

Risk factors associated with sensitization to hydroxyisohexyl 3-cyclohexene carboxaldehyde

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Summary

Background. Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) is a synthetic fragrance chemical and an important contact allergen, at least in Europe. Despite this importance, little is known about risk factors associated with this allergen.

Objective. To examine factors from the history and clinical presentation of patch tested patients associated with HICC sensitization.

Methods. Contact allergy surveillance data of 95 637 patients collected by the Information Network of Departments of Dermatology (IVDK, www.ivkd.org) in 2002–2011 were analysed. Point and interval estimates of the relative risk were derived from multifactorial logistic regression modelling.

Results. The overall prevalence of HICC sensitization was 2.24%. The strongest risk factors were polysensitization and dermatitis of the axillae, followed by dermatitis at other sites. No consistent and significant time trend was observed in this analysis. As compared with the youngest patients, the odds of HICC sensitization increased approximately three-fold in the 52–67-year age group, and strongly declined with further increasing age.

Conclusions. The risk pattern with regard to age and affected anatomical site differed from that observed with other fragrance screening allergens. Cosmetic exposure, as broadly defined here, was a stronger and more prevalent individual risk factor than occupational exposure.

Key words: CAS 31906-04-4; CAS 51414-25-6; contact allergy; hydroxyisohexyl 3-cyclohexene carboxaldehyde; risk factors.

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Fragrances, together with metals, are the most common allergens, with some temporal and geographical variation. One allergen in particular, an entirely synthetic chemical not found in nature, stands out because it has caused numerous cases of sensitization in the last decade in Europe: hydroxyisohexyl 3-cyclohexene carboxaldehyde (INCI name) (HICC) (1, 2). The compound is actually a mixture of two chemicals, namely 4-(4-hydroxy-4-methylpentyl)cyclohex-3-enecarbaldehyde (CAS 31906-04-4) and 3-(4-hydroxy-4-methylpentyl)cyclohex-3-enecarbaldehyde (CAS 51414-25-6). The former CAS number is regarded as the main identifier, assigned to 'HICC' (1). As another acronym and trade name, respectively, HMPCC and Lyrall[®] have previously been used.

Around the turn of the 21st century, HICC surfaced as an important contact allergen (3, 4), and it was soon included in the German baseline series (3), and also, a few years later, in the European baseline series (5). Considerable scientific work went into understanding the dose–elicitation relationship, and generally into exposures capable of causing contact allergic reactions in sensitized persons [reviewed in (1, 2)].

Despite the great importance of this synthetic fragrance chemical as an allergen, detailed analyses of risk factors associated with HICC sensitization have hitherto not been undertaken. The present multifactorial analysis of Information Network of Departments of Dermatology (IVDK) data is aimed at filling this gap and providing quantitative information on the role of individual risk factors.

Methods

The IVDK, a network dedicated to the clinical surveillance of contact allergy, has been described in detail elsewhere (6). All members of the IVDK are members of the German Contact Dermatitis Research Group, and follow international patch test guidelines, which have been refined in some respects (7). For the present analysis, data of all patients patch tested with HICC 5% in petrolatum (material provided by Hermal/Almirall, Reinbek, Germany) between 2002 (the first full year in which HICC was included in the German baseline series) and 2011 were considered. The number of patients was 95 637 tested in the course of 97 085 consultations; in cases of multiple consultations (patch tests), only the first result was used for analysis, to achieve comparability with the previous trend analysis (8) in this regard. If no reading on day 3 after application of the test was performed, the day 4 reading was used, aggregated to a 'positive' outcome (comprising +, ++ and +++ patch test reactions) versus a 'non-positive' outcome (comprising negative, doubtful and irritant reactions).

Statistical analyses were performed with R [version 2.13 (9)], in accordance with published guidelines on the statistical analysis of contact allergy data (10). In particular, multifactorial logistic regression analysis was used to obtain mutually adjusted estimates of individual risk factors in terms of odds ratios (ORs) accompanied by 95% confidence intervals (CIs) obtained with the profile likelihood method. The set of explanatory factors included: (i) age (categorized according to the quartiles of the age distribution); (ii) sex (female or male); (iii) atopic eczema (past or present); (iv) anatomical site (aggregated to six categories: hand/arm, leg/foot, head/neck, axillae, 'other', and, as reference, trunk); (v) occupational

causation ('yes' versus 'no' or 'unknown'); (vi) dermatitis presumably caused by contact with cosmetics or perfumes (versus no eliciting contact); (vii) polysensitization; and (viii) the year of patch testing. Polysensitization was defined as the number of additional reactions to baseline series allergens, categorized as none, 1, 2, 3, and ≥ 4 . It should be noted that additional reactivity to fragrance mix II was not considered as polysensitization, unless there was no simultaneous reaction to HICC. Reactions to pairs of strongly related allergens (thiuram mix and zinc diethyldithiocarbamate, and mercapto mix and mercaptobenzothiazole) were counted as one positive reaction for the calculation of polysensitization, if both respective tests were positive.

Results

Among the 95 637 patients tested with HICC, 2141 positive reactions were observed, yielding a prevalence of 2.24% (95% CI 2.14–2.33). Because, in previous analyses, a strong positive association between age at patch testing and prevalence of contact allergy to fragrances had been found (11, 12), sensitization prevalence was descriptively analysed in 5-year age strata, stratified by sex (Fig. 1).

The results of a multiply adjusted logistic regression analysis of risk factors for HICC sensitization is shown in Table 1. In view of the low prevalence of HICC sensitization, ORs can be interpreted as estimates of the relative risk.

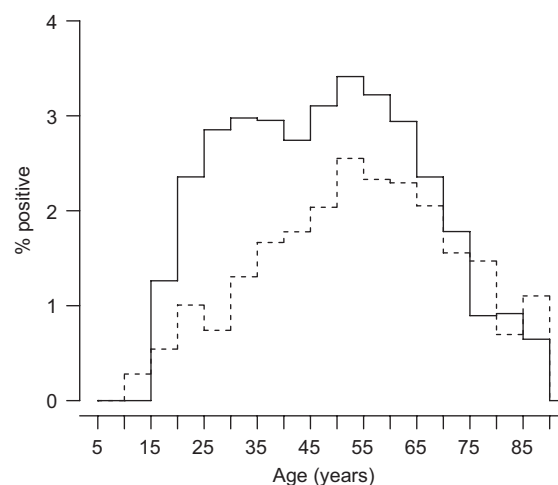


Fig. 1. Prevalence of sensitization to hydroxyisohexyl 3-cyclohexene carboxaldehyde in females (solid line) and males (dashed line) in 5-year age groups (6–10, 11–15, etc., until 91–95; younger and older patients excluded, owing to very low numbers).

Table 1. Results of a logistic regression analysis quantifying the association of sensitization to hydroxyisohexyl 3-cyclohexene carboxaldehyde with a set of individual risk factors (see methods) in 95 637 patients tested in the Information Network of Departments of Dermatology, 2005–2011

Exposure	%	OR	95% CI
Female sex	62.2	1.18	1.07–1.31
Atopic eczema	18.8	1.30	1.17–1.45
Age (years)			
< 38	26.0	1.00	Reference
38–52	26.6	1.38	1.21–1.57
53–65	24.2	1.77	1.55–2.02
> 65	23.2	1.19	1.01–1.39
Site			
Trunk	16.7	1.00	Reference
Axillae	0.6	4.19	3.00–5.75
Leg/foot	15.7	0.55	0.45–0.67
Hand/arm	22.1	1.19	1.02–1.39
Head/neck	29.1	1.23	1.07–1.42
Other	9.0	0.90	0.72–1.11
Occupational cause	15.1	1.24	1.09–1.41
Perfumes/cosmetics	39.9	1.43	1.30–1.58
Polysensitization			
0	57.7	1.00	Reference
1 further positive	22.4	3.05	2.67–3.49
2 further positive	10.4	5.38	4.68–6.19
3 further positive	4.7	7.42	6.30–8.72
≥ 4 further positive	4.7	13.98	12.14–16.11
Year of patch test			
2002	6.9	1.00	Reference
2003	8.9	0.98	0.78–1.23
2004	9.6	1.11	0.90–1.38
2005	8.7	1.04	0.83–1.31
2006	9.4	1.12	0.90–1.40
2007	10.8	1.05	0.84–1.31
2008	11.3	1.11	0.90–1.38
2009	11.5	0.88	0.71–1.10
2010	11.6	0.96	0.78–1.20
2011	11.3	0.93	0.75–1.16

CI, confidence interval; OR, odds ratio. Column '%' indicates exposure (risk factor) prevalence.

Female sex, atopic eczema and age were among the significant risk factors for HICC sensitization. Interestingly, risk decreased considerably in the oldest age group, as compared with the middle age groups. As compared with the reference anatomical site trunk, leg and foot dermatitis was negatively, and hand dermatitis positively, and significantly, associated with HICC sensitization. In this analysis, some non-significant variation in the prevalence of HICC sensitization across the years was noted. The strongest risk factor was 'polysensitization', with a steady increase in HICC sensitization risk with an increasing number of additional positive reactions to other baseline series allergens. Cosmetics or perfumes were documented quite often as

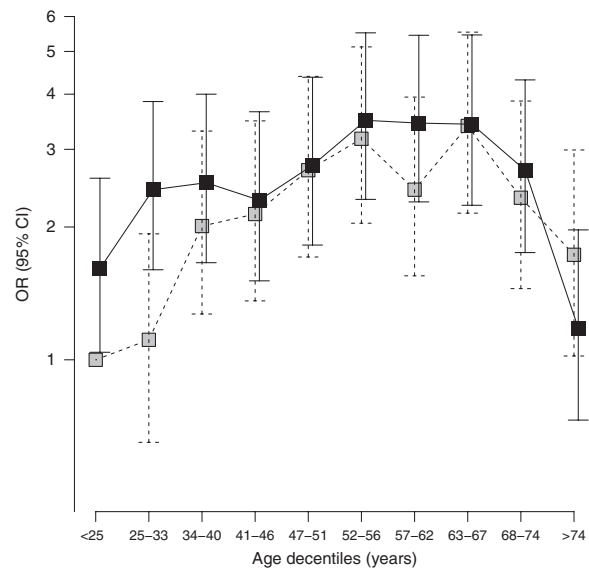


Fig. 2. Risk of hydroxyisohexyl 3-cyclohexene carboxaldehyde sensitization in female patients [odds ratio (OR), black squares; 95% confidence interval (CI), solid line] and male patients (OR, grey squares; 95% CI, dashed line) in age deciles (see text). Reference: males aged 1–24 years (lowest decile). Estimates are adjusted for the factors other than age and sex included in the logistic regression analysis presented in Table 1 (see text).

probable causes of current dermatitis (39.9% of cases), and were associated with a 43% increase in HICC sensitization risk, whereas occupational causation was a less frequent and weaker risk factor.

The peculiar shape of the age distribution of HICC sensitization (Fig. 1) was not represented in detail in the standard age categorization chosen in the above logistic regression analysis (Table 1). Therefore, an additional logistic regression analysis was performed, with age categorization based on the deciles of the overall age distribution (see x-axis in Fig. 2). Moreover, the differences between the sexes evident from Fig. 1 were considered by use of a combined (interaction) variable of age (in deciles) and sex, giving 20 levels, with the youngest males as reference. The remaining variables remained unchanged. The results of this second logistic regression analysis, focusing on age-associated risk in males and females, respectively, are graphically presented in Fig. 2. The shape of age-associated risk found in the unadjusted analysis (Fig. 1) was largely confirmed in this adjusted analysis, which identified a peak risk between 52 and 67 years of age, declining thereafter, reaching about the same magnitude as in the youngest age group. Moreover, females (black squares) had a significantly higher risk at the youngest age, which thereafter converged to that found in males. Estimates of the other risk factors

(sites, atopic eczema, etc.) remained almost unchanged in this analysis; that is, the change in estimate was well below 10%.

Discussion

This unprecedented analysis identified individual risk factors associated with sensitization to HICC. The role of HICC as a fragrance screening allergen and the basic characteristics of patients sensitized to HICC (e.g., MOAHLFA index) have been examined previously (13, 14). This merely descriptive level of data analysis has thus not been addressed here.

It is interesting to note that, in other areas of the world, namely the United States, a much lower prevalence of HICC sensitization [e.g. 0.4% with the same test concentration of 5% HICC (15)] has been found. Different consumer habits or fashions may have an impact on sensitization risk. As one speculation, the preferred use of antiperspirants in the United States and of masking perfumes as deodorants in Europe may, at least partly, explain the observed difference (D.V. Belsito, personal communication 2012). However, significant variation is also found between European countries (16), and is probably indicative of differing levels and modes of exposure. The extent of exposure to HICC has been highlighted by a few studies. Rastogi et al. (17) identified HICC in 18 of 25 perfumes analysed, in concentrations up to 0.21%, Buckley, examining the INCI labelling information on 300 cosmetic and household products, found HICC in 29% of products (18).

A broad range of potential risk factors have been examined by logistic regression modelling in this analysis. Female sex and (past or previous) atopic eczema slightly increased the risk of being sensitized to HICC. With increasing age, a more marked increase in risk was seen; however, this trend was broken in the oldest age category, in which a decrease was observed. This is in striking contrast to two other fragrance screening allergens, fragrance mix I (11) and *Myroxylon pereirae* (balsam of Peru) (12), which show a stronger and, moreover, steady increase in risk with increasing age, according to categorization into four age strata. A finer, albeit bivariate and thus unadjusted, analysis of prevalence of sensitization to fragrance mix I identified a slight decline above age 70 years (19); however, this was of a much lower magnitude than that seen with HICC. The supplemental logistic regression analysis involving age deciles for finer representation of age-associated risk confirmed the peculiar shape. Moreover, female patients also showed an increase in risk occurring earlier in life, not only in the unadjusted, bivariate analysis (Fig. 1),

but also in this adjusted analysis (Fig. 2). The reason for this divergence is not entirely clear; possibly, the lower risk in the oldest group reflects less previous exposure to HICC-containing products.

One important topic addressed by the present analysis is the estimation of risk associated with consumer and occupational exposure. Regarding consumer exposure, consideration of cosmetics, and particularly of perfumes, deodorants (20, 21), after-shaves, and the like, is a natural choice. 'Occupational exposure' was broadly defined by the diagnosis of (probable) occupational causation at the final evaluation of the patient. Evidently, such an occupational context will often refer to occupations and occupational contacts in which fragrances in general, and HICC in particular, may play no role. Hence, the relatively small, although significant, increase in risk associated with occupational causation is not surprising.

Regarding the anatomical sites affected by dermatitis, HICC sensitization was inversely associated with leg/foot dermatitis, whereas a significant (if rather weak) positive association was found with hand dermatitis, which was also observed with fragrance mix I, but not with *M. pereirae*. Accordingly, in patients with allergic contact dermatitis of the hands, a high share of 11.9% contact sensitization to fragrance mix I has been found (22). On the basis of a relatively small number of patients suffering from axillary dermatitis ($n = 578$), the important role of exposure to HICC-containing deodorants as sources of elicitation (20, 21), and presumably also sensitization, has been shown. Whereas, in a previous analysis of the same data, a significant, albeit minute, downward trend was identified (8), no such trend was identified in the present analysis, which was further adjusted. Similarly, no trend was found in Denmark in a sex-stratified analysis (23). The difference from the previous analysis is most likely explained by the minuteness of the effect, which now, with additional adjustment – apparently including some slight confounders – slightly moved towards unity and became non-significant (also when taken into account as a linear effect, $p = 0.13$).

As in previous multifactorial analyses with other allergens that have taken this explanatory factor in account (24), polysensitization (usually defined as ≥ 3 further positive reactions to unrelated allergens of the baseline series; here operationalized as shown in Table 1) is by far the most prominent risk factor. In the case of HICC, there are a number of potential co-reactive allergens, including all fragrance markers from the baseline series, owing to concomitant exposure and independent sensitization, for example via perfumes, deodorants, or perfumed products. Chemical cross-reactivity appears unlikely, in view of the unique chemical structure

of HICC in relation to other baseline series allergens. One exception is, of course, fragrance mix II, of which HICC is a component. However, additional reactions to fragrance mix II were not considered for the calculation of polysensitization in the HICC-positive patients, but only in HICC-negative patients, as positive reactions to fragrance mix II may be attributable to other constituents, such as, most often, citral, farnesol, and hexyl cinnamal (13). The (additional) role of genetic factors favouring polysensitization (25) cannot be further elucidated on the basis of the clinical data analysed.

Conclusion

The pattern of risk factors associated with HICC sensitization differs from the pattern observed with other fragrance screening allergens with regard to age and anatomical site, and this may point to a different pattern of sensitizing (and eliciting) exposures or a cohort effect. Exposures evidently include cosmetics and perfumes; however, occupational dermatitis is also associated with HICC sensitization. This association may be indirect, via the application of emollients or other 'everyday' contactants containing HICC by patients who suffer from occupational contact dermatitis caused by other irritants or allergens.

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