0.8 to 1.0 (perfect agreement).

Results

Of the 1092 patients studied in our unit who had been referred for suspected contact dermatitis, 673 (61.6%) were women and 419 (38.4%) were men. Only 15 patients had a positive reaction to Euxyl K-400: 10 (66.7%) men and 5 (33.3%) women, with a mean age of 41.8 (16.1) years (range, 17–70 years). The prevalence was 1.4%, and higher in men (2.4%) than in women (0.7%). Individual sensitization to Euxyl K-400 was significantly higher in men (OR, 0.30; 95% CI, 0.1–0.9; $P<.035$). The distribution of prevalence of Euxyl K-400 sensitization according to age bracket is shown in the Figure.

The most common site for the lesions presented by patients were the hands (28.6%), and the occupations most commonly affected by sensitization were metal workers (5 patients, 33.3%), followed by health care workers (2 patients, 13.3%). Only 1 (6.7%) patient met the criteria for atopy. Among the patients who had a positive reaction to this contact allergen, 73.3% (11) were clinically relevant.

In the overall sample, 17 patients were positive for MDGN; of these, 11 also had a positive reaction to Euxyl K-400 and 2 to phenoxyethanol (these 2 were also sensitized to Euxyl K-400), as listed in Tables 1 and 2. The agreement between sensitization to Euxyl K-400 and MDGN was high ($\kappa=0.68$), but only fair between Euxyl K-400 and phenoxyethanol ($\kappa=0.23$).
In recent years, the incidence of Euxyl-400 allergy has been gradually rising in Europe and the United States, and the prevalence is estimated at 2% to 4% among patients with suspected allergic contact dermatitis. In our series, this allergen accounted for 1.4% of positive patch tests, the same percentage found in the most recent Spanish study, but much higher than that found in the Occupational Dermatology Department of the Instituto de Salud Carlos III, Madrid, Spain (0.5%). Most positive reactions are clinically relevant and, therefore, the GEIDAC, the most important consulting body in Spain on contact sensitizations, recommended in 2001 that all dermatologists include these substances in the standard panel.

Allergic reactions to Euxyl K-400 are almost always due to sensitization by the MDGN component, and were described for the first time in 1988. This increase in the number of patients sensitized to MDGN is due to the progressive use of this component in personal skin care products (liquid soaps, shampoos, detergents, wet wipes, or creams). It is also used industrially as an additive in paints, glues, metal-working fluids, lubricants, polyvinyl chloride adhesives, wood preservatives, photography developer solutions, and the paper industry, among others. Recently, cases of allergic reactions to ultrasound gels containing MDGN have also been described.

The gradual rise in the number of sensitizations to MDGN recently led the European Commission on MDGN to prohibit the use of this preservative in cosmetic creams and lotions. Nevertheless, it can still be used in products that require rinsing, for instance, shampoos and liquid soaps, but at concentrations not above 1000 ppm. The optimal concentration for patch testing of MDGN is still unclear; some authors believe that concentrations below 0.3% can cause a high number of false negatives. Therefore, the recommended concentration is between 0.3% and 0.5%. This reduces the number of false negatives, but causes a slight increase in irritative reactions.

In our series, sensitization to Euxyl K-400 was significantly more common in men. The occupations most likely to be sensitized were metal workers, because the preservative is used in cutting oils. One of the reasons for the significant differences between sexes is that men are more likely to be exposed to these fluids in the metal-working industry. We should add that metal working is a particularly representative occupation in our patients in view of the importance of the automobile industry in our city. In fact, the highest prevalence was observed between 50 and 59 years of age (1.8%). Hence, the allergen is also implicated in occupational allergic contact dermatitis.

We detected 6 patients who were sensitized to MDGN but did not react to Euxyl K-400; in 3 of them, these positive reactions were relevant from a clinical standpoint.
We believe that this is because MDGN is present at a higher concentration in the isolated patch (0.3%) than in the blend (0.25%); hence, in this case the blend produced false negatives.

In conclusion, Euxyl K-400 is commonly used not only in cosmetics, but also in industry, and allergic reactions are mainly due to sensitization caused by MDGN. This result was corroborated in our study, which found considerable agreement between Euxyl K-400 and MDGN, compared to fair agreement with phenoxyethanol. The results are also consistent with the lower number of allergic contact dermatitis caused by phenoxyethanol described since the substance was first launched.¹⁴

We believe that Euxyl K-400 and, in particular, MDGN as active component, is an important allergen because it is widely used, rather than because it has a capacity for sensitization. Compliance with the recent European legislation will contribute to a considerable decline in sensitization in the future.

Conflicts of Interest
The authors declare no conflicts of interest.

References