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*Published in:*
Jama dermatology

*DOI:*
10.1001/jamadermatol.2022.5991



*Publication date:*
2023

JAMA Dermatology | Original Investigation

# Trends in the Prevalence of Methylchloroisothiazolinone/Methylisothiazolinone Contact Allergy in North America and Europe

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**IMPORTANCE** The common use of isothiazolinones as preservatives is a global cause of allergic contact dermatitis. Differences in allowable concentrations of methylisothiazolinone (MI) exist in Europe, Canada, and the US.

**OBJECTIVE** To compare the prevalence of positive patch test reactions to the methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) combination and MI alone in North America and Europe from 2009 to 2018.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective analysis of North American Contact Dermatitis Group, European Surveillance System on Contact Allergies (ESSCA), and the Information Network of Departments of Dermatology (IVDK) databases included data from patients presenting for patch testing at referral patch test clinics in North America and Europe.

**EXPOSURES** Patch tests to MCI/MI and MI.

**MAIN OUTCOMES AND MEASURES** Prevalence of allergic contact dermatitis to MCI/MI and MI.

**RESULTS** From 2009 to 2018, participating sites in North America and Europe patch tested a total of 226 161 individuals to MCI/MI and 118 779 to MI. In Europe, positivity to MCI/MI peaked during 2013 and 2014 at 7.6% (ESSCA) and 5.4% (IVDK) before decreasing to 4.4% (ESSCA) and 3.2% (IVDK) during 2017 and 2018. Positive reactions to MI were 5.5% (ESSCA) and 3.4% (IVDK) during 2017 and 2018. In North America, the frequency of positivity to MCI/MI increased steadily through the study period, reaching 10.8% for MCI/MI during 2017 and 2018. Positive reactions to MI were 15.0% during 2017 and 2018.

**CONCLUSIONS AND RELEVANCE** The study results suggest that in contrast to the continued increase in North America, isothiazolinone allergy is decreasing in Europe. This trend may coincide with earlier and more stringent government regulation of MI in Europe.

*JAMA Dermatol*. 2023;159(3):267-8. doi:10.1001/jamadermatol.2022.5991
Published online January 18, 2023.

Supplemental content

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Preservatives are essential ingredients in personal care products for prevention of microbial growth; however, preservatives may cause allergic contact dermatitis (ACD). The combination methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) has been used as a preservative under the trade name Kathon CG, a 3:1 mixture of MCI and MI, since the 1980s. Reported rates of contact sensitization in patch-tested patients were generally low (1.8-3.6%).[1,2] Isothiazolinones are commonly found in cosmetics or personal care products, household products, and industrial chemicals.[3]

There has been an increase in the concentrations at which MI is used. In 2005, US and European regulators approved MI alone as a preservative in personal care products at concentrations of up to 100 parts per million (ppm), representing a greater than 25-fold increase in MI exposure for consumers.[4] Erroneously felt to be less sensitizing than MCI due to a reporting error in the local lymph node assay data,[5] this approval of MI in personal care products, coupled with consumer concerns about other preservatives, such as parabens (a rare allergen),[6] was associated with increased use of MI in personal care products. Subsequently, a global increase in prevalence of contact allergy to isothiazolinones was reported.[7-12] In Europe, regulatory action in 2013 limited the concentration and presence of MI in personal care products, especially leave-on products, and has been associated with decreasing rates of MI positivity.[13-16] Restrictions in Canada were implemented in 2015, and the US continues to allow MI in leave-on products.

This retrospective study examines trends in MI contact allergy in North America and Europe. This analysis also examines trends in sensitization to the mixture MCI/MI. Because testing for MI alone was only added to screening series after the prevalence of MI allergy started to increase, the trend of MI allergy can be inferred by examining the prevalence of MCI/MI sensitization over time.

### Key Points

**Question** How does the prevalence of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) allergy compare between Europe and North America?

**Findings** In this cohort study of individuals who underwent patch testing, isothiazolinone allergy in Europe peaked during 2013 and 2014, with MCI/MI positivity reaching 7.6% (European Surveillance System on Contact Allergies [ESSCA]) and 5.4% (Information Network of Departments of Dermatology [IVDK]) before decreasing to 4.4% (ESSCA) and 3.2% (IVDK) during 2017 and 2018; in North America, MCI/MI positivity steadily increased from 2.5% in 2009 and 2010 to 10.8% in 2017 and 2018. Comparing Europe with North America, positive reactions to MI were 5.5% (ESSCA) and 3.4% (IVDK) vs 15% (North American Contact Dermatitis Group) during 2017 and 2018.

**Meaning** The study results suggest that isothiazolinone allergy is decreasing in Europe, whereas in North America, allergy continues to increase; differences in regulation may be contributing to the trend.

## Methods

This study was approved by the University of Wisconsin institutional review board, and informed consent was waived due to use of deidentified data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

### Patch Testing Results

Deidentified patch test results of patients tested between 2009 and 2018 with MCI/MI (0.01% aqueous [aq], 0.02% aq, or thin-layer rapid use epicutaneous test [4 μg/cm$^2$ in gel vehicle]) and/or MI (0.02% aq, 0.05% aq, or 0.2% aq) were retrieved along with relevant clinical information from the databases of the North American Contact Dermatitis Group (NACDG), European Surveillance System on Contact Allergies (ESSCA), and Information Network of Departments of Dermatology (IVDK). The NACDG is based in US and Canada. During this study, the NACDG tested MCI/MI at 0.01% aq from 2009 to 2016[17] and increased the concentration to 0.02% aq in 2017 and 2018.[18] From 2013 to 2018, MI was tested at 0.2% aq.[17-19] The IVDK is a clinical surveillance network in Europe.[20] The IVDK tested MCI/MI at 0.01%. Methylisothiazolinone, 0.05% aq, was added to the IVDK baseline series in 2014.[14] The ESSCA collects data from 12 European countries, comprising 44 departments.[21,22] During this study period, ESSCA tested MCI/MI at 0.01% and 0.02% and MI at 0.02%, 0.05%, and 0.2%. Deidentified data from the 3 research groups were pooled (avoiding duplication between IVDK and ESSCA), including the following information: country, sex, age, primary or main site of dermatitis, and test result (and allergen concentration) for MCI/MI and MI, respectively.

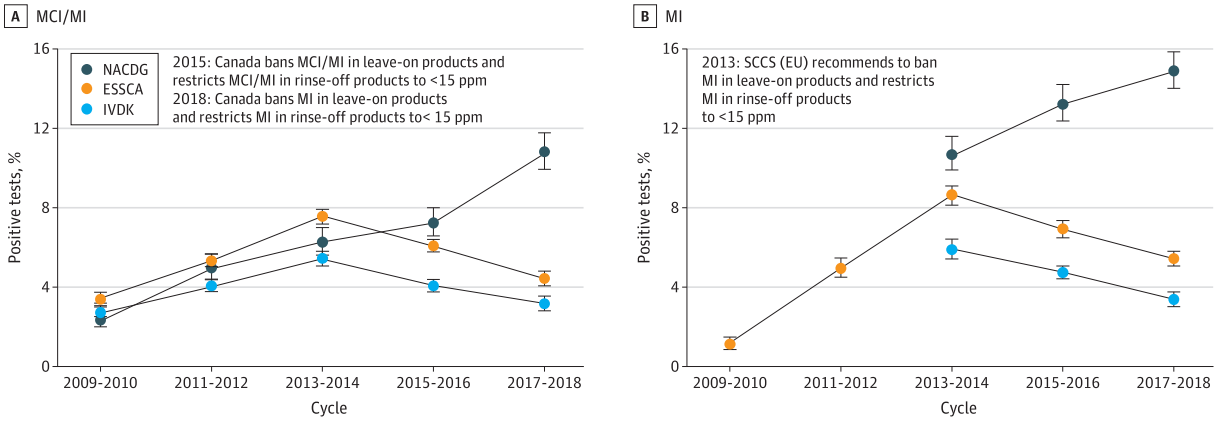
### Definition of Clinical Allergy

Patch testing was performed per International Contact Dermatitis Research Group/European Society of Contact Dermatitis guidelines.[23] Patch test materials were from different suppliers, including SmartPractice Europe (Barsbüttel, Germany), allergEAZE (SmartPractice, Calgary, Alberta, Canada), and Chemotechnique Diagnostics (Vellinge, Sweden). Most participants were tested with Finn Chambers on Scanpor tape. The NACDG also records a final interpretation of allergic or not allergic. For the purposes of this study, a positive result for NACDG data was defined as a final interpretation of allergic.

### Statistical Analysis

For data management at the Göttingen data center, SAS software (version 9.4; SAS Institute) was used. The ESSCA used various electronic data capture systems.[21] The NACDG used Microsoft Excel and Access (Redmond, Washington) for data management. For data analysis, the R statistical software package (version 3.6; R Foundation) was used. The MOAHLFA[24] index of consecutively patch-tested patients who were positive to MI and/or MCI/MI compared with those testing negative for MI and MCI/MI in Europe and North America (US and Canada) was used to examine

Figure 1. Time Course of Sensitization to Combination Methylchloroisothiazolinone (MCI)/Methylisothiazolinone (MI) and MI Alone Diagnosed by Patch Testing Consecutive Patients in Context of Regulatory Timeline




A, The MCI/MI was tested at concentrations of 0.01%, 0.02%, or thin-layer rapid-use epicutaneous test. By US regulations, MCI/MI should not exceed 7.5 ppm in leave-on products or 15 ppm in rinse-off products.[25] B, The MI was tested at concentrations of 0.01%, 0.02%, or 0.2%. Maximum recommended concentration for MI in rinse-off products is 100 ppm and is considered to be safe in leave-on products provided the concentration is nonsensitizing.[26] ESSCA indicates European Surveillance System on Contact Allergies; IVDK, Information Network of Departments of Dermatology; NACDG, North American Contact Dermatitis Group; ppm, parts per million; SCCS, EU Scientific Committee on Consumer Safety.

patients with different demographic (age, sex, and occupation) or clinical characteristics (such as regional dermatitis). Patients were divided into 2 groups, respectively: isothiazolinone positive (Is$^+$; positive to MCI/MI and/or MI) and isothiazolinone negative (Is$^-$; negative to MCI/MI and MI, when tested).

## Results

### Patch-Tested Population

In the European and North American study sites, 226 161 patch tests were performed with MCI/MI and 118 779 with MI. The distribution of patch tests by region was as follows: Europe, MCI/MI, 202 166 and MI, 102 667; and North America, MCI/MI, 23 995 and MI, 16 102.

### Positivity to MCI/MI and MI

The trend of positive reactions to MI and MCI/MI is displayed in **Figure 1**[25,26] as stratified by IDVK, ESSCA, and NACDG. Positivity for MI in European countries peaked in 2013 and 2014 at 8.7% (ESSCA) and 5.9% (IVDK) before considerable decline. In North America, positive reactions to MCI/MI and MI continue to rise. During the study period, MCI/MI positivity increased from 2.5% (2009/2010) to 10.8% (2017/2018). For MI, the reaction frequency increased from 10.8% (2013/2014) to 15.0% (2017/2018). Detailed data by contributing countries, with Europe aggregated to central Europe (Austria, Germany, and Switzerland), eastern Europe (Finland, Lithuania, Poland, and Slovenia), southern Europe (Italy and Spain), and western Europe (the Netherlands and UK), are presented in **Figure 2** and **Figure 3**.

### Is$^+$ Patients in Europe and North America

The MOAHLFA index[24] for all patch-tested patients is listed in **Table 1**. Patch-tested patients were predominantly female and older than 40 years. The MOAHLFA index by contributing country is listed in the eTable in Supplement 1.

### Comparison of Is$^+$ Patients With Is$^-$ Patients

**Table 2** shows the MOAHLFA index of individuals positive to MCI/MI or MI in Europe and North America, respectively. Patients who were Is$^+$ in Europe and North America had increased frequency of occupationally related skin disease, as well as either hand or face involvement. Patients who were Is$^+$ were more likely to be older than 40 years in Europe and North America. Patients who were Is$^+$ in Europe were significantly more likely to be female, whereas in North America, no differences in sex were noted.

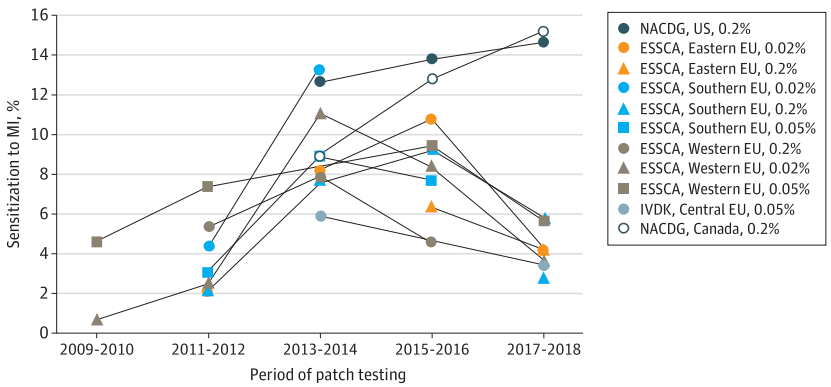
## Discussion

Between 2009 to 2018, the global burden of isothiazolinone allergy showed divergent trends between North American and European countries. Allergy to MCI/MI and MI peaked for IVDK and ESSCA during 2013 and 2014 before gradually decreasing. In contrast to Europe, the prevalence of MI allergy steadily increased in North America during the study period.

### Regulation of MI in Europe and North America

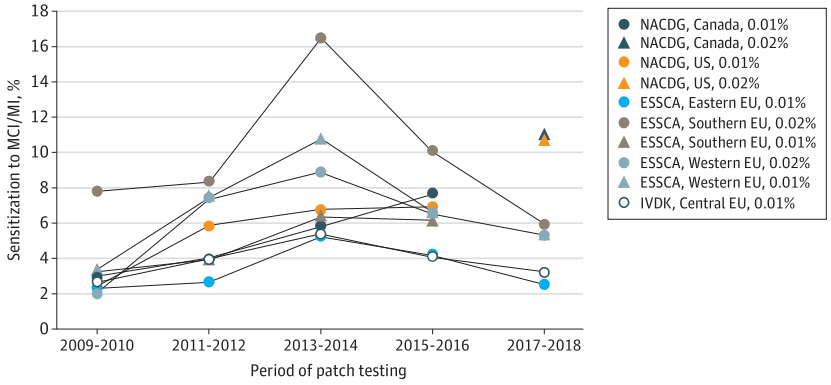
The observed trend in Europe may be associated with the growing awareness of increasing contact allergy to MCI/MI and MI and subsequent regulatory actions to limit their

Figure 2. Sensitization to Methylisothiazolinone (MI) From 2009 to 2018




Time course of sensitization to MI, diagnosed by patch testing consecutive patients with 0.02% aqueous (aq), 0.05% aq, and 0.2% aq, respectively, between 2009 and 2018 in the participating departments of the North American Contact Dermatitis Group (NACDG), European Surveillance System on Contact Allergies (ESSCA), and Information Network of Departments of Dermatology (IVDK). Results with fewer than 200 patients per 2-year interval were omitted; data from "West" during the final period were omitted owing to a substantial reduction of contributing UK departments from 4 to 1 during that period and freshly joined departments in the Netherlands; thus, there was no continuity.

Figure 3. Sensitization to Methylchloroisothiazolinone (MCI)/Methylisothiazolinone (MI) From 2009 to 2018




Time course of sensitization to MCI/MI, diagnosed by patch testing consecutive patients with 0.01% aqueous (aq) and 0.02% aq, respectively, between 2009 and 2018 in the participating departments of the North American Contact Dermatitis Group (NACDG), European Surveillance System on Contact Allergies (ESSCA), and Information Network of Departments of Dermatology (IVDK). Results with fewer than 200 patients per 2-year interval were omitted. Furthermore, 200 parts per million data from the "East" were omitted.

Table 1. Summary Data of Consecutively Patch-Tested Patients According to the MOAHLFA Index and the Number of Patch Tests With the Different Preparations of MCI/MI and MI

| Group | Male,[a] % | Occupational, % | Atopic eczema, % | Hand, % | Leg, % | Face, % | Age, >40 y, % | MCI/MI | | MI | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 0.01% | 0.02% | 0.02% | 0.05% | 0.2% |
| IVDK | 35.5 | 16.0 | 21.6 | 28.2 | 9.9 | 15.7 | 72.2 | 103 473 | NT | NT | 45 094 | NT |
| ESSCA | 31.3 | 9.9 | 23.9 | 24.0 | 5.6 | 19.2 | 57.5 | 71 419 | 27 274 | 16 808 | 9640 | 31 130 |
| NACDG | 29.9 | 10.2 | 28.2 | 20.9 | 4.0 | 16.0 | 67.0 | 19 136 | 4922 | NT | NT | 15 523 |
| Total | NA | NA | NA | NA | NA | NA | NA | 193 966 | 32 195 | 16 808 | 54 734 | 47 237 |

Abbreviations: ESSCA, European Surveillance System on Contact Allergies; IVDK, Information Network of Departments of Dermatology; NACDG, North American Contact Dermatitis Group; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; NA, not applicable; NT, not tested.

[a] Data for female participants were not included.

use.[13-15] Before 2005, consumers were only exposed to MI in combination with MCI in personal care products at a maximum concentration of MCI/MI, 15 ppm, or MI, 3.75 ppm. The decision to allow MI in concentrations of up to 100 ppm coupled with the increased use of MI as a preservative was associated with greatly increased consumer exposure to MI, which was also likely associated with the increase in the prevalence of contact allergy to MCI/MI.

In Europe, the trend of isothiazolinone allergy peaked during 2013 and 2014 before decreasing. This decrease may be partly explained by the advocacy of the European Society of Contact Dermatitis, which met with Cosmetics Europe to re-

Table 2. MOAHLFA[24] Index of Consecutively Patch-Tested Patients Positive to MI and/or MCI/MI Compared With Those Testing Negative to MI and MCI/MI as Stratified for US and Canada vs Europe

| | Europe | | | US/Canada | | |
|---|---|---|---|---|---|---|
| Factor | Is$^+$, %[a] | Is$^-$, %[a] | OR (CI) | Is$^+$, %[a] | Is$^-$, %[a] | OR (CI) |
| No. | 11 430 | 207 783 | | 2580 | 21 478 | |
| Male[b] | 29.3 | 32.1 | 0.88 (0.84-0.91) | 29.5 | 29.9 | 0.98 (0.90-1.07) |
| Occupational | 19.5 | 12.1 | 1.76 (1.68-1.85) | 16.4 | 9.5 | 1.87 (1.67-2.10) |
| Atopic eczema | 13.3 | 11.3 | 1.20 (1.14-1.27) | 30.0 | 28.7 | 1.06 (0.97-1.16) |
| Hand dermatitis | 34.0 | 24.0 | 1.63 (1.57-1.70) | 31.5 | 19.6 | 1.89 (1.73-2.07) |
| Leg dermatitis | 4.7 | 7.7 | 0.59 (0.54-0.65) | 2.4 | 4.1 | 0.56 (0.43-0.73) |
| Face dermatitis | 20.6 | 15.8 | 1.38 (1.32-1.45) | 18.1 | 15.8 | 1.18 (1.06-1.31) |
| Age, ≥40 y | 67.1 | 61.3 | 1.29 (1.24-1.34) | 72.0 | 66.4 | 1.31 (1.19-1.43) |

Abbreviations: Is, isothiazolinone; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; OR, odds ratio.

[a] Is$^+$ is MCI/MI$^+$ and/or MI-positive patients. Is$^-$ is negative to MCI/MI and MI.

[b] Data for female participants were not included.

view increased reports of contact allergy to MI. Cosmetics Europe subsequently published a memo in 2013 urging companies to remove MI from leave-on products.[27] Later that year, the EU Scientific Committee on Consumer Safety recommended against the use of MI in leave-on consumer personal care products and moved to restrict the concentration in rinse-off products to less than 15 ppm.[28] This recommendation was implemented in December 2015. Canada banned the use of MCI/MI in leave-on products in 2015, but MI alone was permitted in leave-on products until 2018. The total concentration of MI and MCI in wash-off products was limited to less than 15 ppm.[29]

In the US, to our knowledge, there are no formal governmental regulations restricting the use of MCI/ MI or MI. The Expert Panel for Cosmetic Ingredient Safety establishes restrictions for personal care products, and member companies of the Personal Care Products Council generally follow the recommendations of the panel. Both MCI/MI and MI are currently approved by the Expert Panel for Cosmetic Ingredient Safety for use in leave-on and wash-off personal care products with certain restrictions. The panel recommends that the concentration for MCI/MI should not exceed 7.5 ppm in leave-on products or 15 ppm in rinse-off products.[25] For MI, the concentration should not exceed 100 ppm in rinse off products and is safe in leave-on products when formulated to be nonsensitizing.[26]

## Association of Regulation of Potential Allergens With Sensitization

There is precedent that regulation of preservatives can be associated with the frequency of contact allergy in studied populations. In 2011, the National Toxicology Program for the US Department of Health and Human Services classified formaldehyde as a carcinogen,[30] leading some US manufacturers to remove formaldehyde from consumer products.[31] Since then, positivity to formaldehyde and formaldehyde-releasing preservatives has significantly decreased in North America from 1994 to 2016.[32] A decrease in the frequency of positive patch test results to formaldehyde and formaldehyde-releasing preservatives has also been seen in European populations.[33] This suggests that reducing exposure may be associated with a reduction in reported allergy.

## Characteristics of Patients Allergic to MI in Europe and North America

### Is$^+$ vs Is$^-$ Patients: Europe

An analysis from the IDVK showed changing trends of patients who were allergic to MI from 2009 to 2018. Patients positive to MI in 2008 and again in 2017 and 2018 were more likely to be male, whereas at the height of the European epidemic during 2013 and 2014, frequency of allergy was higher in female individuals.[13] This may be explained by the greater use of personal care products by female individuals.[34-42] After MI use was regulated in 2013 and 2014, exposure decreased in personal care products. This may explain the changing pattern of facial involvement in Europe, with greatest odds of facial involvement noted during 2013 and 2014, which occurred in parallel to increased proportion of Is$^+$ female individuals.

### Is$^+$ vs Is$^-$ Patients: North America

Facial involvement was also more common in Is$^+$ patients in North America. A review of isothiazolinone allergy in North America from 2013 to 2014 found that patients allergic to MI were most commonly exposed to MI from general personal care products (not otherwise specified) (33%); shampoo (22.8%); moisturizers, lotions, and creams (12.5%); wipes (6.9%); and soaps (4.2%).[38] This pattern of exposure fit with increased face and hand involvement noted in Is$^+$ patients. Unlike in European patients, there was no significant difference in sex between Is$^+$ and Is$^-$ groups. Isothiazolinone exposure may also be due to sources other than personal care products, such as industrial chemicals or medical devices, including adhesives.[39-41]

### Occupation

In Europe and North America, Is$^+$ patients were more likely to have occupational skin disease. Occupational contact dermatitis to MI is well described.[42-44] Occupations at high risk include painters, hairdressers, and personal care workers.[13] In a separate NACDG analysis from 2001 to 2016, a significant increase in occupationally relevant reactions to MCI/MI were ob-

served during the study period, with common sources including soaps, lotions, and waterless hand cleansers.[45] In the US, lack of formal regulation of MI in industrial chemicals and incomplete labeling on safety data sheets make it difficult to obtain complete ingredient information for industrial chemicals. However, in Europe, regulation since 2018 requires declaration of MI in safety data sheets if present in concentrations of more than 1.5 ppm and a warning of sensitizing if MI is present in concentrations of more than 15 ppm.

### Limitations

This study had several limitations. Methylisothiazolinone alone was added to most screening series only after the increase in MCI/MI positivity, thereby associated with potential underdiagnosis of MI allergy during the initial years of the study. Older product formulations may continue to be sold to consumers after regulations have been implemented, delaying the effect of regulations on MCI/MI and MI in personal care products. Different patch test concentrations of MCI/MI and MI were used among the IDVK, ESSCA, and NACDG. Some ESSCA members patch test MI at a concentration of 0.02%, and the IDVK patch tests MI, 0.05%, both of which are lower than the recommended 0.2% to detect MI allergy.[9] Although attempts were made to standardize patch testing practices, variations also exist between patch test preparation, haptens, procedure, patient populations, and coding.[46] Longer follow-up times and more consistent patch testing protocols will be needed to formally establish causality between the regulation and trends observed.

## Conclusions

The results of this cohort study suggest that although contact allergy to isothiazolinones has decreased in Europe, it continues to increase in North America. Earlier and more stringent regulation of MI in Europe is associated with these divergent trends.

ARTICLE INFORMATION

**Accepted for Publication:** November 17, 2022.

**Published Online:** January 18, 2023. doi:10.1001/jamadermatol.2022.5991

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**Author Contributions:** Dr Reeder had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Reeder, Warshaw, Geier, Silverberg, Houle, Uter.
*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* Reeder, Aravamuthan, Belsito, Geier, Yu, Uter.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Reeder, Aravamuthan, Geier, Pratt, Houle, Dickel, Uter.
*Administrative, technical, or material support:* Reeder, Warshaw, Belsito, Geier, Maibach, Botto, Giménez-Arnau, Houle, Dickel, Yu.
*Supervision:* Reeder, Warshaw, Belsito, White, Buhl, Botto, Lang, Johnston, Brockow, Houle, Schuttelaar, Filon Larese, Valiukeviciene.
*Other:* Gallo.

**Conflict of Interest Disclosures:** Dr Reeder reported personal fees from the American Contact Dermatitis Society and UpToDate outside the submitted work. Dr Warshaw reported grants and personal fees from Wen by Chaz Dean and personal fees from Noven Pharmaceuticals outside the submitted work. Dr Geier reported grants from VCI, the German Cosmetic, Toiletry, Perfumery and Detergent Association, and Schuelke during the conduct of the study and outside the submitted work. Dr Atwater reported employment with Eli Lilly and Company, grants from Pfizer, and personal fees from Henkel, Household & Commercial Products Assoc, and NC Derm Society outside the submitted work. Dr Taylor reported other noncontrolling stock and dividends from Cigna Health, Johnson and Johnson, AstraZeneca, Merck, and Opko Health, grants from Kao Corporation, and personal fees from Bayer Monsanto outside the submitted work; his child is a Pfizer employee. Dr Fowler reported personal fees from SmartPractice Inc outside the submitted work. Dr Giménez-Arnau reported grants from Uriach Pharma/Neucor, Novartis, Instituto Carlos III- FEDER and personal fees from Leo Pharma, Celldex, Thermo Fisher Scientific, GSK, Sanofi-Regeneron, Amgen, and Avene outside the submitted work. Dr Johnston reported personal fees from Sanofi and Canute outside the submitted work. Dr Pratt reported personal fees from AbbVie, Novartis, Leo, Sanofi, Janssen, Sun Pharma, and UCB outside the submitted work. Dr Adler reported grants from AbbVie and personal fees from Skin Research Institute, LLC outside the submitted work. Dr Spiewak reported personal fees from the Institute of Dermatology (Krakow, Poland) outside the submitted work. Dr Uter reported travel reimbursement and research funding from the International Fragrance Research Organisation. No other disclosures were reported.

**Data Sharing Statement:** See Supplement 2.

**Additional Contributions:** We recognize the following collaborators for their data contribution: Ulrike Beiteke, Andrea Bauer, Burkhard Kreft, Sibylle Schliemann, Detlef Becker, Jörg Fischer, Andreas Recke, Jana Witte, Joachim Dissemond, Wolfgang Pfützner, Brigitte Coras-Stepanek, Christoph Skudlik, Nicola Wagner, Birger Kränke, Steffen Emmert, Jens Malte Baron, Katharina Siedlecki, Vera Baur, Jan Nicolay, Elke Weisshaar, Heidrun Grunwald-Delitz, Knut Schäkel, Axel Trautmann, Karin Hartmann, Christiane Szliska, Johannes Weiß, Isaak Effendy, Michael Jünger, Randolf Brehler, Claudia Pföhler, Franziska Rueff, Thomas Werfel, Juliane Rieker-Schwienbacher, Dieter Vieluf, Rudolf Stadler, Dagmar Simon, Guido Heine, Regina Treudler, Stefan Nestoris, Dirk Mechtel, Claudia Schröder-Kraft, Harald Löffler, Michal Gina, André Koch, Ulrike Raap, Philip Spring, Welf Prager, Daniel Wilfinger, Javier Sánchez-Pérez, Juan Fco. Silvestre, José C. Amario-Hita, Pedro Mercader, Inmaculada Ruiz, Juan García-Gavín, Maria Pesonen, Anna Balato, Andrea Peserico, Francesca Caroppo, Anna Belloni Fortina, Maria Teresa Corradin, Thomas Rustemeyer, Marta Kieć-Świerczyńska, Beata Kręcisz, Magdalena Czarnecka-Operacz, Aleksandra Dugonik, Maja Kalac Pandurovic, Tanja Kmecl, Marko Vok, Mojca Simončič Godnič, Tomaž Lunder, Nada Kecelj, Susan M. Cooper, Sharizan Ghaffar, Cathy M. Green, Jane E. Sansom, Codagh M. King, Philippa Cousen, Mahbub M.U. Chowdhury, Natalie Stone, Catherine Holden, Ruth Sabroe, and Anthony D. Ormerod.

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