

Title: The epidemic of contact allergy to methylisothiazolinone—an analysis of Danish consecutive patients patch tested between 2005-2019.

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Abstract:

Background. In 2005, methylisothiazolinone (MI) was allowed as a stand-alone preservative in cosmetics. This resulted in an epidemic of allergic contact dermatitis to MI, mainly affecting women exposed to leave-on cosmetics. Consequently, a regulation of Annex V in the European Union in 2017, banned the use of MI in leave-on cosmetics and greatly reduced the allowed concentration in rinse-off products.

Objective. To analyze the temporal trends in contact allergy to MI in Danish patients in relation to key-events including European regulations over time.

Methods. A retrospective study of consecutive patients patch tested with methylisothiazolinone from 2005 to 2019. Demographics and clinical characteristics in terms of MOAHLFA (male, occupational, atopic dermatitis, hand dermatitis, leg dermatitis, facial dermatitis and age > 40 years), sources of exposure and clinical relevance were analyzed in relation to key historical events.

Results. 380 of 12494 (3.0% (95CI 2.7-3.4) patients tested from 2005 to 2019 were sensitized to MI. An increasing trend in the prevalence of MI contact allergy from 2005-2019 ($P < .01$) was observed, though a decline in the absolute number of patch test positive patients was seen from 2013 and onwards. A reduction in leave-on cosmetics as a source

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of exposure was observed following the legislative ban in 2017, from 24.8% from in 2010-2013 to 6.2% in 2017-2019 ($P < .01$).

Conclusion. The epidemic of MI contact allergy is declining in absolute terms, though the prevalence in the patch tested population has not returned to its pre-epidemic levels. The legislative regulation of MI in 2017 has been effective in terms of leave-on cosmetics as a source of exposure in MI allergic patients. The process of post-marketing risk assessment of contact allergens in the European Union needs improvement.

Key words: epidemic; methylisothiazolinone, preservatives, prevention, risk assessment

1. Introduction

Preservatives are widely used additives in industrial and consumer products to prevent bacterial decomposition. While these properties are beneficial to both manufacturers and consumers, preservatives tend to have a sensitizing potential, thus posing a risk of sensitization and subsequent allergic contact dermatitis (ACD).

Introduction of new preservatives has historically led to outbreaks of contact allergy. This has previously been seen for formaldehyde in the 1960s, methylchloroisothiazolinone (MCI) in combination with methylisothiazolinone (MI) in the 1980s, methyl dibromo glutaronitrile (MDBGN) in the 1990s and most recently with MI as a stand-alone preservative in the 2000s.¹

MI was introduced on the market in the 1980s as an ingredient in a series of biocides known as Kathon™ in a 3:1 ratio of MCI and MI. Around the millennium, with the expiration of the patent for Kathon™, MI as a stand-alone preservative was applied in industrial settings.² The first case reports of ACD to MI in workers were published in 2004 and 2006, describing reactions to wall covering glue and paint.^{3,4} Despite these early cases, the Scientific Committee on Cosmetic Products and Non-Food Products (the predecessor to the Scientific Commission On Consumer safety (SCCS)) deemed MI safe in cosmetic products and MI was subsequently adopted in Annex V (list of allowed preservatives in the European Union) in 2005, permitted in concentrations of 100 ppm.^{5,6} The first case reports of consumers affected by MI contact allergy from cosmetics emerged in 2010, describing reactions to wet-wipes and make-up remover.⁷ The same year, a retrospective analysis of MI contact allergy from 2006-2010, found that 32% of the cases were caused by exposure to cosmetics.⁸ From then on a dramatic increase in the prevalence of MI contact allergy arose across Europe.⁹ In Germany the prevalence increased from 1.9% in 2009 to 6.0% in 2012, mainly affecting female patients exposed to MI-containing cosmetics and in Finland, Portugal and the British Isles, the prevalence exceeded a staggering 10% by 2012-2013.¹⁰⁻¹³

This increase in the prevalence urged the European Society of contact Dermatitis in 2011 to write a letter to the European Commission, to sound the alarm of an ongoing epidemic. This was responded to with *no priority*, inspiring an editorial in this journal to draw on the Great Fire of Rome, famous for the inactions of the political power of the time.¹⁴ It was not until 2013, that the SCCS revised its opinion on the safety of MI, recommending that no safe limit existed for leave-on cosmetics and only concentrations up to 15 ppm to be used in rinse-off products.¹⁵ In 2015, this was settled in a final opinion and by February 2017 this change was adopted in Annex V.^{16,17}

MI has been included in the Baseline Series at Gentofte Hospital since 2005, as the data and conclusion in the SCCS opinion led us to believe that major problems with contact allergy to MI could be expected. In this study we aimed to analyze the temporal trends in contact allergy to MI in Danish patients in relation to key-events including European regulation over time.

2. Methods

This study is a retrospective analysis of patients patch tested with MI at The Department of Dermatology and Allergy, at Gentofte Hospital in Denmark. Data was obtained from The National Database for Contact Allergy. Permissions were obtained from the Danish Data Protection Agency and The Regional Clinical Database Program.

2.1 Data extraction

Data from consecutive patients, patch tested with MI at Gentofte Hospital, from January 1st, 2005 to December 31st, 2019 was extracted from the database. The following covariates were extracted for analysis: Patient demographics in terms of sex, age and occupation, history of atopic dermatitis (current or past), patch test year, patch test result to MI and relevance, source of exposure, location of the dermatitis and whether the dermatitis was related to occupational exposures or not.

2.2 Patch testing

A test concentration 1000 ppm. aq. (0.1%) MI was used in 2005, while a concentration of 2000 ppm aq. (0.2%) was used for the remainder of the study period. Patch testing was performed with Finn Chambers (Epitest, Oy Finland and SmartPractice, Phoenix, Arizona) on Scanpor tape (Norgesplaster A/S (Norgesplaster A/S, Alparma, Venesla, Norway) applied on the upper back. Reading was done at day 2, 3, 4 and 7. A reaction of +, ++ or +++ was considered positive, while a negative, irritant or doubtful reaction was considered negative.

2.3 Stratification of the study period (study period I-IV)

Based on four key events, the study period was stratified into four periods. (I) from 2005 when MI was allowed as a preservative in cosmetics, (II) from 2010 when the first case reports describing MI allergy from cosmetics was published, (III) from 2013 where the SCCS revised its opinion on MI in cosmetics and (IV) from 2017 where the EU regulation of MI was implemented. This gives study period (I) from 2005-2009, (II) from 2010-2013, (III) from 2014-2016 and (IV) from 2017-2019 (figure 3).

2.4 Statistical analysis

The prevalence was calculated as the proportion of patch test positive patients out of all patch tested patients. Comparison of clinical characteristics were done by a Chi Square test or Fischer's Exact Test when two periods were compared. An independent sample t-test was used for comparison of the mean age. Analysis of temporal trends was done by a Chi square test for trend. The risk of being MI patch test positive for each patch test year in relation to the whole study period, was calculated as crude odds ratios. To test for a significant difference between two odds ratios, a Z-value was calculated from the absolute difference between two log odds ratios, divided by the corresponding standard error. A *P*-value of .05 was considered significant. Statistical analysis was performed in IBM SPSS version 25 and MS Office 365 Excel.

3. Results

Data from 12494 consecutive MI patch tests performed between 2005 and 2019 were available (supplementary table 1). These originated from 12091 individual patients as 456 (3.6%) patients were patch tested more than once. In the study population, 11543 patients were tested 1 time, 417 patients were tested 2 times, 27 patients were tested 3 times, 4 patients were tested 4 times and 1 patient was tested 5 times.

The MI patch test positive patient tended to be female (OR 1.3 (95CI 1.0-1.6), *P* = .03), having occupational dermatitis (OR 1.7 (95CI 1.3-2.1), *P* < .01), hand dermatitis (OR 1.7 (95CI 1.4-2.1), *P* < .01), facial dermatitis (OR 2.0 (95CI 1.6-2.3), *P* < .01) and being > 40 years of age (OR 1.6 (95CI 1.2-2.0), *P* < .01) (table 1). When stratifying for sex, men tended more often to have hand dermatitis (OR 3.0 (95CI 1.9-4.9), *P* < .01), occupational dermatitis (OR 3.0 (95CI 1.9-4.9), *P* < .01) with cutting fluids (OR 17.10 (95CI 2.0-143.6, *P* < .01) and various chemicals (OR 2.6 (95CI 1.1-6.2), *P* = .02) being the main sources of exposure. Women were mainly affected by facial dermatitis (OR 2.8 (95CI 1.6-4.659), *P* > .01) and exposed to leave-on cosmetics (OR 2.1 (95CI 1.1-4.0), *P* = .02). Most patients were aged between 41-60 years, with significantly more male patients being in this age group (OR 1.7 (95CI 1.1-2.7), *P* = .02), while female patients tended to be younger aged between 19-40 years (OR 2.3 (95CI 1.2-4.2), *P* = .01) (table 2).

3.1 Overall trends from 2005-2019

During the 14-year study period, 380 of 12494 (3.0% (95CI 2.7-3.4) patients were patch test positive to MI. The number of patch test performed ranged from 469 in 2005 to 1136 in 2014, with a prevalence of MI allergy ranging from 1.1% (95CI 0.4-2.2) in 2007 to 5.4% (95CI 4.1-6.9) in 2013. A significant trend in the increase in MI allergy from 1.5% (95CI 0.6-3.1) in 2005 to 3.3% (2.1-5.0) in 2019 was observed ($P_{\text{trend}} < .01$). No significant trend in the prevalence was found from 2014 and onwards (figure 1).

When comparing data from the stratified periods (I-IV), a significant trend in the prevalence of patch test positive women ($P_{\text{trend}} < .01$) from 1.2% (95CI 0.8-1.8) in period (I), 3.7 (3.0-4.5) in period (II), 4.4 (3.6-5.3) in period (III) to 3.7 (95CI 2.8-4.8) in period (IV) was found. No significant trend was seen for men ($P_{\text{trend}} = .41$) with the prevalence being 1.8% (95CI 1.1-2.7), 3.4 (2.4-4.6), 2.2 (1.4-3.3) and 2.8 (95CI 1.8-4.2) respectively.

The proportion of MI patch test positive patients that were female, increased from 56.8% (period I) to 72.8 (period IV) with a borderline significant trend ($P_{\text{trend}} = .05$). No significant trends were found for age groups being affected, when analyzed as a whole or when stratified by sex. Occupational dermatitis affected less MI patch test positive patients, decreasing from 40.9% in period (I) to 25.9% in study period (IV) ($P_{\text{trend}} = .02$) and less patients had hand dermatitis, with the percentage decreasing from 72.7% (I) to 42.0% (IV) ($P_{\text{trend}} < .01$) (table 3).

3.2 2010-2013 vs. 2017-2019

Since the study period spanned both the beginning and the potential decline of the epidemic, a trend analysis of parameters that may follow a bell curve by returning to their pre-epidemic levels, may not reflect a difference between the peak and decline of the epidemic. To address this issue, we compared study period (II) and (IV), thus comparing the beginning and the peak of the epidemic with the period following the regulation of MI in the European Union.

We observed a decrease in the prevalence of MI contact allergy from 3.6% (95CI 3.0-4.2) to 3.4% (95CI 2.7-4.2), though not statistically significant ($P = .70$). Nor was a significant difference found when comparing period (III) and (IV) ($P = .55$) or men and women in period (II) and (IV), ($P = .48$) and ($P = .97$).

Though no significant trend was seen for facial dermatitis across entire study period, a significant decrease from 45.3% to 28.4% ($P = .03$) was observed when comparing study period (II) and (IV). For hand dermatitis, in accordance with the decreasing trend, a decline in the proportion of patients affected from 45.9% to 42.0% ($P < .01$) was observed. This was accompanied by, a decreasing percentage of the patients having leave-on cosmetics ($P < .01$) and house-hold products ($P = .05$) as a source of exposure (table 3).

Less MI allergic patients had a currently relevant patch test as the proportion declined from 70.1% to 43.2% ($P < .01$) and less had a debut of contact dermatitis within one year of a positive patch test with 46.9% and 31.4% ($P = .11$) being affected respectively. No significant difference was found for the percentage of the MI patch test positive patients being male, having occupational dermatitis or being >40 years of age ($P = .84$), ($P = .20$) and ($P = .75$).

3.3 Exposure from cosmetic products

The proportion of patients with MI contact allergy caused by cosmetics, in relation to all MI patch tested patients within a study year, ranged from 0.15% in 2006 to 2.5% in 2015. All cases caused by leave-on cosmetics were seen between 2007 and 2017 and ranged from 0.15% in 2007 to 1.5% in 2015. No cases due to leave-on cosmetics were observed in 2018 and 2019 following the changed status of MI in Annex V. Rinse-off products were evident throughout the entire study period, ranging from 0.13% in 2009 to 1.0% in 2015 (figure 2). A significant increase in leave-on cosmetics from 0.36% to 1.37% was seen between 2010-2013 ($P_{\text{trend}} = .01$) followed by a decrease from 1.50% to 0.70% between 2014-2016 ($P_{\text{trend}} = .11$) and from 0.52% to 0% between 2017-2019 ($P_{\text{trend}} < .01$). No significant trends were found for rinse-off cosmetics.

3.4 Risk of MI contact allergy

The unadjusted odds ratio of the risk of MI contact allergy for each patch test year, ranged from 0.33 (95CI 0.16-0.71) in 2007 to 1.95 (95CI 1.45-2.61) in 2013. From 2011 and onwards the odds ratio was ≥ 1 , though a decline seemed apparent after the revision of the SCCS opinion on MI in 2013. Nevertheless, the odds ratio stayed above 1 for the remainder of the study period, except for 2016 (figure 3).

The odds ratios of period (I-IV) were 0.38 (95CI 0.28-0.52), 1.30 (95CI 1.10-1.61), 1.34 (95CI 1.10-1.67) and 1.16 (95CI 0.91-1.49) respectively. A significant increase was found when comparing period (I) with period (II), (III) and (IV) ($P < .01$). No difference was found when comparing period (II) with period (III) or period (IV), ($P = .87$) and ($P = .51$). When grouping period II and III, thus encompassing the period from the beginning of the epidemic to the regulation of MI, an odds ratio of 1.64 (95CI 1.32-2.03) was found. When compared to study period (IV) a borderline significant difference is found ($P = .08$).

4. Discussion

We found a decrease in the absolute number of patients with MI allergy and a reduction in prevalence from 2013 and onwards, however not statistically significant. Nevertheless, both the number of MI allergic patients and MI patch tested patients were declining in absolute terms, indicating that the epidemic is waning off. This was further

supported by a decline in MI patch test positive patients with current relevance from 70.1% in 2010-2013 to 43.2% in 2017-2019 ($P < .01$) and the number of patients with a debut of contact dermatitis within one year of patch testing from 46.9% in 2010-2013 to 31.4% in 2017-2019 ($P = .11$). Considering that 96.4% of the study population were patch tested only once, the prevalence may serve as a proxy for the incidence, indicating that the rate of MI contact allergy has not yet returned to its pre-epidemic levels. This is in line with the odds ratios of MI allergy in relation to patch test year, where no significant difference was seen when comparing 2010-2013, 2014-2016 or 2010-2016 with 2017-2019. Recent multicenter studies were able to demonstrate a significant downward trend in the prevalence of MI allergy in Europe, this perhaps due to a larger study population or different patterns of exposure among the contributing institutions.^{18,19} The decline in prevalence in our study was accompanied by a reduction in MI allergic patients with hand- and facial dermatitis and with less being exposed to MI from leave-on cosmetics and household products. Leave-on cosmetics accounted for 24.8% of patients in 2010-2013 and 6.2% in 2017-2019 ($P < .01$) illustrating the effect of the ban in February of 2017. No reduction was observed from 2010-2013 to 2014-2016. The exposure from household products declined from 2010-2013 to 2014-2016 ($P = .01$) perhaps due to the producers of such products responding faster to the recognition of MI as an allergen or changed consumer behavior following increased public awareness of MI as an allergen.

The chain of events in of the MI epidemic, follows a well described pattern, previously identified for other epidemics of contact allergy.²⁰ As seen with the preservatives formaldehyde, MCI/MI and MDBGN, the primary cases were occupational, subsequently followed by reports of consumers being affected, indicating a forthcoming epidemic that remains unrecognized until high numbers of consumers are sensitized. It is thought provoking with this knowledge in mind, that from the first case reports of workers and consumers being affected in 2004/2010 and the subsequent surge in the prevalence of MI allergy up until 2013, that it took until 2017 to update the status of MI in Annex V. Despite the EC was warned about a developing epidemic in 2011, more patients were allowed to be sensitized for half a decade, before the status of MI was updated in Annex V. Though the SCCS revised its opinion in 2013, a decline in cases was first noted in 2015 and a significant downward trend only found in study period IV (2017-2019), which underlines the importance of effective processing of post-marketing evaluation and quick adaption of Annex V when necessary.

The consulting group COWI has estimated the total cost of contact allergy to MI in cosmetics to be 48.4m Euro per 1000 cases.²¹ This gives a cost of 18.4m Euro (95CI 16.3-20.6) just for the MI allergic patients seen at Gentofte hospital from 2005-2019. Based on the CE-DUR method to estimate the prevalence in the general population, 0.64% ($n = 37.120$) of the population in Denmark are sensitized based on a medium cases scenario, potentially costing 1.80b Euro according to the COWI estimates.²²

The delay of a ban of MI in cosmetics has led to an unnecessary increase in MI sensitized patients and financial burden on health care systems. The process of communicating the evidence of an emerging epidemic from the scientific community to the EC has not functioned optimally to protect the consumers from MI, delayed partly by neglect of the EC and opposing evidence by Cosmetics Europe.^{14,23} It has previously been suggested to adopt preservatives in Annex V on a time-limited entry, thus requiring reevaluation after a certain time period.²⁴ It is not unreasonable to suggest that this would have limited the magnitude of the epidemic of contact allergy to MI.

In a previous publication, the early introduction of MI in the baseline series at Gentofte hospital, made it possible to show that a large proportion of patients were sensitized by cosmetics before the escalation in the prevalence of MI allergy. It may therefore be beneficial when future preservatives are introduced in consumer products, to be proactive in routinely patch testing with these early on, whenever a reasonable doubt exist about the allergenic properties.⁸

A recent shift in patient characteristics with MI allergy presenting as occupational dermatitis have been reported.²⁵ We found a significant downward trend in occupational cases, though they continue to account for a major proportion of MI allergic cases. The measures concerning occupational product may therefore be insufficient.

It is a disadvantage to this study, that no information is available on the reasons for referral, as the number of patch tested patients varies across the study period, consequently affecting the prevalence of MI allergy. In addition, MI was only tested for in a concentration of 0.1% aq. In 2005, potentially underestimating the number of affected patients. Lastly, when stratifying the timeline by key events, the timing of any changes in trends may be obscured these predefined strata. It is however of great value to analyze the epidemic with data from a single institution, with the same methods for patch testing throughout the entire study period.

Conclusion

The prevalence of MI contact allergy has not yet returned to its pre-epidemic levels, though a decline in absolute terms is evident. A reduction in MI-associated hand and facial dermatitis as well as leave-on cosmetics and household products as sources of exposure was observed. The regulation of MI in 2017 in stay-on cosmetics has been effective. The process of post-market risk assessment seems inefficient to cope the rapidly developing epidemics of contact allergy. A time-limited adoption of preservatives in Annex V may be a solution to this problem.

6. Conflicts of Interest

None to declare.

7. References

1. Thyssen JP, Engkilde K, Lundov MD, Carlsen BC, Menné T, Johansen JD. Temporal trends of preservative allergy in Denmark (1985-2008). *Contact Dermatitis*. 2010;62(2):102-108.
2. Schwensen JF, Johansen JD. Isothiazolines. In: John SM, Johansen JD, Elsner P, Maibach HI, eds. *Kanerva's Occupational Dermatology*. 3rd ed. Springer; 2020:507-520.
3. Thyssen JP, Sederberg-Olsen N, Thomsen JF, Menné T. Contact dermatitis from methylisothiazolinone in a paint factory. *Contact Dermatitis*. 2006;54(6):322-324. doi:10.1111/j.0105-1873.2006.00850.x
4. Isaksson M, Gruvberger B, Bruze M. Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wallcovering glue and after a chemical burn from a biocide. *Dermatitis*. 2004;15(4):201-205. doi:10.1097/01206501-200412000-00007
5. The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers. *Opinion Concerning Methylisothiazolinone (Colipa No. P94)*. Adopted on 18 March 2003, SCCNFP/0625/02.; 2003. https://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out_201.pdf
6. *The Cosmetics Directive of the European Union*. Dir. 2005/42/EC. Annex VI: List of Preservatives Which Cosmetic Products May Contain.
7. García-Gavín J, Vansina S, Kerre S, Naert A, Goossens A. Methylisothiazolinone, an emerging allergen in cosmetics? *Contact Dermatitis*. 2010;63(2):96-101. doi:10.1111/j.1600-0536.2010.01754.x
8. Lundov MD, Thyssen JP, Zachariae C, Johansen JD. Prevalence and cause of methylisothiazolinone contact allergy. *Contact Dermatitis*. 2010;63(3):164-167.
9. Lundov MD, Opstrup MS, Johansen JD. Methylisothiazolinone contact allergy - A growing epidemic. *Contact Dermatitis*. 2013;69(5):271-275.
10. Johnston GA. The rise in prevalence of contact allergy to methylisothiazolinone in the British Isles. *Contact Dermatitis*. 2014;70(4):238-240. doi:10.1111/cod.12185
11. Gameiro A, Coutinho I, Ramos L, Gonçalo M. Methylisothiazolinone: Second "epidemic" of isothiazolinone sensitization. *Contact Dermatitis*. 2014;70(4):242-243. doi:10.1111/cod.12200
12. Lammintausta K, Aalto-Korte K, Ackerman L, et al. An epidemic of contact allergy to methylisothiazolinone in Finland. *Contact Dermatitis*. 2014;70(3):184-185. doi:10.1111/cod.12186
13. Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitization. *Contact Dermatitis*. 2013;69(4):231-238.
14. Gonçalo M, Goossens A. Whilst Rome burns: The epidemic of contact allergy to methylisothiazolinone. *Contact Dermatitis*. 2013;68(5):257-258. doi:10.1111/cod.12098
15. SCCS. Scientific Committee on Consumer Safety Opinion on Methylisothiazolinone (MI) (P94) Submission III (

Sensitisation only). *Scs/1557/15*. 2015;(March). doi:10.2772/7297

16. European Commission. COMMISSION REGULATION (EU) 2017/1224 of 6 July 2017 amending Annex V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products. *Comm Regul No 752/2014*. 2017;15(1223):1-71. doi:http://eur-lex.europa.eu/pri/en/oj/dat/2003/l_285/l_28520031101en00330037.pdf
17. The European commission. Commission Regulation (EU) No 2016/1198. 2016;(1223):22-24. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_2016.198.01.0010.01.ENG
18. Uter W, Aalto-Korte K, Agner T, et al. The epidemic of methylisothiazolinone contact allergy in Europe: follow-up on changing exposures. *J Eur Acad Dermatology Venereol*. 2020;34(2):333-339. doi:10.1111/jdv.15875
19. Schwensen JF, Uter W, Bruze M, et al. The epidemic of methylisothiazolinone: a European prospective study. *Contact Dermatitis*. 2017;76(5):272-279. doi:10.1111/cod.12733
20. Thyssen JP, Johansen JD, Menne T. Contact allergy epidemics and their controls. *Contact Dermatitis*. 2007;56(4):185-195. doi:10.1111/j.1600-0536.2006.01058.x
21. COWI. *Effektivradering Af Kemikalieindsatsen 2014-2017*.;2017.
22. Thyssen JP, Menné T, Schnuch A, et al. Acceptable risk of contact allergy in the general population assessed by CE-DUR - A method to detect and categorize contact allergy epidemics based on patient data. *Regul Toxicol Pharmacol*. 2009;54(2):183-187. doi:10.1016/j.yrtph.2009.04.001
23. Bruze M, Uter W, Goncalo M, Lepoittevin JP, Diepgen T, Orton D. Incompetence and failure to regulate methylisothiazolinone. *Contact Dermatitis*. 2015;72(6):353-354. doi:10.1111/cod.12416
24. Schwensen JF, Thyssen JP. Contact allergy to preservatives-is the European commission a commendable risk manager? *Cosmetics*. 2016;3(3):1-8. doi:10.3390/cosmetics3030029
25. Schnuch A, Schubert S, Lessmann H, et al. The methylisothiazolinone epidemic goes along with changing patients' characteristics—After cosmetics, industrial applications are the focus. *Contact Dermatitis*. 2020;82(2):87-93. doi:10.1111/cod.13414

Table 1. Baseline characteristics of the study population

	MI positive n = 380	MI negative n = 12114	P-Value MI positive vs. negative
Age	48.9	46.9	.04
Male	103 (27.1)	3929 (32.4)	.03
Occupational dermatitis	113 (29.7)	2444 (20.2)	<.01
Atopic dermatitis	59 (15.5)	2526 (20.9)	.01
Hand dermatitis	201 (52.9)	4755 (39.2)	<.01
Leg dermatitis	8 (2.1)	314 (2.6)	.56
Facial dermatitis	150 (39.5)	2997 (24.7)	<.01
Age > 40	280 (73.7)	7803 (64.4)	<.01

P-value calculated by Chi Square test.

Table 2. Characteristics of MI patch test positive patients stratified by sex

	Total % (n)	Men % (n)	Women % (n)	P-value Men vs. women
MI patch test positive	3.0 (380)	2.5 (103)	3.3 (277)	.03
Age mean years +/- SD	48.9 +/- 15.8	49.5 +/- 16.0	48.6 +/- 15.7	.63
Age group				
0-18 y	2.9 (11)	4.9 (5)	2.2 (6)	.17
19-40 y	24.2 (92)	14.6 (15)	27.8 (77)	.01
41-60 y	50.3 (191)	60.2 (62)	46.6 (129)	.02
> 60 y	22.6 (86)	20.4 (21)	23.5 (65)	.52
MOAHLFA				
Male	27.1 (103)			
Occupational dermatitis	29.7 (113)	47.6 (49)	23.1 (64)	<.01
Atopic dermatitis	15.5 (59)	12.6 (13)	16.6 (46)	.34
Hand dermatitis	52.9 (201)	71.8 (74)	45.8 (127)	<.01
Leg dermatitis	2.1 (8)	1.0 (1)	2.5 (7)	.69
Facial dermatitis	39.5 (150)	23.3 (24)	45.5 (126)	<.01
Age > 40	73.7 (280)	80.6 (83)	71.1 (197)	.06
Current relevant exposures				
Cosmetics, leave-on	22.1 (84)	13.6 (14)	25.3 (70)	.02
Cosmetics, rinse-off	15.8 (60)	12.6 (13)	17.0 (47)	.30
Household products	6.3 (24)	6.8 (7)	6.1 (17)	.81
Paint	6.3 (24)	8.7 (9)	5.4 (15)	.24
Chemicals	6.1 (23)	10.7 (11)	4.3 (12)	.02
Cutting fluids	1.8 (7)	5.8 (6)	0.4 (1)	<.01

P-value calculated by Chi Square test. Fischer's Exact test were used when $n < 5$.

Table 3. Characteristics of MI patch test positive patients, relevance and source of exposure, stratified by patch test year

	2005-2009 % (n)	2010-2013 % (n)	2014-2016 % (n)	2017-2019 % (n)	2010-2013 vs 2017-2019
MI positive	1.4 % 44/3147	3.6% 137/3803	3.7 % 118/3174	3.4% 81/2370*	.70
Mean age years +/- SD	51.6 +/- 14.7	47.7 +/- 14.7	47.7 +/- 17.3	51.1 +/- 15.6	.10
Age group					
0-18 y	0 (0)	3.6 (5)	4.2 (5)	1.2 (1)	.42
19-40 y	25 (11)	21.2 (29)	28.8 (34)	22.2 (18)	.86
41-60 y	54.5 (24)	54 (74)	43.2 (51)	51.9 (42)	.75
>60 y	20.5 (9)	21.2 (29)	23.7 (28)	24.7 (20)	.55
MOAHLFA					
Women	56.8 (25)	71.5 (98)	80.5 (95)	72.8 (59)	
Male	43.2 (19)	28.5 (39)	19.5 (23)	27.2 (22)	.84
Occupational dermatitis	40.9 (18)	34.3 (47)	22.9 (27)	25.9 (21)*	.20
Atopic dermatitis	11.4 (5)	16.1 (22)	16.1 (19)	16.0 (13)	.99
Hand dermatitis	72.7 (32)	56.9 (78)	51.7 (61)	42.0 (34)*	.03
Leg dermatitis	11.4 (5)	1.5 (2)	0.8 (1)	0 (0)*	.28
Facial dermatitis	29.5 (13)	45.3 (62)	44.1 (52)	28.4 (23)	.01
Age > 40	77.3 (34)	75.9 (104)	66.9 (79)	77.8 (63)	.75
Relevance of positive patch test reactions[†]					
Current	56.8 (25)	70.1 (96)	70.3 (83)	43.2 (35)*	<.01
Past	18.2 (8)	17.5 (24)	23.7 (28)	22.2 (18)	.39
Unknown	0 (0)	17.3 (22)	16.0 (16)	33.3 (18)*	.02
Debut of dermatitis in patients with current relevance					
<1 year	28 (7)	46.9 (45)	42.2 (35)	31.4 (11)	.11

Current relevant exposures					
Leave-on	9.1 (4)	24.8 (34)	34.7 (41)	6.2 (5)	<.01
Rinse-off	11.4 (5)	16.8 (23)	18.6 (22)	12.3 (10)	.38
Paint	0.0 (0)	5.8 (8)	8.5 (10)	7.4 (6)	.65
Household products	4.5 (2)	11.7 (16)	2.5 (3)	3.7 (3)	.05
Cutting fluids	2.3 (1)	1.5 (2)	0.8 (1)	3.7 (3)	.36
Chemicals	11.4 (5)	5.8 (8)	5.9 (7)	3.7 (3)	.75
Other	15.9 (7)	7.3 (10)	1.7 (2)	13.6 (11)	.13

P-value calculated by Chi Square test. Fischer's Exact test were used when $n < 5$.

†Missing in 15 positive patients

* $P_{\text{trend}} (2005-2019) < .05$

Figure legends

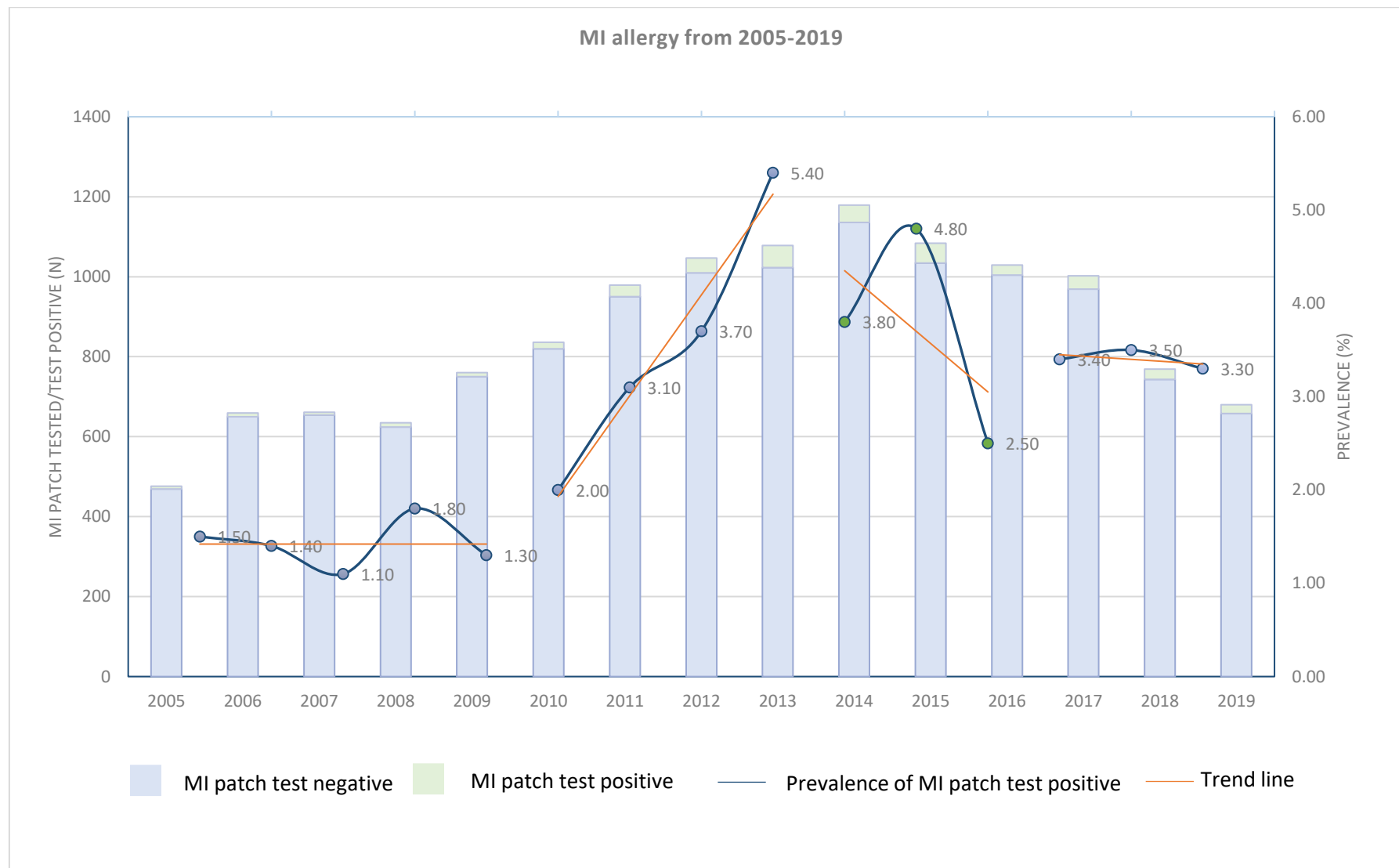
Figure 1. MI patch tested patients across the entire study period. $P_{\text{trend}} 2005-2019 < .01$, $P_{\text{trend}} 2005-2009 = .96$, $P_{\text{trend}} 2010-2013 < .01$, $P_{\text{trend}} 2014-2016 = .13$, $P_{\text{trend}} 2017-2019 = .96$, $P_{\text{trend}} 2014-2019 = .27$.

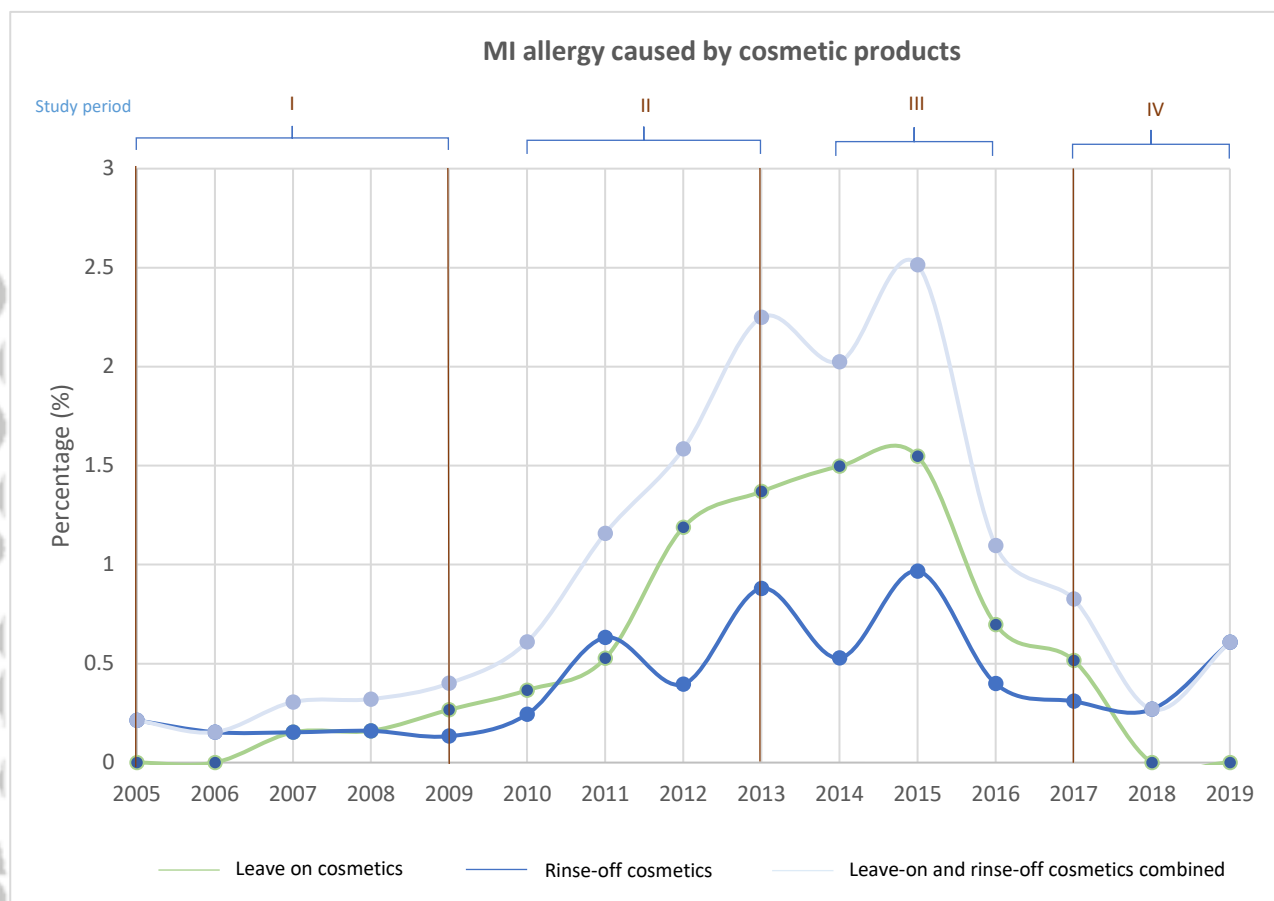
Figure 2. Yearly proportion of patients with MI allergy caused by cosmetics, in relation to all patch tested patients within the respective study year. Trends for Leave-on cosmetics: $P_{\text{trend}} 2005-2019 = .66$, $P_{\text{trend}} 2005-2009 \text{ (I)} = .12$, $P_{\text{trend}} 2010-2013 \text{ (II)} = .01$, $P_{\text{trend}} 2014-2016 \text{ (III)} = .11$, $P_{\text{trend}} 2017-2019 \text{ (IV)} = .02$.

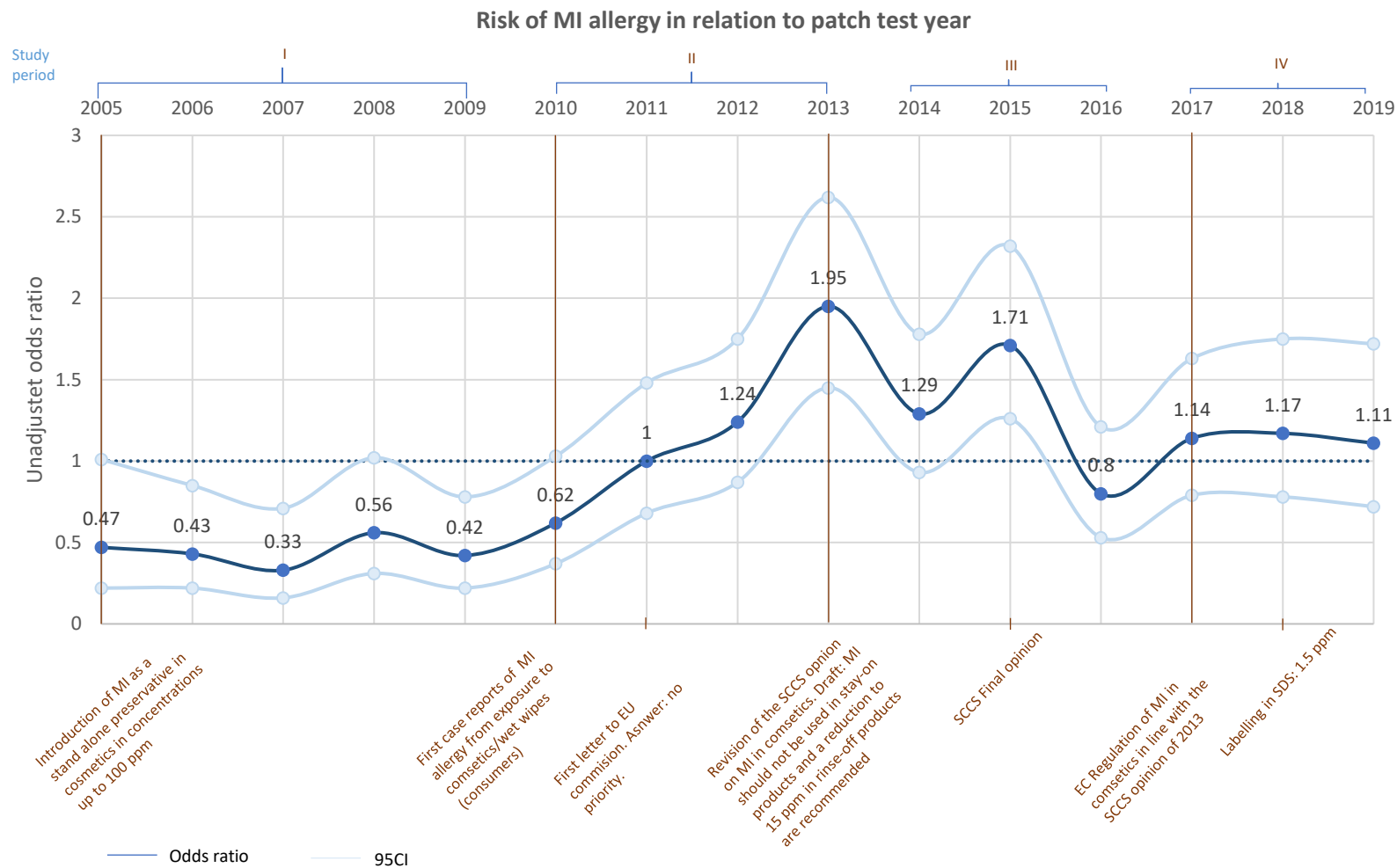
Figure 3. Yearly risk of MI allergy (unadjusted odds ratios with 95% CI) compared to the total study period (2005-2019). Vertical red lines indicate stratification of the study period by key events (I-IV).

Appendices

See supplementary table 1







Year	Total tested with MI (n)	MI positive	MI positive % (95CI)	Not tested sensitized	Not tested for unknown reason
2005	469	7	1.5 (0.6-3.1)	0	0
2006	650	9	1.4 (0.6-2.6)	0	20
2007	654	7	1.1 (0.4-2.2)	1	1
2008	624	11	1.8 (0.9-3.1)	1	0
2009	750	10	1.3 (0.6-2.4)	5	0
2010	820	16	2.0 (1.1-3.1)	0	1
2011	950	29	3.1 (2.1-4.4)	4	4
2012	1010	37	3.7 (2.6-5.0)	6	0
2013	1023	55	5.4 (4.1-6.9)	3	0
2014	1136	43	3.8 (2.8-5.1)	1	2
2015	1034	50	4.8 (3.6-6.3)	5	2
2016	1004	25	2.5 (1.6-3.7)	5	4
2017	969	33	3.4 (2.4-4.7)	2	0
2018	743	26	3.5 (2.3-5.1)	6	1
2019	658	22	3.3 (2.1-5.0)	3	0
Total	12494	380	3.0 (2.7-3.4)	42	35

Supplementary table 1. Prevalence of MI patch test positive patients from 2005-2019