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Is hydroxyisohexyl 3-cyclohexene carboxaldehyde sensitization declining in central Europe?

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In several studies conducted during the last decade, the synthetic fragrance hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC; CAS 31906-04-4) has been shown to be a frequent sensitizer, with a prevalence of >2% among patients tested (1–6). Recent publications, however, have reported prevalences of sensitization of <2%, both in Denmark (7) and in Germany (8). However, in the most recent re-analysis (9) of the original data from the Gentofte Hospital in Denmark (7), the declining trend was not confirmed. The present article focuses on a time trend analysis of HICC contact sensitization based on Information Network of Departments of Dermatology (IVDK) data registered between 2002 and 2011.

Methods

The IVDK as a network dedicated to the clinical surveillance of contact allergy has been described elsewhere (Table 1) (11). For the present analysis, annual prevalences of sensitization to HICC (5% pet.), tested as part of the baseline series (12), from 2002 to 2011 were evaluated. Allergic reactions (+ to +++) versus non-allergic reactions (neg., ?, irritant reaction) were considered as outcomes. Data analysis included (i) a chi-squared test for trend of the proportion of allergic reactions across the years and (ii) a logistic regression analysis to achieve an age-adjusted and sex-adjusted statistical test for trend and estimate of change per year,. The latter included the year of patch testing (modelling a linear trend) as the factor of interest, and age (dichotomized into <40 versus ≥40 years) and sex as adjustment factors. In an alternative, equally adjusted, analysis, the year of patch testing was replaced by an aggregated factor, namely, years 2002–2004 as reference, and 2005–2008 and 2009–2011 as periods of interest. All odds ratio (OR) estimates were supplemented with 95% confidence intervals (CIs) obtained by the profile likelihood method. Analyses were performed with the statistical software R (version 2.13; www.r-project.org).

Results

The number of patients included was 95 452. In cases of multiple consultations by a patient, only test results obtained at the first consultation were considered. Patch test reactions per year, as crude prevalences (%) and prevalences standardized for sex and age (%), accompanied by a 95% CI, are shown in Table 2. According to both unadjusted ($p = 0.025$) and adjusted ($p = 0.013$) anayses, the sensitization prevalence decreased significantly, if very slightly: the effect estimate of the average annual decrease, with 2002 as reference, was an OR of 0.981 (95% CI 0.966–0.996) in the adjusted logistic regression analysis, that is, regarding the OR as a representation of relative risk, an average relative decrease by 1.9% (not percentage points) from year to year. In the alternative analysis, employing three aggregated periods, with 2002–2004 as reference, the subsequent period until 2008 did not show a significant difference (OR 1.02, 95% CI 0.92–1.14), whereas during 2009–2011, the prevalence of HICC contact sensitization was significantly lower (OR 0.87, 95% CI 0.78–0.98) than in the initial period. The time trend of positive reactions to HICC is shown in Fig. 1.

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Conflicts of interest: A.S. is engaged occasionally as *ad hoc* consultant for the cosmetic and fragrance industry (associations), and is partly remunerated for this. The IVDK is sponsored by the cosmetic and fragrance industry (associations). W.U. has received honoraria and travel reimbursement for presentations given to cosmetic industry associations.

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Table 1. Frequencies of sensitization to hydroxyisohexyl 3-cyclohexene carboxaldehyde in different periods of time and in different countries; whereas study populations of the Information Network of Departments of Dermatology (IVDK) were similar, the study population of Gentofte/DK (7) is a subsample of the Danish Contact Dermatitis Group (DCDG) study (10)

Period of patch testing	Country	Study group (n)	Frequency of sensitization (%)	Reference
2005–2008	Denmark (DCDG)[1]	12 302	2.4	Heisterberg et al. (10)
2005–2008	D/CH/A IVDK	40 709	2.4	Uter et al. (6)
2008–2007/2010	Denmark Gentofte	1502*	2.3*	Heisterberg et al. (7), (9)*
2010	D/CH/A IVDK	12 574	1.9	Geier et al. (8)

IVDK, Information Network of Departments of Dermatology; DCDG, Danish Contact Dermatitis Group.
*According to erratum to (7) in 2012 (9).

Table 2. Annual prevalence of sensitization to hydroxyisohexyl 3-cyclohexene carboxaldehyde (5% pet.) tested as part of the baseline series in the Information Network of Departments of Dermatology, 2002–2010, in 84 733 patients

Year of patch test	Number of patients tested	Crude prevalence (%)	Age-standardized and sex-standardized prevalence (%)	95% CI
2002	6583	2.34	2.26	1.88–2.64
2003	8488	2.04	2.08	1.75–2.41
2004	9169	2.37	2.28	1.95–2.60
2005	8337	2.43	2.39	2.04–2.75
2006	8953	2.50	2.46	2.11–2.81
2007	10 303	2.15	2.08	1.78–2.38
2008	10 749	2.16	2.16	1.85–2.46
2009	10 961	1.81	1.75	1.48–2.02
2010	11 097	2.05	1.88	1.61–2.15
2011	10 794	2.12	1.91	1.63–2.18

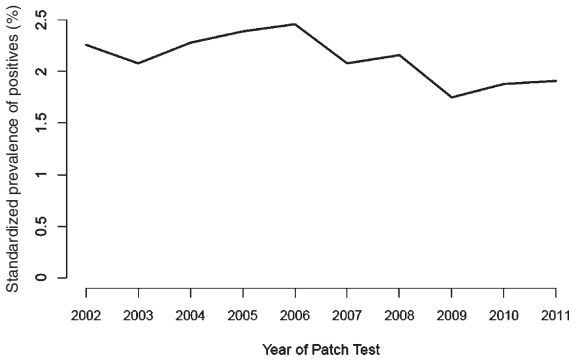


Fig. 1. Time trend of hydroxyisohexyl 3-cyclohexene carboxaldehyde sensitization prevalence [standardized prevalence of positives (%)] during 2002–2011. The decrease over time is statistically significant.

Comment

The sensitization frequencies observed during the last decade have to be considered as a public health issue of concern (13), with probably approximately 4 in 1000 persons being affected in the general population (14, 15). The present time trend analysis indicates a slight decrease in sensitization, particularly during the last few years (Fig. 1). Although the decrease in absolute terms is not overwhelming, it could be regarded as the first evidence of a decline in sensitization prevalence. The decrease observed may be the result of diminished exposure to HICC, because it is being used less often in products or is being used in lower concentrations, the latter having been recommended by International Fragrance Association standards (www.ifraorg.org), which has, since 2009, provided guidance to industry regarding use concentrations that may be regarded as more adequate (16). However, further continuous surveillance is needed to monitor closely the trend of contact sensitization to this synthetic fragrance, and thus the effectiveness of various preventive actions.

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