

The methylisothiazolinone epidemic goes along with changing patients' characteristics – After cosmetics, industrial applications are the focus

Axel Schnuch  | Steffen Schubert  | Holger Lessmann | Johannes Geier  |
for the IVDK |

Information Network of Department of Dermatology (IVDK), Institute at the University Medical Center Göttingen, Göttingen, Germany

Correspondence

Axel Schnuch, IVDK a.d. Universitätsmedizin Göttingen, Geiststr. 3, D 37073 Göttingen, Germany.
Email: aschnuc@gwdg.de

Abstract

Background: Sensitization to methylisothiazolinone (MI) has seen an exceptional epidemic, mainly attributed to its use in cosmetics.

Objectives: To trace the epidemic of MI allergy (2009–2018), and to analyze a possible change of patients' characteristics.

Methods: Informationsverbund Dermatologischer Kliniken-data of patients patch tested between 2009 and 2018 with MI (0.05% aq.) were analyzed concerning anamnestic items and sensitization frequencies.

Results: Overall, 4.9% reacted positive to MI. Comparing sensitization to MI in three periods (2009, 2013/14, and 2017/18), there was an increase to 7% in 2013 and a decrease to 3.4% in 2018. The MOAHLFA Index (M=Men, O=Occupational Dermatitis, A=Atopic Dermatitis, L=Leg Dermatitis, F=Face Dermatitis, A= Age > 40) for the period 2013/14 is characterized by a lower proportion of occupational dermatitis and a higher proportion of face dermatitis. The period 2017/18 is characterized by increases of occupational dermatitis and hand dermatitis, and a decrease of face dermatitis. Painters, personal care workers, and hairdressers were particularly affected. Sensitization in hairdressers and personal care workers (mostly cosmeticians) decreased after the peak in 2013/14, whereas sensitization to MI in painters continued to increase.

Conclusions: After an unprecedented epidemic of MI allergy, mainly caused by its use in cosmetics, the continuous use of MI in industrial applications, for example, paints, and subsequent sensitization remain a matter of concern.

KEYWORDS

CAS no. 2682-20-4, clinical epidemiology, contact sensitization, face dermatitis, methylisothiazolinone, occupational dermatitis, patch testing

1 | INTRODUCTION

The last decade has seen an unprecedented epidemic of contact allergy to methylisothiazolinone (MI). Shortly after the first publication pointing to the dawning epidemic already in 2012, with sensitization rates rising from <2% in 2009 to >4% in 2011,¹ reports from all over

Europe,^{2,3} North America,^{4,5} and other parts of the world^{6,7} disclosed the full-blown epidemic showing sensitization frequencies of >7% in patch-tested dermatitis patients. In the preceding years, MI sensitization rates had remained <2%,^{8–11} attributed mainly to the use of MI (and mixture of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) acting via cross-reactions) in occupational applications,^{10,12}

for example, paints.^{2,13-15} In contrast, the sudden rise of MI allergy in 2010 and thereafter is thought to be caused mainly by sensitization through MI-containing cosmetics,² as was shown, for example, by risk factor analysis.¹⁵

The epidemic did not remain unnoticed by the EU regulatory bodies. The Scientific Committee on Consumer Safety of the European Commission (SCCS), as well as Cosmetics Europe (the association of the cosmetic industry) recommended that MI be banned from use in leave-on cosmetics in 2013. The overall frequency of sensitization decreased thereafter but remained at a high level,^{16,17} for which continued occupational exposure, rinse-off or household products, still too high use concentrations, and undisclosed occurrence in a variety of products were thought to be responsible.^{2,18-21}

We wondered whether the changes in the course of the epidemic were reflected in changes of the characteristics of patients in the surveillance system informationsverbund dermatologischer kliniken (IVDK). Certain patients' characteristics, namely parts of the MOAHLFA Index (M = Men, O = Occupational, H = Hands, F = Face Dermatitis, A = Age > 40) might be regarded as a rough proxy for causative exposures.

2 | PATIENTS AND METHODS

The IVDK (<http://www.ivdk.org>), a contact allergy surveillance network with 56 participating departments of dermatology from Germany, Switzerland, and Austria, has been described in detail elsewhere.²² Briefly, results of all patients who were patch tested (PT) are electronically recorded in local hospital databases, along with important demographic and clinical data. The diagnostic procedure follows international guidelines.²³ Following the recommendations of the deutsche kontaktallergie gruppe (DKG), MI was tested at 0.05% and MCI/MI at 0.01% in aq., as these are the only patch test preparations authorized and available in Germany. Patch test preparations were purchased from Almirall Hermal, Reinbek, Germany, and SmartPractice Europe, Barsbüttel, Germany. Finn Chambers on Scanpor (inner diameter of 8 mm) (Smart-Practice Europe) were used as test chambers in 92% of the patch tests. Patch test exposure time was 24 h in 17.8% and 48 h in 82.2% of the patients. Data are subject to standardized quality control and analyzed according to international standards.^{24,25} Patch test reactions on day (D) 3 or 4 were considered. Reactions coded as +, ++, or +++ were rated as positive.

For the present analysis, we considered data recorded between 2009 and 2018, in total from 119 322 patients, and focused on those tested with the cosmetics preservative series ($n = 70\,720$; 59.3%). Of these, 97.3% were tested with the DKG baseline series, too. MI (0.05% aq.) was patch tested in 67 643 patients and MCI/MI (0.01% aq.) in 67 563 patients. To analyze the change of population characteristics in the study period, we selected three subgroups of patients, namely those tested in 2009 (before epidemic), 2013–2014 (epidemic peak), and 2017–2018 (current decline). Anamnestic items and crude sensitization frequencies of these three subgroups were compared, and differences were regarded as significant in case of nonoverlapping 95% confidence intervals (95% CIs). Statistical significance of proportions of occupations among MI-positive

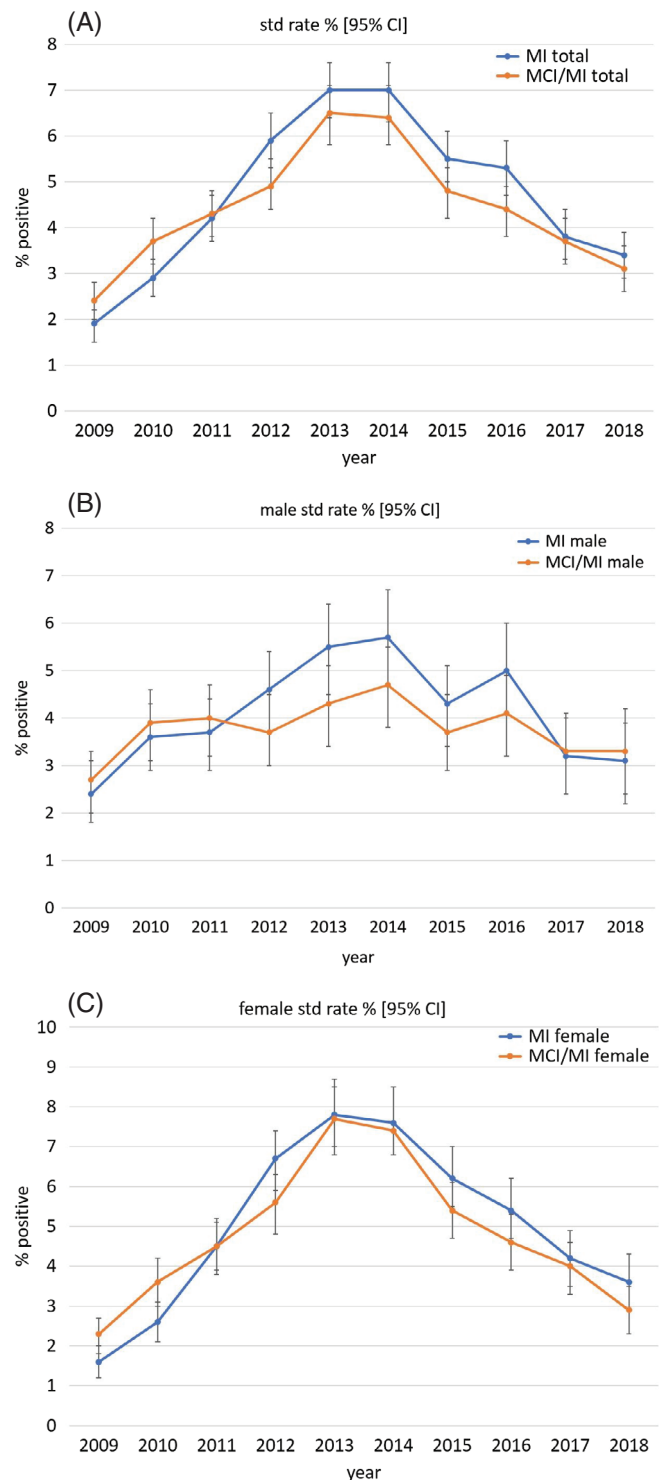


FIGURE 1 Frequencies of sensitization to MI and MCI/MI over time (2009 to 2018) in the total study population (A), in men (B), and in women (C), standardized for sex and age (A) or for age (B,C)

and MI-negative patients, respectively, was tested with the χ^2 ; a P -value of <0.05 was regarded as significance limit. Sex- and age-standardization of reaction frequencies was done as published.²² Logistic regression analyses were performed with a positive reaction to MI as outcome (dependent variable), with true negative reactions as reference (doubtful and

FIGURE 2 The MOAHLFA index in MI positives in the three periods of interest (2009, 2013/14, and 2017/18), accompanied by the respective 95%CI. As one outstanding result MI positives of the third period (2017/18), can be characterized by a higher proportion of occupational dermatitis and hand dermatitis, and a lower proportion of face dermatitis (differences significant), when compared with the second period (2013/14)

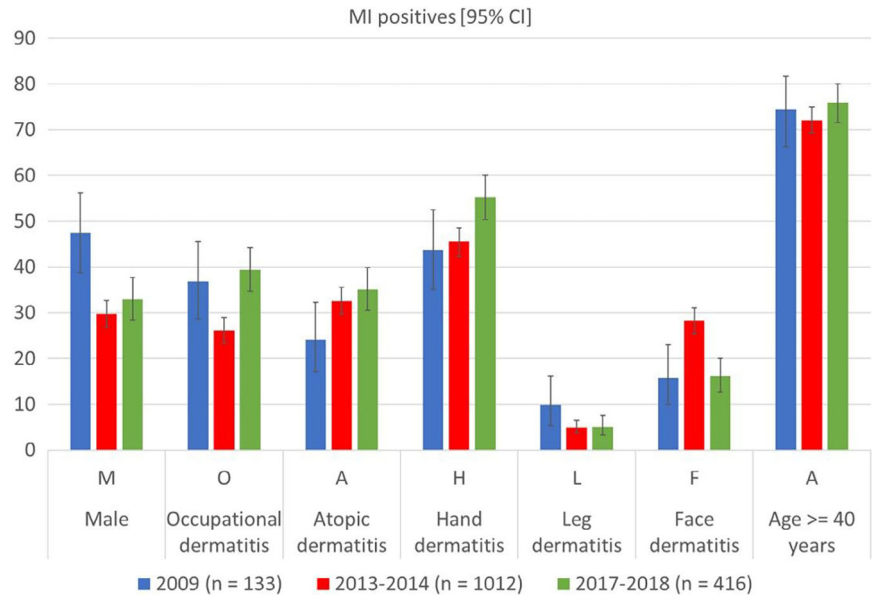


TABLE 1 IVDK, 2009–2018: frequencies of sensitization to MI (tested 0.05% aq.) in the three most frequently affected occupations, stratified for sex and standardized for age

	Men				Women			
	n tested	n positive	%pos. (crude) [95%CI]	% pos. (std.) [95%CI]	n tested	n positive	%pos. (crude) [95%CI]	% pos. (std.) [95%CI]
Painters	428	66	15.4 [12.1–19.2]	14.5 [11.3–17.8]	83	8	9.6 [4.3–18.1]	10.6 [3.3–17.9]
Personal care workers	5	0	0	0	447	56	12.5 [9.6–16.0]	12.2 [9.2–15.2]
Hairdressers	95	4	4.2 [1.2–10.4]	4.8 [0.2–9.5]	1176	94	8.0 [6.5–9.7]	9.6 [7.6–11.5]

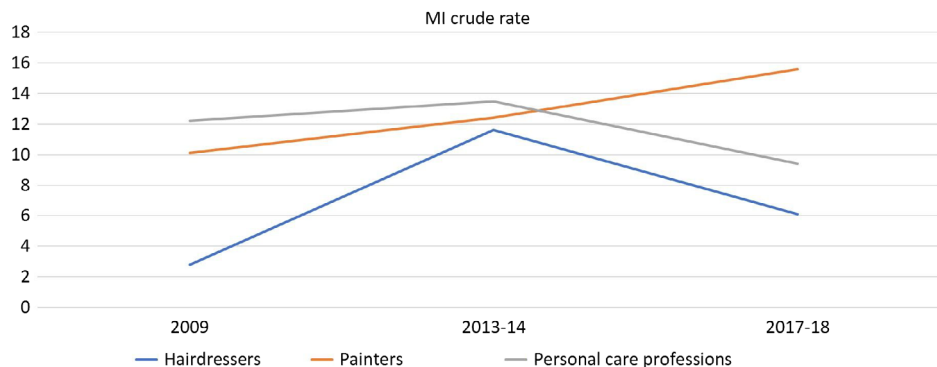


FIGURE 3 Frequencies of sensitization to MI in the three periods of interest (2009, 2013/14, and 2017/18) in three occupations most often affected (hairdressers, personal care professions, and painters). Frequencies of sensitization to MI in the two first occupations changed together with the rise and fall of the cosmetic-related epidemic, whereas MI allergy in painters even increased, both indicating a (partial) shift from cosmetic-related to paint-related MI allergy

irritant reactions were excluded from this analysis) for the respective study periods (2009; 2013–2014; 2017–2018). Independent explanatory variables were primarily suspected allergen sources (cosmetics, metal working fluids, paints/lacquers) and male sex. The model was checked with the Hosmer-and-Lemeshow goodness-of-fit test ($P > .05$). Results are presented as odds ratio (OR) estimates with profile-likelihood CIs (95%). Data were managed and analyzed using the statistical analysis software SAS, version 9.4 (SAS Institute, Cary, North Carolina).

3 | RESULTS

Overall, 4.9% (95%CI: 4.8%–5.1%) reacted positive to MI and 4.6% (95%CI 4.4%–4.8%) to MCI/MI (frequencies as crude rates). In men, reaction prevalences were 4.4% (95%CI: 4.2%–4.7%) to MI, and 4.0% (95%CI: 3.8%–4.3%) to MCI/MI. Among women, positive reactions were significantly more common: 5.2% (95%CI: 5.0%–5.4%) to MI, and 4.9% (95%CI: 4.7%–5.2%) to MCI/MI.

TABLE 2 IVDK, 2009–2018: frequencies of sensitization to MI (tested 0.05% aq.) in subgroups defined by different contactants

Contactant	Men				Women			
	n tested	n positive	%pos (crude) [95%CI]	% pos (std.) [95%CI]	n tested	n positive	%pos (crude) [95%CI]	% pos (std.) [95%CI]
Cosmetic, leave-on	7239	316	4.4 [3.9–4.9]	4.1 [3.5–4.6]	17 471	1086	6.2 [5.9–6.6]	5.9 [5.6–6.3]
Cutting fluids	1646	119	7.2 [6.0–8.6]	7.0 [5.7–8.2]	152	15	9.9 [5.6–15.8]	10.0 [5.0–15.0]
Paints, lacquers	467	54	11.6 [8.8–14.8]	10.5 [7.8–13.3]	146	17	11.6 [6.9–18.0]	11.5 [6.3–16.7]
Wall paint, freshly painted rooms	73	22	30.1 [19.9–42.0]	31.1 [19.0–43.1]	76	28	36.8 [26.1–48.7]	37.5 [26.5–48.6]

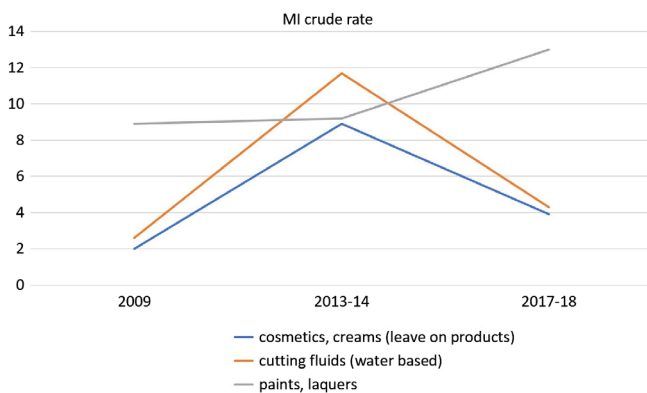


FIGURE 4 Frequencies of sensitization to MI in the three periods of interest (2009, 2013/14, and 2017/18) in three subgroups defined by the most often suspected causal exposure ("contactants"): Cosmetics (leave-on), cutting fluids, and paints. Frequencies of sensitization to MI in the two first contactants changed together with the rise and fall of the cosmetic-related epidemic, whereas MI allergy in the contactant subgroup, paints' even increased. The increase and decrease of MI allergy in the contactant subgroup cutting fluid is very probably due to the use of protective creams (and not to cutting fluids themselves) (see legend to Figure 3)

3.1 | Sensitization frequencies over time

Time courses of standardized reaction frequencies are illustrated in Figure 1A–C. When the three periods of interest were compared, namely, 2009, 2013/14, and 2017/18, there were increases and decreases in sensitization to MI and MCI/MI, in all patients, as well as in men and in women. All changes from 2009 to 2013/14 and from 2013/14 to 2017/18 were statistically significant, except for the decrease of MCI/MI sensitization in men from 2013/14 to 2017/18.

Furthermore, comparison of the gender ratios in the three periods showed women to be significantly more often sensitized in the period 2013/14, both to MI and MCI/MI. Of interest, this female gender dominance in MI and MCI/MI sensitization was not observed in 2009 and in 2017/18. This means that, at the end of the epidemic, the gender ratio returned to the pattern seen before the epidemic.

The MOAHLFA Index of MI-positive patients changed over time (Figure 2). Considering the MOAHLFA Index of the "peak epidemic" period (2013/14), it is characterized by a much lower proportion of men ("M") (i.e., a female dominance) compared to 2009 (29.7% vs 47.4% [significant]), a lower proportion of occupational dermatitis

("O") (26.1% vs 36.8%; not significant), and a higher proportion of face dermatitis ("F") (28.2% vs 15.8%; significant).

In contrast, the MOAHLFA index of the "postepidemic period" (2017/18 compared to 2013/14) is characterized by an increase in occupational dermatitis ("O"), from 26.1% to 39.4% (significant); an increase in hand dermatitis ("H"), from 45.5% to 55.3% (significant); and a decrease in face dermatitis, from 28.1% to 16.1% (significant). The other items of the MOAHLFA Index, namely, atopic dermatitis ("A"), leg dermatitis ("L"), and age ≥ 40 ("A"), did not change significantly over time. Remarkably, the proportion of patients at age ≥ 40 years was significantly higher in MI-positive patients than in MI-negative patients (73.4% [95%CI: 71.2–75.6%] vs 70.0% [95%CI: 69.5%–70.5%]) when considering the entire period 2009–2018.

A number of occupations were found significantly more often among MI-positive patients, when compared to MI-negative patients. These were painters (2.2% vs 0.7%), hairdressers (2.9% vs 1.8%), and personal care-related professions (e.g., cosmeticians) (1.7% vs 0.6%). In these professions, an increased specific occupational exposure to MI-containing materials is obvious. Other occupational groups overrepresented among MI-positive patients (compared to MI-negative ones) were health care workers (9.4% vs 7.8%), mechanics (5.3% vs 4.2%), and chemists and laboratory assistants (1.0% vs 0.7%), where an indirectly related exposure via, for example, MI-containing protective creams or skin care products may play a role. In contrast, in the group of office clerks, who were also overrepresented among MI-positive patients (13.9% vs 12.2%), a specific occupational exposure is less clear or even absent, and private MI exposure would be more plausible, instead. Frequencies of sensitization to MI (2009–2018) in the most frequently affected occupations are presented in Table 1. High frequencies are seen in painters (14.5% in men), in personal care workers (12.2% in women), and in hairdressers (9.6% in women), following the known distribution of occupations among the two sexes. The time course of sensitization frequencies to MI (as crude rates) in different occupations is illustrated in Figure 3. Sensitization in occupations probably exposed to cosmetics, that is, hairdressers and personal care workers (mostly cosmeticians) decreased after the peak in 2013/14, whereas sensitization to MI in painters continued to increase.

In the IVDK documentation, up to three suspected causative exposures (contactants) can be entered, the most probable source of allergen exposure being the first one. Among patients sensitized to

TABLE 3 Logistic regression analysis: odds ratios for a positive reaction to MI in three time periods. Dependent variables were male sex and three different first line contactants

Time period	Male sex	Cosmetics (leave-on)	Cutting fluids	Paints/lacquers
2009	1.49 [1.05–2.11]	1.13 [0.79–1.63]	1.18 [0.42–3.32]	4.64 [1.79–12.04]
2013/2014	0.69 [0.59–0.79]	1.58 [1.38–1.81]	2.76 [1.99–3.76]	1.95 [1.01–3.42]
2017/2018	0.80 [0.65–0.996]	1.04 [0.84–1.28]	1.33 [0.73–2.26]	4.20 [2.25–7.29]

MI, cosmetics (leave-on), cutting fluids (water-based), paints and lacquers, and wall paint/freshly painted rooms were most often mentioned as first contactant. Sensitization to MI in subgroups of patients defined by these contactants are presented in Table 2. The contactant “wall paint/freshly painted rooms” was the least-often mentioned category of these four ($n = 149$), particularly, when compared to the contactant “cosmetic, leave-on” ($n = 24\,710$). However, age- and sex-standardized frequency of sensitization to MI was by far the highest in this subgroup, with 35.3% (95%CI: 27.0%–43.6%), thus substantiating the suspected cause. The time course of sensitization rates in the three most important contactant subgroups are presented in Figure 4. Whereas sensitization rates increased until 2013/14 and decreased until 2017/18 in the subgroups “cosmetic (leave-on)” and “cutting fluid (water based)”, prevalences in the subgroup “paints, lacquers” were already high in the first period (2009), remained high in 2013/14, and even increased in 2017/18.

Logistic regression analyses (Table 3) were done separately for the three time periods—2009, 2013/14, and 2017/18—with a positive reaction to MI (0,05% aq.) as dependent (outcome) variable and a negative reaction as reference (doubtful and irritant reactions excluded from the analysis). Dichotomized explanatory variables included male sex, cosmetics (leave-on), cutting fluids (water-based), and paints, lacquers as first-line contactants. Analyses revealed that male sex was a significant risk factor only in 2009, and female sex a significant risk factor in the two other periods. Cosmetics (leave-on) and cutting fluids (water based) were only a significant risk factor in the period 2013/14, whereas “paints, lacquers” was a significant risk factor in all three periods.

4 | DISCUSSION

This analysis of IVDK data from 2009 to 2018 traces the time course of MI allergy, from the beginning of the epidemic in 2010 to its peak in 2013/14, and until its recent decline and leveling off in 2017/18 (Figure 1).

Before 2010, sensitization was clearly below 2%.^{8,9,11} In retrospective analyses, several publications identified the years 2010/11 as the years of the beginning of an epidemic.^{1,2} Most of the published studies covered the period 2010 to 2015 or parts of it, where sensitization rates were high (>7%).^{2–7,26,27} The peak of the epidemic was reached in 2013/14¹⁷ and a decline noted for 2014/15.¹⁶ Reports on the further development (2016–2018) are, however, sparse. In one study from Turkey, a decrease was shown in a very small sample.²⁸ In Australia, covering the period 2011 to 2017, extremely high

sensitization rates (possibly driven by a selection bias) were found in a tertiary referral center, with a peak in 2015 (>20%) and a decline to 11.4% in 2017.⁶

A clear, distinct, and consistent picture of the development of MI allergy emerges when demographic and clinical data are analyzed:

1. An “occupational dermatitis pattern” in the preepidemic period (2009), as expressed by the MOAHLFA Index in MI-positive patients (Figure 2) with high proportions of men (“M”), and patients with occupational dermatitis (“O”), and hand dermatitis (“H”). In analyses of the period before 2010 from the IVDK⁹ and Denmark,⁸ MI sensitization was associated with occupational dermatitis (in the IVDK: 41%; in DK: 38%).
2. A “cosmetic dermatitis pattern” is discernible in the period after 2010, in particular 2013/14. This pattern is characterized by a relative decrease of occupational factors, and an increase of cosmetic-associated factors (Figure 2), as expressed by female predominance, face dermatitis, and high sensitization rates and an increased risk for MI-allergy in the contactant subgroup “cosmetics” (Figure 4, Table 3). Furthermore, MI sensitization was high in cosmetic-related occupations (Figure 3): Personal care (12.2% in women) and hairdressers (9.6% in women) as examples for an occupational exposure to cosmetics.
3. In former analyses of the IVDK, Geier et al had already linked the increase of MI to exposure to MI-containing cosmetics,¹ and Uter et al found the increase driven mainly by female patients ≥ 40 years, patients with face dermatitis, and the use of cosmetics.¹⁵ In this analysis, beauticians (occupationally exposed to cosmetics) had an OR of 3.18 (95%CI: 1.68–6.09) for a sensitization to MI. A European multicenter study was conducted in 2015, that is, a time when sensitization had already begun to decline.²⁹ For the majority of cases in this study, the year of onset of contact dermatitis was, however, 2014. The hands (43.4%), the face (32.7%), and the eyelids (11.7%) were most frequently affected. Relevant exposures were leave-on and rinse-off cosmetics. The North American Contact Dermatitis Group analyzed data from 2013/14⁴ and found a sensitization rate to MI of 10.7%. The MOAHLFA Index was compatible with a “cosmetic dermatitis pattern.” In another study from the United States, where sensitization to MI had increased from 2.5% in 2012 to 6.8% in 2014, the most commonly affected sites were hands and face.²⁶ A multicenter study in France analyzed data from 2010 to 2012. A significant increase from 1.5% to 5.6% was noted; 73% of products thought responsible for the MI allergy were cosmetics, 17% household

products, and (only) 6% industrial products.²⁷ In the study from Australia mentioned above,⁶ MI-containing cosmetics (rinse-off and leave-on products) accounted by far for the majority of cases of contact allergy to MI. Only 8% of products were occupational contactants.

4. In 2013, Lundov et al reported on the “growing epidemic” of MI-contact allergy in Denmark,³⁰ with significant increases up to 2012. Among MI positives, the proportion of men was low (25%) and the proportion of patients with face dermatitis high (31%), hinting at a cosmetic exposure. Although, in this sample, the rate of occupational dermatitis was also high (32%), this finding would not contradict the leading role attributed to cosmetics. In a Finnish study, hairdressers and beauticians constituted the largest occupational group with sensitization to MI or MCI/MI,¹² and Urwin et al noted a significant increase of occupational sensitization to MI or MCI/MI in those exposed to personal care products in the workplace as primary exposure (health care workers, beauty workers, hairdressers).¹⁰ Because MI (without MCI) at higher concentrations is not used frequently in water-based cutting fluids, our findings of a high rate of MI allergy in the corresponding contactant subgroup “cutting fluids” in the 2013/14 period and the subsequent decline parallel to the contactant “cosmetics” can probably be explained by the use of (protective) skin creams.

In summary, our data and the bulk of published reports are supporting the notion of the MI epidemic from 2010 to 2015 being caused mainly by cosmetics. In this period, MI was used increasingly by the cosmetic industry to replace the parabens as preservatives for questionable reasons.³¹

5. Finally, a (partial) return in 2017/18 to patterns of the pre-epidemic period is seen, in particular with occupational factors again gaining importance (Figures 2–4): No longer a female gender predominance, higher proportion of occupational dermatitis, decreased rate of face dermatitis, increased rate of hand dermatitis, decrease of sensitization rate in hairdressers, decrease of the contactant “cosmetics.” The high share of hand dermatitis in the MOAHLFA description for 2017/18 can be attributed to a high proportion of occupational cases. However, one should have in mind that exposure to household products, of which MI content is not regulated, may have caused hand dermatitis, as in about one-fifth of positive MI cases, cleaning agents and disinfectant were suspected (data not shown), and 17% of MI cases were thought to be linked to household products.²⁷ To our surprise, we did not find a systematic or epidemiologic workup of the period after 2015 which could confirm or question our findings.
6. However, the role of paints, which, in some cases, were shown to contain MI in very high concentrations (>300 ppm)^{32–35} is seen in all three periods, with even a further increase in the last period 2017/18 (Figure 4). Painters were the occupation with the highest sensitization rate (14.5% in men) (Table 1) and the contactant “paints” was identified as significant risk factor in all three periods (Table 3). Most importantly, although the contactant “wall paints/

freshly painted rooms” was not suspected frequently, it stood out with the highest sensitization rate to MI (35%) (Table 2), thus substantiating the suspected cause.

7. In a former analysis of the IVDK,¹⁵ painters had the highest risk of being sensitized (OR: 4.86 [95%CI: 2.62–92]), and during the period 2009 to 2012, sensitization to MI in the contactant subgroup “freshly painted rooms” increased from 11.1% to 38.1% (statistically significant). The latter exposure is increasingly considered. Amsler et al. reviewed 44 cases of airborne contact dermatitis due to exposure to paints (the use of paints or MI emitted from painted walls),³⁶ and Schwensen et al reporting the results of a European study found 15 patients (7.3%) having experienced allergic reactions when exposed to newly painted rooms.²⁹
8. In several studies and reports, paints were shown to be associated with occupational dermatitis and sensitization to MI. In a study of the Danish Contact Dermatitis Group, MI was the leading occupational allergen in painters, with 27% positive patch test reactions (in selected testing), exceeding other isothiazolinone biocides like MCI/MI, OIT, BIT and the other important occupational allergen, epoxy resin.¹³ Accordingly, in another publication from Denmark, painters, with 22.4%, were the most often affected occupation by sensitization to MI.¹⁴

5 | CONCLUSION

After an unprecedented epidemic of MI allergy caused mainly by the use of MI in cosmetics, the continuous use of MI in industrial applications, for example, paints, and subsequent sensitization remain a matter of concern.

CONFLICT OF INTEREST

The IVDK, maintained by the IVDK e.V., of which the authors are employees, is sponsored by the cosmetic and chemical industry (associations) as well as by public funds. A.S. works as an ad hoc consultant for the cosmetic industry (associations), partly remunerated.

ORCID

Axel Schnuch  <https://orcid.org/0000-0002-5725-7734>

Steffen Schubert  <https://orcid.org/0000-0002-2359-2518>

Johannes Geier  <https://orcid.org/0000-0002-5047-8948>

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