

Methylchloroisothiazolinone/ Methylisothiazolinone and Methylisothiazolinone Allergies Can Be Detected by 200 ppm of Methylchloroisothiazolinone/ Methylisothiazolinone Patch Test Concentration

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Background: Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and methylisothiazolinone (MI) contact allergies are rising dramatically. Moreover, 100 ppm of MCI/MI patch test might not detect an important number of MCI/MI and MI allergies.

Objectives: This study aimed to present the prevalence of contact allergy to both preservatives in an area of Spain and to investigate if 100 ppm of MCI/MI is an adequate concentration for a proper diagnosis.

Methods: A prospective study was conducted from October 2011 to September 2013. All patients were patch tested with the Spanish baseline series (containing 100 ppm of MCI/MI) and with 200 ppm of MCI/MI and 2000 ppm of MI.

Results: A total of 490 patients were patch tested. The MCI/MI prevalence was 10% and increased from 7.8% in last term of 2011 to 14.3% in the first 9 months of 2013. The MI prevalence was 4.5% and increased from 1% to 7.7% in the same period. One hundred parts per million of MCI/MI could not diagnose 24.5% of MCI/MI allergies. All MI allergies were detected by 200 ppm of MCI/MI, whereas only 68.2% were positive to 100-ppm concentration.

Conclusions: For a correct diagnosis of MCI/MI and MI contact allergies, we advocate increasing the MCI/MI patch test concentration to 200 ppm along with a temporal inclusion of MI in the North American Contact Dermatitis Group baseline series.

Methylchloroisothiazolinone (MCI; 5-chloro-2-methyl-4-isothiazolin-3-one) and methylisothiazolinone (MI; 2-methyl-4-isothiazolin-3-one) have been widely used as preservatives in a fixed combination at a ratio of 3:1 (MCI/MI) since the 1970s in the United States and Europe in cosmetics,¹ household,² and industrial products. Because of the increasing cases of allergies to MCI/MI that rose to 8%,³ in 1989, the European Union restricted the MCI/MI concentration to an upper limit of 15 ppm in cosmetics, and in 1992, a lower limit of 7.5 ppm in leave-on products was recommended by the US Cosmetic Ingredient Review. In 2000, MI, claimed to be a weaker

sensitizer,^{4,5} was introduced as a single-agent preservative in industrial products, and since 2005, it is permitted in cosmetic products in the United States and Europe at a maximum of 100 ppm. Currently, an alarming increase in prevalence of allergy to MCI/MI and MI, which had been stable since its regulation, is noted by multiple authors who warn about a possible epidemic.⁶⁻⁹ Hence, MI has recently been included in the European baseline series¹⁰ and is the American Contact Dermatitis Society's allergen of the year 2013.¹¹ Moreover, it is likely that MCI/MI at 100 ppm as it is included in the European and North American Contact Dermatitis Group (NACDG) baseline series does not detect an important number of cases of MCI/MI and MI allergies.¹²⁻¹⁵ Finally, cross-reactions between the 2 biocides make the primary allergen very difficult to elucidate.

For this reason, since October 2011, we have added in our baseline series MI at 2000 ppm and MCI/MI at 200 ppm. The main objectives of the study were to quantify the prevalence of contact allergy to both preservatives, to investigate if 100 ppm was an adequate concentration for a proper diagnosis, and to better understand the concomitant reactions between MCI/MI and MI. Our

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TABLE 1. Year Trend Prevalence of MCI/MI and MI Delayed Hypersensitivity From October 2011 to September 2013

	2-Year Study (N = 490)	2011 (October–December) (n = 102)	2012 (n = 220)	2013 (January–September) (n = 168)	P
MCI/MI	49 (10)	8 (7.8)	18 (7.7)	24 (14.3)	NS
MI	22 (4.5)	1 (1)	8 (3.6)	13 (7.7)	0.024

Values are presented as n (%).

NS indicates not significant.

hypotheses were that MCI/MI and MI allergies are increasing, that 100 ppm is not sufficient to diagnose an allergy to MCI/MI, and that a higher concentration of MCI/MI could also detect more cases of MI allergy.

MATERIALS AND METHODS

This prospective study was conducted in the Cutaneous Allergy Unit in the Dermatology Department of Hospital General Universitario de Alicante between October 2011 and June 2013.

Beginning in October 2011, MCI/MI in water at 200 ppm was added to our baseline series in addition to the regular concentration of 100 ppm present in the European baseline series. Methylisothiazolinone at 2000 ppm in water was also included in our baseline series. Test preparations were supplied by Chemotechnique. All patients were patch tested with the baseline series systematically regardless of their clinical history or the need of additional baselines to reach diagnosis. The allergens were applied on the upper back in Finn Chambers on Scanpor tape and occluded for 2 days. Readings were done on days 2 and 4 using the International Contact Dermatitis Research Group criteria. Irritant responses, doubtful responses, or negative readings were interpreted as negative.

The clinical data were recorded using a standardized database including age, sex, occupation, site of lesions, series tested, positive allergens and number of positives, their relevance, and origin of sensitization, patient's diagnosis, and follow-up.

Reaction frequencies in subgroups of patients defined by the MOAHLFA (male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg eczema, facial dermatitis, and age older than 40 years) index were analyzed. Comparisons were made between MCI/MI-positive patients and all the patch tested patients and between the group of MI-positive patients and all patch tested patients.

In the descriptive study, variables were expressed as absolute and relative frequencies. Differences in time trend prevalence and comparisons between allergic patients and nonallergic patients were performed using the χ^2 test. Statistical significance was accepted for *P* of less than 0.05. Data analysis was performed with the statistical software package SPSS for Windows version 22.0 (IBM, Chicago, Ill).

RESULTS

A total of 490 patients were patch tested in our department over the 2-year period. Of these, 49 (10%) had a positive reaction to

MCI/MI regardless of the concentration and 37 (7.3%) had a delayed hypersensitivity reaction to 100 ppm of MCI/MI. Twenty-two (4.5%) patients had an allergic contact dermatitis to MI (Table 1). No irritant reactions or cases of active sensitization were noted.

Considering temporal trends, the prevalence of MCI/MI allergy in our population was 7.8% in the last trimester of 2011, 7.7% in 2012, and 14.3% in the first 9 months of 2013 (Fig. 1 and Table 1). The prevalence of sensitization to MI was 1% in 2011, 3.6% in 2012, and 7.7% in 2013 (Fig. 1 and Table 1). Differences in the prevalence of sensitization to MI between 2011, 2012, and 2013 were statistically significant (*P* = 0.024).

Of the MCI/MI-positive patients, 13 (24.5%) were positive at 200 ppm and negative at 100 ppm. This represents the allergies to MCI/MI that would not have been detected with the 100-ppm concentration alone (Table 2).

Of the MI-positive patients, all of them were also MCI/MI positive at 200 ppm. Contrary to that, in this group, in 7 (31.8%) cases, 100-ppm concentration was negative (Table 2). Therefore, all patients with MI allergies would have had a positive MCI/MI patch in the baseline series if the concentration was 200 ppm.

Concomitant allergic reactions to MCI/MI and MI were found in 44.9% (22/49 patients) of MCI/MI allergic patients and in 100% (22/22 patients) of MI allergic patients. The proportion of MI-positive patients among those who reacted to MCI/MI was 12.5% in 2011, 44.4% in 2012, and 54.3% in 2013.

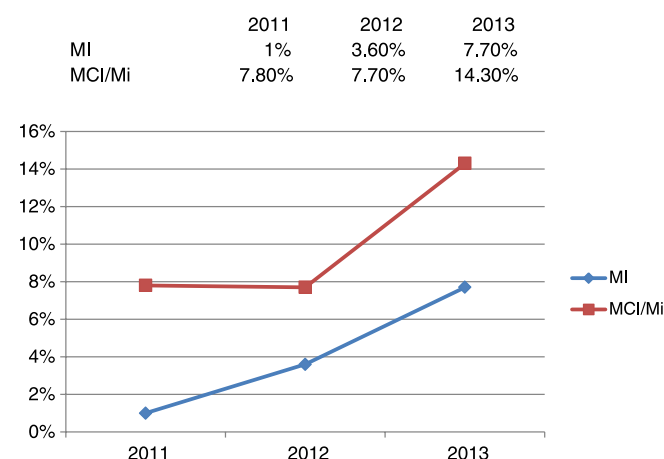


Figure 1. Year trends of sensitization to MCI/MI and MI from October 2011 to September 2013.

TABLE 2. Allergies to MCI/MI and MI That Would Not Have Been Detected With MCI/MI at 100 ppm Present in the European Baseline Series

	n	%
MCI/MI 100 ppm negative and MCI/MI 200 ppm positive	12/49	24.5
MCI/MI 100 ppm negative and MI 2000 ppm positive	7/22	31.8

According to the MOAHLFA index (Tables 3 and 4), MCI/MI and MI contact allergies were significantly more often associated with hand dermatitis. Moreover, patients with MI delayed hypersensitivity were younger and more likely women, but these results were not statistically significant.

Finally, 89.8% (44 cases) of MCI/MI allergies and 95.5% (21 cases) of MI allergies were due to cosmetics and/or household products.

DISCUSSION

In our tested population, the prevalence of MCI/MI allergy was 10% and most of the cases were related to cosmetics (89.8%). This is higher than the delayed hypersensitivity to MCI/MI found in previous studies. The MCI/MI prevalence ranged from 2.2% to 3.6% in 2001–2010 period in the United States,¹⁶ 3.9% in the Information Network of Departments of Dermatology in 2011,⁶ and 4.9% in Britain in 2011 and 2012.⁸ These differences can be partly explained by a better diagnosis with 200 ppm of MCI/MI applied in the study. Two other additional explanations concerning the United States are the lower limit of concentration allowable in leave-on products and the current unavailability of data from the 2011–2012 period.

The prevalence of MCI/MI allergies in our patch tested patients in 2011–2013 is more than double that found (4.49%) in October 2006 to September 2008 (12%). Herein, in our study, we have noted that MCI/MI allergies continue to increase, rising to 14.3% during 2013 (Table 1 and Fig. 1).

As of September 2013, the number of allergies to MCI/MI detected has already exceeded all other allergies diagnosed in 2012.

TABLE 3. MOAHLFA Index Among 490 Patch Tested Dermatitis Patients Compared With MCI/MI Positives

	MCI/MI Positive (n = 49), % (n)	Total (N = 490), % (n)	P
Male	40.8 (20)	36.9 (181)	0.6
Occupational dermatitis	4.1 (2)	5.7 (28)	0.7
Atopic dermatitis	26.5 (13)	23.9 (117)	0.7
Hand dermatitis	46.9 (23)	29.2 (143)	0.01
Leg dermatitis	10.20 (5)	12.9 (63)	0.6
Facial dermatitis	24.5 (12)	26.5 (130)	0.8
Age >40 y	61.2 (30)	64.4 (315)	0.6

TABLE 4. MOAHLFA Index Among 490 Patch Tested Dermatitis Patients Compared With MI Positives

	MI Positive (n = 22), % (n)	Total (N = 490), % (n)	P
Male	27.3 (6)	36.9 (181)	0.4
Occupational dermatitis	4.5 (1)	5.7 (28)	0.8
Atopic dermatitis	18.2 (4)	23.9 (117)	0.5
Hand dermatitis	54.5 (12)	29.2 (143)	0.01
Leg dermatitis	4.5 (1)	12.9 (63)	0.2
Facial dermatitis	22.7 (5)	26.5 (130)	0.7
Age >40 y	45.5 (10)	64.4 (315)	0.07

This outbreak of contact allergy to MCI/MI surpasses the levels of 8% reached in the 1980s that led to concentration limitations in cosmetics and industrial products.³ It is clear that MCI/MI contact allergy is rising,⁶ and our data suggest that it will continue rising if no action is taken. To our knowledge, the prevalence of MCI/MI contact allergy in our study in 2013 is the highest reported, probably because of a correct diagnosis with 200-ppm concentration and actualized data.

Considering MI allergies, we found a delayed sensitivity rate of 4.5% mainly because of cosmetics (95.5%), which is similar to what was detected in Leeds in 2011/2012,⁸ in Germany in selected patients in 2011,⁶ and in London in 2010–2013.⁹ This percentage is somewhat higher than what was found in previous studies in the 2008–2010 period^{17,18} and in Denmark in 2010–2012.¹⁹ In all the studies, an increasing rate was noted.^{6,8,9,17–19} There is no data concerning MI sensitization in the United States, but it is expected to be similar to what was found in Europe because of the same concentration limits and documented exposure to this allergen.¹¹ In our survey, we found a statistically significant rising tendency with an extremely high value in 2013 (7.7%), almost double what was detected in 2012 and, to our knowledge, the highest reported. Moreover, MI was allowed in cosmetics in the United States and Europe in 2005 and has been gradually incorporated as a single preservative in cosmetics.^{1,11,19} Hence, it is likely that its subsequent sensitization will increase with time if no actions are undertaken.⁹ It is clear that there is a rising epidemic of contact allergy to MI in cosmetics, which is especially worrisome, considering that MI itself has been allowed in cosmetics for only 7 years.^{6–9}

We found that 24.5% of the cases of contact dermatitis to MCI/MI would not have been detected with the 100-ppm patch concentration present in the Spanish baseline series. This is consistent with previous results published by our group where 24% of the patients showed positivity to 200 ppm of MCI/MI present in the cosmetic series with a negative 100-ppm patch test in the baseline series.¹²

Optimal MCI/MI patch test concentration is controversial. Indeed, in the NACDG and the European baseline series, MCI/MI is tested at 100 ppm, but some countries such as Sweden test MCI/MI at 200 ppm since 1980 and Britain has recently increased its concentration to 200 ppm.^{20,21} As early as 1986, Björkner¹⁴ et al

warned that 100-ppm patch test did not diagnose up to 50% of the cases of allergic contact dermatitis. In the study carried out by Färm and Wahlberg¹⁵ in Sweden where patients were tested simultaneously with 100 ppm and 200 ppm, up to 50% of the cases would have also been missed by 100-ppm patch test. Davies and Orton¹³ tested all patients with 200-ppm concentration and 100-ppm patch test that was subsequently applied to day 2 positive cases; they found that 100 ppm alone would have missed 46% (16/35) of the cases of MCI/MI allergic contact dermatitis. In a recent survey, Higgins et al²⁰ suggested that 200 ppm detected more cases due to the increase in MCI/MI prevalence after the change from 100 to 200 ppm in the British baseline series. Nevertheless, these results could be influenced by recent increases in MCI/MI allergies. There were more positive reactions in the equivalent 150-ppm MCI/MI patch test concentration present in the TRUE Test compared with the 100-ppm Finn Chamber patch test preparation.²² Our findings are in keeping with our previous study¹² and with those produced in the Swedish^{14,15} and British studies.^{13,20} The prevalence of MCI/MI allergies in the present survey would be 7.3% instead of 10% if 100 ppm had been applied. The epidemic of MCI/MI seems to be underestimated with the current 100-ppm concentration. However, in a study carried out in Denmark in 1998, 200 ppm did not diagnose more cases, but there were an important number of doubtful cases.²³ Although it could not be demonstrated, the authors suspected that 200 ppm caused more irritant reactions based on negative lymphocyte provocation tests. In our study, no irritant reactions to 200 ppm of MCI/MI were found, and at least in 44 of the 49 cases, there was a positive control because 100 ppm of MCI/MI and/or MI was concomitantly positive. Testing at 300-ppm concentration detects more allergies but can cause active sensitization.¹⁴

Additionally, in our study 200 ppm of MCI/MI was positive in 100% of MI allergic patients, whereas 100-ppm patch test was positive in only 68.2% of the cases. So, in our population, 200 ppm of MCI/MI could detect all the cases of delayed hypersensitivity to MI. We consider that more cases were positive to 200 ppm of MCI/MI mainly because it contains the double concentration of MI (50 ppm) compared with 100-ppm MCI/MI patch test (25 ppm). Because in other studies, 50 ppm could not detect all MI allergies,^{17,24,25} in some cases, positivity in MCI/MI and MI may also be due to cross-reactions between both molecules. In cases where allergy to MI is detected because of cross-reaction, 200 ppm of MCI/MI concentration detects MCI/MI allergy better; it will also detect more cases of MI allergies. Because of cross-reactions, the treatment in MCI/MI and MI allergies is the avoidance of both allergens. Herein, in our population, all MI allergic patients who were patched tested with 200 ppm of MCI/MI would receive an adequate treatment. This is of most importance, considering the rising epidemic of MI contact allergy and that MI is not included in NACDG baseline series.

Concomitant allergic reactions to MCI/MI and MI were found in 44.9% (22/49) of MCI/MI allergic patients. Considering that this ratio is increasing with time (14.5% in 2011, 44.4% in 2012, and 54.3% in 2013), it is likely that MI is the primary sensitizer of an increasing proportion of cases. Our results are in keeping with the

study made by Geier et al⁶ that found an increase in MI positives among MCI/MI allergic patients from 43.3% in 2009 to 58.9% in 2012. Formerly, MI was considered a weak to moderate allergen, and when cross-reactions occurred, MCI was pointed as the primary sensitizer, but recent data suggest that MI is a strong sensitizer.²⁶

Hand dermatitis was significantly associated with both MCI/MI and MI allergies. In previous studies, MCI/MI and MI allergies seemed to be more frequently related to hands²⁷ and face.^{6,28} In a recent study that analyzed the risk factors associated with MI sensitization, the increase of MI allergies was mainly driven by face dermatitis.²⁸ Hand dermatitis was also associated with MI sensitization but to a lesser degree. Methylisothiazolinone was tested in cosmetic preservatives series, so this could be a bias that favors face dermatitis. Hand dermatitis is known to cause an important burden in patient's quality of life²⁹ and has a high socioeconomic impact³⁰; this is an additional reason underscoring the importance of an adequate MCI/MI and MI diagnosis and treatment.

As opposed to the findings of McFadden et al⁹ and Uter et al,²⁸ MI allergies were more common in younger patients ($P = 0.07$). It is an expected result because younger patients tend to reflect changes in exposure and subsequent sensitization risk more promptly.²⁸

Finally, the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group have recently made a recommendation to include MI in a separate preparation at 2000-ppm concentration in the European baseline series.¹⁰ We agree that MI should be temporarily added to detect all cases, to monitor this new allergen, and to provide information for legislative actions. However, in previous studies,¹⁰ except the report of Urwin and Wilkinson,⁸ 200 ppm of MCI/MI could detect more than 95.5% of MI allergies. Hence, in our study, all MI cases were detected. In addition to that, 200 ppm of MCI/MI also allows a better diagnosis of MCI/MI allergies that are still more prevalent than MI allergies in most series^{8,18} and are also rising at an alarming rate. Methylisothiazolinone is a new allergen, which makes it more attractive, and therefore, there is a risk that MCI/MI is forgiven. Moreover, MI-positive patients in MCI/MI allergic patients are lower than MCI/MI-positive patients among MI allergic patients.^{6,17,18} This difference could be wider with 200-ppm concentration. Therefore, a positive MI patch test is likely to detect fewer cases of MCI/MI allergies than the amount of MI allergies that could be detected with a positive MCI/MI patch test. For these reasons, we also advocate an increase of MCI/MI patch test concentration to 200 ppm to better diagnose the rising epidemic of both allergens. This measure is also attractive because it does not require the inclusion of an additional allergen in the baseline series. If the only action taken in this epidemic is the inclusion of MI in the European baseline series, an enormous number of MCI/MI allergies will not be diagnosed.

CONCLUSIONS

We are facing a new epidemic of contact allergy to MCI/MI and MI. Allergies to these preservatives must be dealt with as a priority,

and adequate diagnosis and treatment are mandatory. Hence, we advocate a timely increasing of MCI/MI patch test concentration from 100 to 200 ppm in the NACDG and European baseline series. Finally, MI should be temporarily included in the NACDG baseline series, and its current limit concentration in cosmetics should be reviewed.

REFERENCES

1. Lundov MD, Krongaard T, Menné TL, et al. Methylisothiazolinone contact allergy: a review. *Br J Dermatol* 2011;165:1178–1182.
2. Magnano M, Silvani S, Vincenzi C, et al. Contact allergens and irritants in household washing and cleaning products. *Contact Dermatitis* 2009;61:337–341.
3. Fewings J, Menné T. An update of the risk assessment for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) with focus on rinse-off products. *Contact Dermatitis* 1999;41:1–13.
4. Burnett CL, Bergfeld WF, Belsito DV, et al. Final report of the safety assessment of methylisothiazolinone. *Int J Toxicol* 2010;29:187S–213S.
5. Mutschler J, Giménez-Arnau E, Foertsch L, et al. Mechanistic assessment of peptide reactivity assay to predict skin allergens with Kathon CG isothiazolinones. *Toxicol In Vitro* 2009;23:439–446.
6. Geier J, Lessmann H, Schnuch A, et al. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? *Contact Dermatitis* 2012;67:334–341.
7. Gonçalo M, Goossens A. Whilst Rome burns: the epidemic of contact allergy to methylisothiazolinone. *Contact Dermatitis* 2013;68:257–258.
8. Urwin R, Wilkinson M. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: a new 'epidemic'. *Contact Dermatitis* 2013;68:253–255.
9. McFadden JP, Mann J, White JM, et al. Outbreak of methylisothiazolinone allergy targeting those aged ≥40 years. *Contact Dermatitis* 2013;69:53–55.
10. Bruze M, Engfeldt M, Gonçalo M, et al. Recommendation to include methylisothiazolinone in the European baseline patch test series—on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 2013;69:263–270.
11. Castaneda-Tardana MP, Zug KA. Methylisothiazolinone. *Dermatitis* 2013;24:2–6.
12. Cuesta L, Silvestre JF, Toledo F, et al. Delayed hypersensitivity to methylchloroisothiazolinone/methylisothiazolinone not detected by the baseline series of the Spanish group. *Contact Dermatitis* 2010;62:250–251.
13. Davies E, Orton D. Identifying the optimal patch test concentration for methylchloroisothiazolinone and methylisothiazolinone. *Contact Dermatitis* 2009;60:288–289.
14. Björkner B, Bruze M, Dahlquist I, et al. Contact allergy to the preservative Kathon CG. *Contact Dermatitis* 1986;14:85–90.
15. Färm G, Wahlberg JE. Isothiazolinones (MCI/MI): 200 ppm versus 100 ppm in the standard series. *Contact Dermatitis* 1991;25:104–107.
16. Warshaw EM, Belsito DV, Taylor JS, et al. North American Contact Dermatitis Group patch test results: 2009 to 2010. *Dermatitis* 2013;24:50–59.
17. Ackermann L, Aalto-Korte K, Alanko K, et al. Contact sensitization to methylisothiazolinone in Finland—a multicentre study. *Contact Dermatitis* 2011;64:49–53.
18. Schnuch A, Lessmann H, Geier J, et al. Contact allergy to preservatives. Analysis of IVDK data 1996–2009. *Br J Dermatol* 2011;164:1316–1325.
19. Lundov MD, Opstrup MS, Johansen JD. Methylisothiazolinone contact allergy—growing epidemic. *Contact Dermatitis* 2013;69:271–275.
20. Higgins E, Kirby B, Rogers S, et al. Methylchloroisothiazolinone and methylisothiazolinone allergic contact dermatitis and the effect of patch test concentration. *Dermatitis* 2013;24:73–76.
21. Isaksson M, Gruvberger B. Patch test sensitization to methylchloroisothiazolinone + methylisothiazolinone and 4,4'-diaminodiphenylmethane. *Contact Dermatitis* 2003;48:53–54.
22. Wilkinson JD, Bruynzeel DP, Ducombs G, et al. European multicenter study of TRUE Test, panel 2. *Contact Dermatitis* 1990;22:218–225.
23. Fewings J, Menné T. The patch test concentration for methylchloroisothiazolinone/methylisothiazolinone. *Contact Dermatitis* 1998;39:320–321.
24. Lundov MD, Zachariae C, Johansen JD. Methylisothiazolinone contact allergy and dose-response relationships. *Contact Dermatitis* 2011;64:330–336.
25. Waton J, Poreaux C, Schmutz JL, et al. Is 500 ppm a better concentration than 200 ppm for diagnosing contact allergy to methylisothiazolinone? *Contact Dermatitis* 2013;69:251–252.
26. Roberts DW. Methylisothiazolinone is categorised as a strong sensitizer in the murine local lymph node assay. *Contact Dermatitis* 2013;69:261–262.
27. Lundov MD, Thyssen JP, Zachariae C, et al. Prevalence and cause of methylisothiazolinone contact allergy. *Contact Dermatitis* 2010;63:164–167.
28. Uter W, Geier J, Bauer A, et al. Risk factors associated with methylisothiazolinone contact sensitization. *Contact Dermatitis* 2013;69:231–238.
29. Moberg C, Alderling M, Meding B. Hand eczema and quality of life: a population-based study. *Br J Dermatol* 2009;161:397–403.
30. Diepgen TL, Scheidt R, Weisshaar E, et al. Cost of illness from occupational hand eczema in Germany. *Contact Dermatitis* 2013;69:99–106.