

Methylchloroisothiazolinone/methylisothiazolinone contact sensitization: diverging trends in subgroups of IVDK patients in a period of 19 years

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Summary

Background. The preservative methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) is an important allergen, and has thus been subject to regulation in some areas of exposure, mainly in cosmetics.

Objectives. To examine whether a decline in sensitization prevalence and intensity of elicitation (by the patch test) can be observed, either overall, or in certain subgroups defined by causative exposures.

Methods. On the basis of long-term contact allergy surveillance data collected by the Information Network of Departments of Dermatology (www.ivkd.org), 1992–2010, in the course of 171 883 consultations, the time trend of (different grades of) positive patch test reactions to MCI/MI (0.01% aqua) was examined in an age-stratified analysis.

Results. The overall frequency of positive patch test reactions was 2.33% (95% confidence interval 2.26–2.4%). No significant overall trend of positive reactions or of the distribution of +, ++ and +++ reactions ($p > 0.05$) was observed, similarly to what was found for patients in whom cosmetics were recorded as causative exposure ($p = 0.55$). In contrast, in patients with occupational contact dermatitis who were < 40 years of age, a significant increase in prevalence, by 0.87 percentage points per decade, was identified ($p = 0.018$).

Conclusions. Both applications of MCI/MI, cosmetic and industrial, should be the target of further preventive efforts.

Key words: CAS 26172-55-4; CAS 2682-20-4; contact allergy; methylchloroisothiazolinone; methylisothiazolinone; time trend.

In the 1980s, an epidemic of contact sensitization to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) was observed (1). Since then, the level of

contact sensitization has been contained to an, albeit still high, prevalence of 2–4% in consecutively tested patients (2). One of the measures aimed at limiting the MCI/MI contact allergy epidemic has been the reduction of the use concentration to 15 ppm in both 'leave-on' and 'rinse-off' cosmetic products, according to the EU Cosmetics Directive (3). Interestingly, the cosmetic ingredient review (CIR) panel of the Cosmetic, Toiletry and Fragrance Association conservatively recommended a concentration limit in 'leave-on' cosmetic products of 7.5 ppm just a few years later (4). In a recent statement, the Scientific Committee on Consumer Safety (SCCS) concluded that 'Induction and elicitation would be

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less likely in a rinse-off product than when the same concentration is present in a leave-on product' (5).

However, cosmetics are not the only applications. Flyvholm (6) gave an overview on the occurrence of preservatives in chemical products registered in the Danish Product Register Database (PROBAS) in January 2005, and the data were compared with similar data from January 2002. In 2002, MCI/MI was present in 1872 products, and in 2005 it was present in 3563 products. In both periods, paints and lacquers (26.6% in 2002 and 60.1% in 2005) were the main applications. Although the occurrence has apparently increased, regulation on labelling of products with use concentrations of > 15 ppm may have limited the incidence of contact allergy to this compound, via this particular route, to some extent (7).

Thus, the question remains of whether exposure to MCI/MI, at least from cosmetics, has been sufficiently low during the last two decades to allow for a reduction in the cosmetics-related epidemic of MCI/MI contact allergy – either in terms of sufficiently low product concentrations, in terms of few(er) cosmetic products containing MCI/MI, or in terms of both. For example, MCI/MI was present in only 73 of 3541 leave-on cosmetics (2.1%), according to a recent survey in Germany (8). As a consequence: (i) the frequency of contact allergy to MCI/MI associated with this exposure should have declined; and (ii) the intensity of sensitization, as measured by the intensity of patch test reactions to 100 ppm MCI/MI in water, should possibly have decreased. Moreover, a comparison of sensitization related to occupational exposure appears to be interesting. To examine these issues, long-term surveillance data of the Information Network of Departments of Dermatologists (IVDK; www.ivdk.org) were analysed.

Methods

The IVDK, as a network dedicated to the clinical surveillance of contact allergy, has been described elsewhere (9, 10). For the present analysis, data of all patients patch-tested with MCI/MI 0.01% aqua between 1992 and 2010 in the course of 171 883 consultations were considered. The number of patients tested in this period varied from 6757 in 1992 to 12 772 in 2010 (Table 1), owing to (i) the increase in the number of members of the network, and (ii) generally fluctuating numbers of patients; MCI/MI in this same concentration was part of the German baseline series throughout the entire study period.

Both the annual prevalence of positive MCI/MI patch test reactions and the temporal distribution of different grades of positive reactions (+ to + + +) were analysed.

The first set of analyses comprised the entire patient sample. Thereafter, two distinct subgroups were analysed: (i) patients in whom cosmetics were documented as culprit exposures, excluding patients with occupational dermatitis; and (ii) patients with occupational contact dermatitis, excluding those in whom cosmetics had been documented as culprit exposures. Furthermore, analyses were stratified by age (dichotomized as <40 versus ≥40 years of age). For the evaluation of temporal changes in sensitization prevalences, weighted least squares regression analysis was used to detect linear trends in prevalence over the observation period. The weights used in the regression models correspond to the number of tests in that year. This approach addresses the methodological problem of the varying size of the yearly test population. From the analysis of the regression models, the magnitude of a linear trend can be assessed by the estimate of the slope parameter for the temporal effect, and statistical significance can be examined by the statistical test whether the slope is different from zero. For data management and analysis, R statistical software, version 2.13, was used (11), following pertinent guidelines (12).

Results

The overall prevalence of positive patch test reactions to MCI/MI in the study period was 2.33% [95% confidence interval (CI) 2.26–2.4%]. The overall frequencies of the three grades of positive reaction were as follows: +, 1.53%; ++, 0.67%; and + + +, 0.13%. The distributions per year of +, ++ and + + + reactions are shown in Table 1. Although some year-to-year variation in the share of reaction grades can be seen, this was relatively limited and, moreover, showed only an unsystematic pattern.

In the following analyses, we do not present overall results in terms of results comprising all ages, for the following reasons:

- It is known that the average age and, with it, the proportion of patients aged ≥ 40 years routinely used for description, adjustment or standardization (12), significantly increased in the patients patch-tested within the IVDK (13). This phenomenon is also seen in the present analysis, where the proportion of patients aged ≥ 40 years increased from 53.2% in 1992 to 73% in 2010.
- Sensitization to MCI/MI is age-related (14). In the present data, the odds ratio (OR) for being sensitized, if aged ≥ 40 years, was estimated to be 1.32 (95% CI 1.23–1.41). In the subgroup of patients with occupational dermatitis (see below), the age effect was even more marked, with an OR of 1.65 (95% CI 1.41–1.93).

Table 1. Annual number of patients tested and proportion displaying a +, ++ and +++ reaction, respectively, in (i) all patients, (ii) patients in whom cosmetics were considered as culprit exposures, and (iii) patients with occupational dermatitis (for further details, see text)

Year	All patients				Cosmetic				Occupational			
	Tested	% +	% ++	% +++	Tested	% +	% ++	% +++	Tested	% +	% ++	% +++
1992	6703	1.72	1.09	0.09	—	—	—	—	136	3.68	0.74	0
1993	8083	1.5	0.85	0.14	—	—	—	—	159	0	0	0
1994	9161	1.66	0.6	0.17	—	—	—	—	262	3.05	1.91	0.38
1995	8873	1.34	0.51	0.14	1092	1.74	0.27	0	1159	1.55	0.86	0.35
1996	8576	1.69	0.7	0.09	1827	2.08	1.04	0.05	1219	1.56	0.9	0.16
1997	8862	1.55	0.88	0.09	2037	1.67	0.69	0	1101	1.54	1.73	0
1998	9202	1.76	0.46	0.14	2171	1.98	0.23	0	1186	2.02	0.84	0.34
1999	9050	1.38	0.55	0.13	2479	1.57	0.32	0.12	1048	1.24	0.86	0.38
2000	8638	1.61	0.54	0.14	2169	1.89	0.51	0.09	1052	1.43	0.76	0.38
2001	7498	1.44	0.72	0.12	2042	1.62	0.88	0.05	1031	1.55	0.97	0.39
2002	7088	1.31	0.8	0.14	2228	1.48	0.67	0.13	923	1.95	1.73	0.33
2003	8453	1.38	0.54	0.15	2674	1.42	0.49	0.19	1036	1.74	1.16	0.29
2004	9053	1.33	0.72	0.17	2798	1.22	0.75	0.29	1060	1.89	1.32	0.47
2005	8200	1.45	0.52	0.1	2651	1.21	0.41	0.11	929	2.91	0.86	0.22
2006	9112	1.49	0.58	0.12	3362	1.37	0.39	0.06	1044	2.3	1.82	0.29
2007	10 449	1.33	0.57	0.14	3331	1.5	0.57	0.06	1232	2.52	1.06	0.41
2008	10 976	1.43	0.59	0.08	3800	1.29	0.71	0.08	1440	2.57	0.83	0.21
2009	11 227	1.43	0.72	0.1	4667	1.69	0.58	0.11	1308	1.53	1.83	0.23
2010	12 670	2.03	0.89	0.17	4609	2.3	1	0.15	1486	3.1	1.14	0.27
Total	171 874				43 937				18 811			
Average		1.53	0.67	0.13		1.63	0.61	0.1		2	1.16	0.29

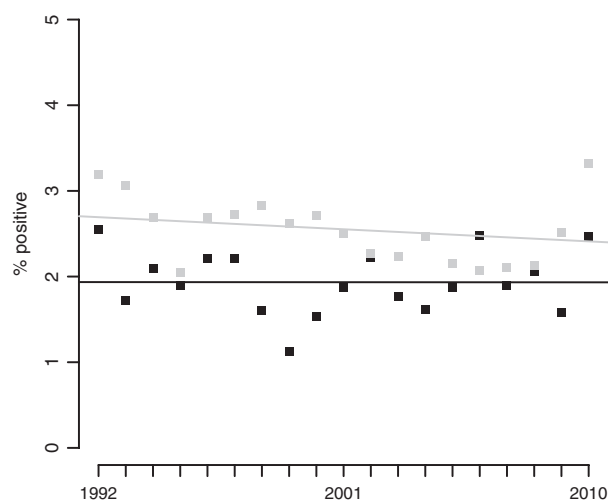
—, no data available.

Thus, confounding of the association between MCI/MI sensitization and time by the marked change in age composition must be expected, calling for suitably adjusted, or, as chosen here, stratified analyses. These should provide an undistorted impression of any time trend, which would otherwise be overestimated or underestimated.

Accordingly, descriptive results in terms of annual prevalences are shown in Fig. 1 separately for patients aged < 40 years and for patients aged ≥ 40 years. As for the younger subgroup, no significant downward trend could be identified (Table 2).

The beneficial effect of the regulation of MCI/MI in cosmetics may be concealed in an overall analysis including all patients. Hence, the same analysis was performed in the subgroup of patients with cosmetics reported as culprit exposures, excluding patients with occupational dermatitis (n = 43 937). Age-stratified results are presented in Fig. 2, and show no significant trend, either in the 'young' subgroup or in the 'old' subgroup (Table 2), notwithstanding a marked divergence of trend in the two age groups. In this analysis, the years 1992–1994 have been omitted, as the documentation of contactants had not been well established before 1995.

As MCI/MI is also used industrially, the subgroup of patients with (suspected) occupational dermatitis,

**Fig. 1.** Annual proportions of positive reactions to methylchloroisothiazolinone/methylisothiazolinone, 100 ppm aqua, between 1992 and 2010 in Information Network of Departments of Dermatology patients, stratified for age: < 40 years (n = 59 754) in black squares; ≥ 40 years (n = 112 120) in grey squares.

excluding those in whom cosmetics were documented as culprit exposures, was examined in a similar fashion (n = 18 811). In Fig. 3, the age-stratified analysis shows that the increase was evidently stronger in the 'young'

Table 2. Results of linear trend analyses derived from weighted least squares regression (for further details, see text)

	Change in MCI/MI prevalence per decade in percentage points	95% confidence interval	<i>p</i> -value	Change per decade relative to baseline period (%)
Total group				
<40 years	−0.001	−0.307 to 0.304	0.99	−0.05
≥40 years	−0.157	−0.479 to 0.165	0.35	−5.32
Cosmetic				
<40 years	−0.373	−1.019 to 0.272	0.28	−14.22
≥40 years	0.318	−0.306 to 0.942	0.33	12.43
Occupational				
<40 years	0.866	0.216 to 1.517	0.018	33.3
≥40 years	0.590	−0.245 to 1.426	0.18	15.42

MCI/MI, methylchloroisothiazolinone/methylisothiazolinone. As 'baseline period', the first years of the study period were pooled to achieve a proportion of at least 10%.

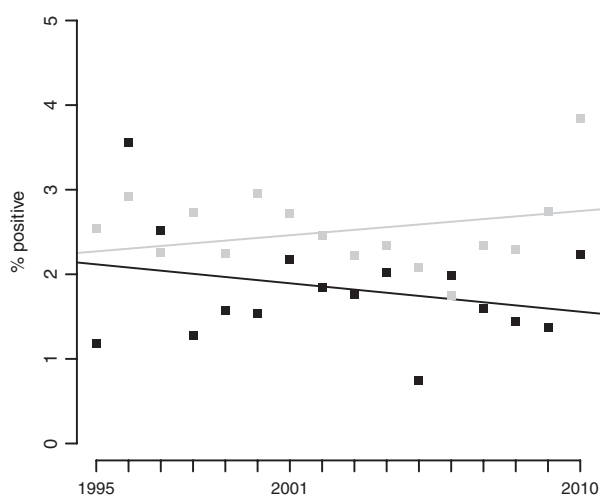


Fig. 2. Annual proportions of positive reactions to methylchloroisothiazolinone/methylisothiazolinone, 100 ppm aqua, between 1995 and 2010 in patients with cosmetics as culprit exposures, stratified for age: < 40 years ($n = 12\,905$) in black squares; ≥ 40 years ($n = 31\,032$) in grey squares.

subgroup than in the 'old' subgroup, and significant in the former subgroup (Table 2), amounting to an increase in prevalence by 0.087 percentage points per year, that is, 0.87 percentage points per decade ($p = 0.018$); see Table 2.

Discussion

The present analysis did not identify an overall trend of MCI/MI contact sensitization in a vast number ($n = 171\,883$) of patients patch tested during a period of almost 20 years, either in a young subgroup (patients aged <40 years at the time of patch testing) or in an older subset. Moreover, no significant and relevant decline in the frequency of positive reactions in the

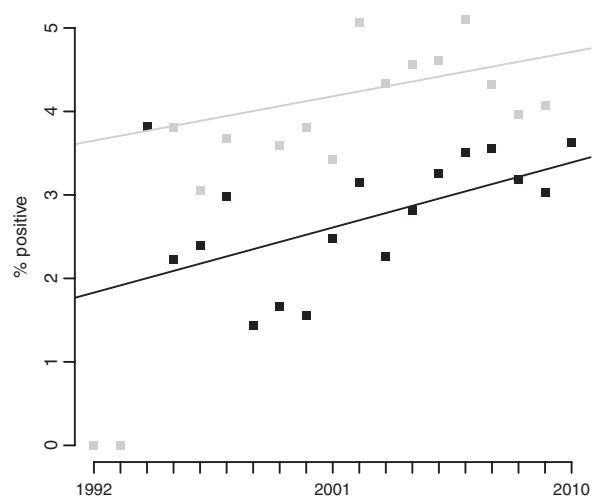


Fig. 3. Annual proportions of positive reactions to methylchloroisothiazolinone/methylisothiazolinone, 100 ppm aqua, between 1992 and 2010 in patients with occupational dermatitis aged < 40 years ($n = 9998$, black squares) and in patients aged ≥ 40 years ($n = 8813$, grey squares). In 1992, a prevalence of 6.46% was noted in the 'young' subgroup, based on 93 patch tests only; this outlier is not shown in the graph, but it is included in the regression analysis.

subgroup with cosmetics as culprit exposures was identified, namely, 'young' patients in whom cosmetics had been documented as culprit exposures, even though a slight downward trend was evident. Furthermore, no evidence for a decrease in average sensitivity in those with positive patch test reactions to MCI/MI was found in the above analyses. Thus, from these two, albeit related, perspectives, it is valid to regard exposure to MCI/MI via cosmetics as a persisting problem. Possibly, the use concentration permitted for 'leave-on' products should be reconsidered, for example by following the recommendation of the CIR panel (4), and also taking up the concerns in the SCCS statement of 2009 (5).

It is possible that the apparently increased use of MI alone (15, 16) may have contributed to the lack of the otherwise expected decline in MCI/MI sensitization frequency in patients exposed to cosmetics. Interestingly, another subgroup analysed for comparison, namely, 'occupational cases', showed a significant and quite marked increase in sensitization frequency (if not of single degrees of reactivity) in the younger subgroup, presumably better reflecting recent changes in exposure. This observation points to a probable increase in the use of MCI/MI (and probably also of MI alone (16)) in the industrial context, and to the need for better regulation of this potent allergen also in this sector.

In conclusion, in view of the increasing trend, both applications of MCI/MI, cosmetic and especially industrial, should be the target of further preventive efforts.

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