

Monitoring levels of preservative sensitivity in Europe

A 10-year overview (1991–2000)

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A 10-year multicentre analysis of the frequency of sensitivity to common preservatives collected in 16 centres in 11 countries has shown stable but persisting high levels of sensitivity to formaldehyde and 5-chloro-2-methyl-4-isothiazolin-3-one + 2-methyl-4-isothiazolin-3-one (MCI/MI). It has also revealed a significant increase in the level of reactivity to methylidibromoglutaronitrile (MDBGN) from 0.7% in 1991 to 3.5% in 2000. The current high level of sensitivity to MDBGN requires an urgent safety re-evaluation and risk assessment update along with consideration of immediate lowering of use concentrations, especially in leave-on products.

Key words: 5-chloro-2-methyl-4-isothiazolin-3-one + 2-methyl-4-isothiazolin-3-one; diazolidinyl urea; formaldehyde; imidazolidinyl urea; methylidibromoglutaronitrile, parabens; patch test sensitization; preservatives; quaternium-15. © Blackwell Munksgaard, 2002.

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Preservatives are an important cause of allergic contact dermatitis in cosmetics (1). The same and similar substances, normally referred to as biocides, are also widely used in household and industrial products. They are often a necessary component in product formulation. Ideally, such substances would not sensitize. In practice, a sensitivity rate of 1% or under in patients attending a patch test clinic is normally regarded as acceptable (2). When sensitivity rates exceed 2% there are concerns, and when the rate exceeds 3% there is usually a problem.

During the 1980s, problems occurred in the UK when quaternium-15 sensitivity rates were high, especially in women in the South of England (3). An 'epidemic' of contact dermatitis occurred in Sweden, Finland, Germany, Italy and Holland, where sensitization rates to MCI/MI were in the 3.4–5.0% range (4–8).

Most monitoring of sensitivity in Europe is reported on a clinic-by-clinic basis, e.g. Goossens et al. (9) and, except for the studies by Jacobs et al. (3) and Schnuch et al. (10), most data normally cover only one or a few years. Few national or international studies of trends in preservative sensitivity have been published (11). Although contact allergy rates alone may not be conclusive for risk assessment, so long as we do not have accurate

*Complete data on preservative sensitivity were not available from every centre for every year.

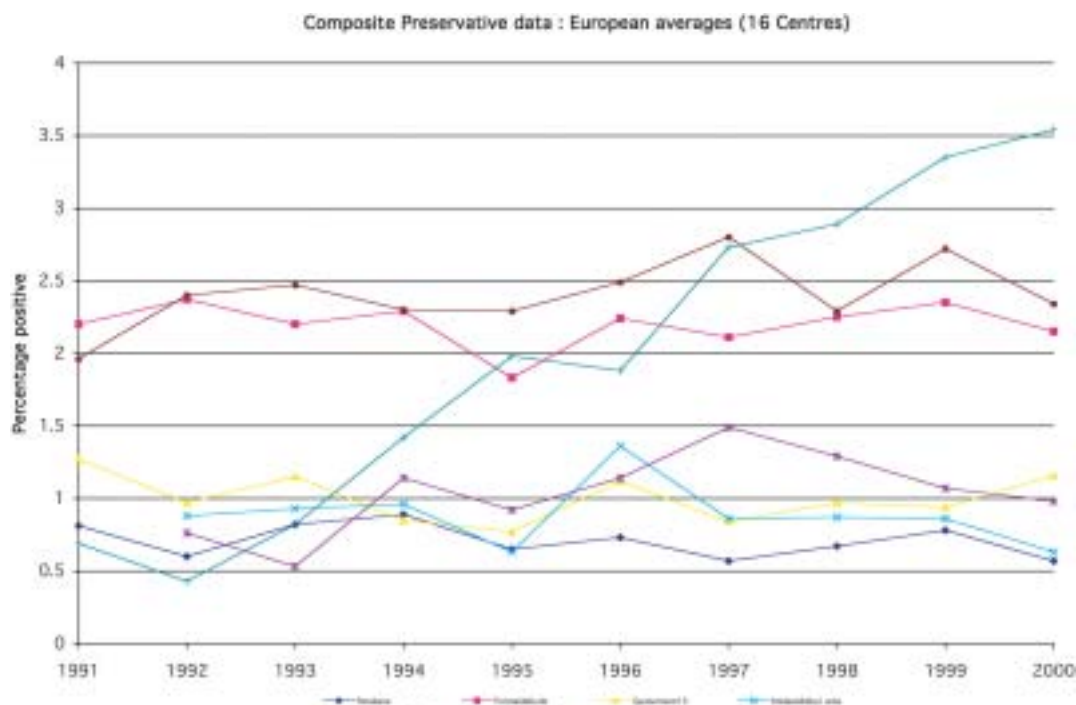


Fig. 1. Percentage of patch test positive reactions to preservatives averaged from data from 16 European centres in a 10-year period.

exposure information on biologically relevant allergens, we have to rely on monitoring the level of sensitivity in various patch test centres (12).

This report covers the period 1991–2000 and concentrates on the 7 most common preservatives that were tested routinely in 16 centres in 11 countries.

Materials and Methods

Patch testing was based on the ICDRG guidelines (13). Readings were normally at day 2 and day 3 or 4, with some centres also re-reading at 6–10 days. Only the results of those preservatives that were tested routinely as part of an extended standard series are reported. These include formaldehyde 1% aq., quaternium-15 1% pet. (Dowicil 200), imidazolidinyl urea 2% pet. (Germal 115), diazolidinyl urea 2% pet. (Germal II), parabens mix 16% pet., 5-chloro-2-methyl-4-isothiazolin-3-one + 2-methyl-4-isothiazolin-3-one 0.01% aq.* (MCI/MI, Kathon CG; Euxyl K 100) and methyldibromoglutaronitrile 0.2% pet.* (MDBGN), the principal allergenic component of Euxyl K 400 (14).

Results

Figure 1 tabulates the 'European average' sensitivity rates for the 7 investigated preservatives. This has been calculated by combining all the positive patch test results for each preservative from all

European centres that submitted data for the year in question. Thus, for example, the data on formaldehyde is based on 1521 positives out of 73,818 and MDBGN on 1064 out of 48,485 patients over the decade.

Trends in sensitivity

Levels of patch test sensitivity to formaldehyde and MCI/MI remained stable, mostly between 2% and 2.5% throughout the decade. The levels of sensitivity to quaternium-15 and imidazolidinyl urea have remained stable at around 1% with sensitivity to diazolidinyl urea being in the 0.5–1.5% range. Parabens remain the preservatives with the lowest level of sensitivity, being in the 0.5–1% range.

The most dramatic change has been in the incidence of positive patch test reactions to methyldibromoglutaronitrile. This increased from a European average level of 0.7% positive patch tests in 1991 to 3.5% in 2000.

Variation between centres

There was some variation in concentration and/or substances used for patch testing at various centres, e.g. MCI/MI was tested at 0.02% in Sweden and Amersham and MDBGN was tested at concentrations of 0.1–0.3%, or by testing Euxyl K 400, at 0.5–1% pet.

Variations in the pattern of sensitization to the various preservatives occur among the various participating centres in Europe.

Discussion

Concerns about MCI/MI sensitivity in the 1980s led the Cosmetics, Toiletries and Fragrance Association (CTFA) (15) to recommend a use concentration of MCI/MI of no more than 7.5 p.p.m. in leave-on products and 15 p.p.m. for rinse-off products. The EU continues to allow MCI/MI at a concentration of 15 p.p.m. for both leave-on and rinse-off products (16). A recent risk assessment of MCI/MI (17) suggested that the risk of primary sensitization from rinse-off products containing up to 15 p.p.m. was negligible. In spite of this, the frequency of MCI/MI sensitization remains relatively high.

Formaldehyde sensitivity levels also remain high, partly because of continued high levels of use of formaldehyde in detergents and other products, partly perhaps because of the effects of other formaldehyde-releasing biocides. Some preservatives such as formaldehyde and MCI/MI are also widely used as biocides in industry.

Sensitization rates of contact allergens are dependent not only on the inherent sensitizing capacity of the chemical, but also on the dose and type of exposure (17), the amount of allergen per unit area surface of skin (18), the vehicle (19) and the condition of the skin (20). An approach to allergic contact sensitization risk assessment has been published (21).

The rapidly increasing level of sensitivity to MDBGN in Europe is a cause for concern. MDBGN is now widely used for both leave-on and rinse-off products and in some countries, such as the Netherlands, the use of Euxyl K400 increased significantly during the early 1990s (14).

The majority of positive patch test reactions to MDBGN were considered to be relevant. There is still some controversy over the most appropriate concentration at which to test MDBGN (10, 14, 22, 23). It is possible that testing at concentrations lower than 0.2% pet. or with Euxyl K400 0.5% pet. will miss some cases of sensitivity, whilst testing MDBGN at 0.3% or above may cause erythema (?+) reactions, which may reflect either irritancy or low level sensitivity. The data that we present represent a crude estimation of the level of preservative sensitivity in patch test centres in Europe. We have very little knowledge about actual exposure levels for any preservative/biocide and little information about the true level of clinical sensitivity in the population. Further studies are needed. Recent experimental work on the sensitizing capacity of

MDBGN suggests that the guinea pig maximization test may have failed to detect the true sensitizing capacity of MDBGN (24). This, together with the very high levels of sensitivity that are now being seen in Europe, requires an urgent re-evaluation of the current use concentrations combined with a new risk assessment.

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