

Frequency of allergic contact dermatitis to isoeugenol is increasing: a review of 3636 patients tested from 2001 to 2005

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Summary

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Key words

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Conflicts of interest

None declared.

Background Isoeugenol is an important fragrance allergen. The cosmetic industry was recommended voluntarily to reduce concentrations of isoeugenol in finished cosmetic products from 0.2% to 0.02% in 1998. It was suspected that this would reduce the incidence of patch test positivity in individuals undergoing routine patch testing after approximately 2–3 years (the Dillarstone effect).

Objectives To review our patch test data since the change in practice by industry, to see if there has been an observable decrease in isoeugenol contact sensitivity.

Methods We retrospectively analysed all subjects patch tested to isoeugenol 1% pet. in the St John's Department of Cutaneous Allergy over a period of 5 years, commencing 3 years after the changes.

Results We identified 3636 subjects, 97 of whom were positive for isoeugenol. Year-on-year incidence shows an increasing trend, with an overall incidence of 2.67%. Using the exact Cochran–Armitage test, this ascending trend is statistically significant ($P = 0.0182$). Seventy-two of 97 isoeugenol-positive subjects were also positive to fragrance mix I. Other fragrances positive in these 97 patients included *Myroxylon pereirae* (30%), *Evernia prunastri* (22%) and eugenol (15%).

Conclusions We suspect that the increasing trend may be due to allergen substitution with compounds chemically related to isoeugenol, or which hydrolyse to isoeugenol itself.

Isoeugenol is an important fragrance allergen.¹ It is a constituent of the Hermal (Reinbek, Germany) fragrance mix I and the Chemotechnique (Malmö, Sweden) perfume and fragrance mix. The incidence of isoeugenol allergic contact dermatitis reported from our group up to 1996 was increasing.² The International Fragrance Association recommended to its members the reduction of concentrations of isoeugenol from 0.2% to 0.02% in finished cosmetic products³ in May 1998, as a response to high levels of allergic contact dermatitis. It was assumed that the frequency of patch test positivity would decrease over a few years (an effect described by Dillarstone⁴ in relation to cosmetic preservatives). European Union legislation⁵ concerning isoeugenol is now in the seventh amendment to the Cosmetic Directive, where labelling is required if isoeugenol is present at ≥ 10 p.p.m. in leave-on products or ≥ 100 p.p.m. in rinse-off cosmetic products. We have reviewed our patch test data since the change in practice by industry, to see if there has been an observable decrease in isoeugenol contact sensitivity.

Patients and methods

All patients patch tested with isoeugenol were identified retrospectively for the time period January 2001–December 2005 inclusive. All case notes for this period were examined by J.M.L.W. Isoeugenol was tested at 1% pet. (Trolab[®]; Hermal). For those with +, ++ or +++ reactions (according to International Contact Dermatitis Research Group criteria⁶), a record was made of age, sex and positivity to fragrance mix, *Myroxylon pereirae* and other fragrances. All other fragrances tested were from Hermal. Statistical analysis was undertaken using SAS software (SAS Institute, Cary, NC, U.S.A.).

Results

We patch tested 3636 patients (2238 women and 1398 men) to isoeugenol 1% pet. over the stated time period. There were 712 (401 women and 311 men) in 2001; 785 (494 women and 291 men) in 2002; 805 (476 women and 329 men) in

2003; 641 (399 women and 242 men) in 2004 and 693 (468 women and 225 men) in 2005. A total of 97 patients had a positive reaction to isoeugenol, of whom 31 were men and 66 were women. The reactions were graded as follows: 61 + reactions; 34 ++ reactions and two +++ reactions. The total incidence of isoeugenol positivity was 2.67% in the tested population [31 positive men out of 1398 tested (2.2%) and 66 women out of 2238 tested (2.9%)].

Breaking down the population according to year, the following incidences of isoeugenol positivity were calculated (with observed frequencies in brackets): 2001, 2.95% (21/712); 2002, 1.91% (15/785); 2003, 2.11% (17/805); 2004, 3.12% (20/641); 2005, 3.46% (24/693). Analysing the year-on-year data using the exact Cochran–Armitage test (which corrects for small samples) reveals a statistically significant ascending trend for the study period ($P = 0.0182$).

Subanalysing the frequencies in the same format according to sex, the following incidences were calculated: 2001 men, 4.2% (13/311); 2001 women, 2.0% (8/401); 2002 men, 1.0% (3/291); 2002 women, 2.4% (12/494); 2003 men, 2.4% (8/329); 2003 women, 1.9% (9/476); 2004 men, 0% (0/242); 2004 women, 5.0% (20/399); 2005 men, 3.1% (7/225); 2005 women, 3.6% (17/468). Given the small numbers involved, these results seem to be broadly consistent year on year.

Total mean age of positives for both sexes was 46.3 years (median 45; range 15–82). Mean ages in years were as follows: 2001, 45.1; 2002, 44.9; 2003, 48.0; 2004, 45.3; 2005, 48.0. The proportion of isoeugenol-positive subjects under 25 years of age did not drop during the study period. Indeed, rates of isoeugenol positivity in the under-25s increased in comparison with those who were older: 2001, 0% (0/21); 2002, 0% (0/15); 2003, 0% (0/17); 2004, 15% (3/20); 2005, 12.5% (3/24).

Other MOAHLFA data (see Table 1) to investigate whether the year groups are comparable and consistent revealed no obvious inconsistencies. The frequency of males fluctuated considerably; however, there was no sustained trend and the analysis above of the entire test population excludes there being systematic bias in this regard.

Before 2001, patients were not routinely tested to isoeugenol, other than as a component of fragrance mix I. Extrapolating data of known fragrance mix-positive reactions with known rates of isoeugenol positivity in the 5 years prior to

2001 (i.e. 1996–2000), a predicted total of 2.5% has been calculated. Other collaborative work from various European centres around this time (1995) showed an incidence of 1.86% positivity to isoeugenol.⁷ While comparing data from different centres is difficult because populations may not be comparable, the reported and extrapolated figures are of the same order of magnitude. Our data, having a mean of 2.7% for the period 2001–2005, show a higher incidence than that previously reported. Although extrapolation of data is far from ideal, our latest figure is considerably higher than rates from other centres in Europe. Also, we have established a significantly increasing trend within our data collection period independent of any previous extrapolated incidence.

Of the 97 isoeugenol-positive patients, 23 were negative for the standard fragrance mix I and there were 72 positives (34 + reactions, 34 ++ reactions and four +++ reactions). Two patients were not tested with fragrance mix. Again regarding the 97 isoeugenol-positive patients, 68 patients were negative for *M. pereirae* and there were 29 positive reactions (30%) (23 + reactions, four ++ reactions and two +++ reactions). Positive reactions to other components of the standard fragrance mix I series (until 20 June 2005) and the fragrance mix II series (from 20 June 2005) included the following: cinnamyl alcohol [seven positives (7%), including one ++ reaction]; cinnamal [four positives (4%), including one ++ reaction]; alpha-amyl cinnamal [one positive (1%)]; *Evernia prunastri* [21 positives (22%), including eight ++ reactions]; eugenol [15 positives (15%), including two ++ reactions]; geraniol [three positives (3%)]; hydroxycitronellal [six positives (6%)]; sorbitan sesquioleate [two ++ positives (2%)] and farnesol [one positive (1%)].

Discussion

Our data show that the incidence of isoeugenol positivity is not decreasing; indeed, it has increased over the study period. Although our study did not set out to investigate why the incidence has changed, nor do our data give any tangible explanation for the increasing incidence, we postulate a number of reasons for this trend. The reduction may yet make an impact; however, this does not seem likely as the recommended changes were made some years ago. The lower concentration of 0.02% isoeugenol in finished cosmetic products may not be sufficiently low to cause a significant reduction in the

Table 1 MOAHLFA data for the study period (incidences are given with observed frequencies in brackets)

	2001	2002	2003	2004	2005
Male	62% (13/21)	20% (3/15)	47% (8/17)	0% (0/20)	29% (7/24)
Occupational	0% (0/21)	0% (0/15)	0% (0/17)	0% (0/20)	0% (0/24)
Atopic eczema	29% (6/21)	20% (3/15)	24% (4/17)	25% (5/20)	29% (7/24)
Hand	24% (5/21)	20% (3/15)	18% (3/17)	15% (3/20)	25% (6/24)
Leg	14% (3/21)	0% (0/15)	18% (3/17)	0% (0/20)	4% (1/24)
Face	14% (3/21)	20% (3/15)	35% (6/17)	20% (4/20)	17% (4/24)
Age > 40 years	57% (12/21)	67% (10/15)	76% (13/17)	70% (14/20)	52% (11/21)

frequency of patch-test positivity. This again seems unlikely, as we have not merely demonstrated an absence of reduction: we have actually shown an ascending trend. Products high in isoeugenol may be being obtained by the consumer, which do not conform to standards. Alternatively, as ageing populations show increased rates of fragrance allergies,⁸ such subjects may have been exposed to isoeugenol before the changes. However, the data show that mean age is not rising in our population; therefore, we cannot attribute the increasing incidence to exposure prior to the changes by an ageing population. In this situation, the number of isoeugenol-positive subjects under 25 years of age would have decreased during the study period, which was not the case.

We suspect that the most likely explanation for the continued, increasing trend of isoeugenol positivity is that isoeugenol has been substituted with related compounds (such as isoeugenyl acetate and isoeugenyl phenylacetate) which either cross-react or are hydrolysed to isoeugenol itself.⁹ This would circumvent the usage recommendations.

It is clear from our data that standard fragrance mix I does not identify all those with allergic contact dermatitis to isoeugenol. The sensitivity in our cohort was 75.8%. The high rate of *M. pereirae* positivity in isoeugenol-positive subjects may be explained by the fact that it contains isoeugenol at approximately 0.85% (in fresh *M. pereirae*).¹⁰ The concentration of isoeugenol within *M. pereirae* (which is tested at 25%) is therefore relatively high.

The isoeugenol positivity rates from 2001 to 2005 between men and women are similar. Previously published work from our group² has shown that fragrance allergy is more common in women than men (by a factor of 1.3 : 1). Figures from our unit² from 1980–96 showed a slight predominance of men testing positive for isoeugenol over women (16.7% males and 15.4% females of those positive to fragrance mix I), although methodology differs from the current study. Our latest results show similar rates for men and women, although the ratio has reversed. This may merely reflect small sample sizes, or perhaps changing marketing strategies. Other fragrance ingredients show different ratios (e.g. increased male positivity with eugenol).²

It has been shown that it is common to have multiple fragrance allergies.¹¹ *Evernia prunastri* is a frequent fragrance allergen and therefore high simultaneous reactivity is both

anticipated and demonstrated in our study. The cross-reactivity to eugenol in isoeugenol-sensitive subjects was modest at 15%. This is despite it being structurally very similar to isoeugenol, differing only in the position of the double bond in the alkyl chain.

In conclusion, the frequency of allergic contact dermatitis to isoeugenol is increasing, despite a reduction in the concentration of isoeugenol in finished products. Allergen substitution would seem to be the most likely cause for the increasing rates of isoeugenol sensitization. There is a need for the trend to be confirmed from other geographical areas. Future legislation on restriction of allergens should address the problem of allergen substitution in order to protect the consumer.

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